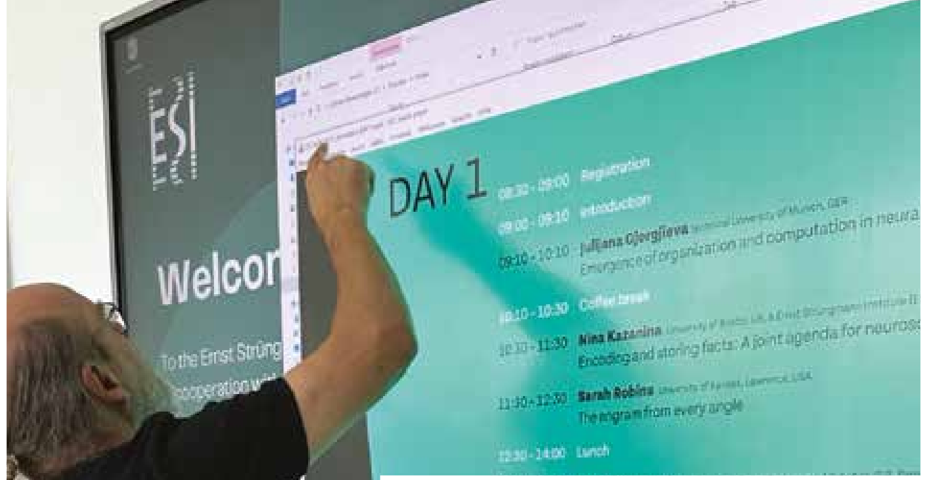
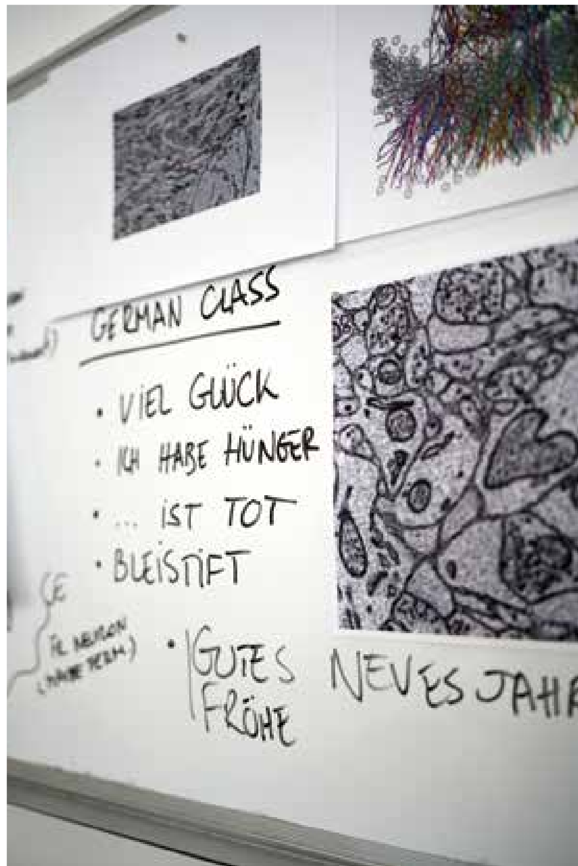
GROWTH & ChaNGE

RESEARCH REPORT 2021–2023


Ernst Strüngmann Institute
Parkflächen
nur für Mitarbeitende und Gäste
des Ernst Strüngmann Instituts


Welcom
DAY 1
08:30 - 09:00 Registration
09:00 - 09:10 Introduction
Julijana Gjorgjieva
Emergence of organization and computation in neura
Coffee break
Nina Kazanina
Encoding and storing facts: A joint agenda for neuros
Sarah Robins
The engram from every angle
12:30 - 14:00 Lunch
STAFF


GERMAN CLASS
• VIEL GLÜCK
• ICH HABE HÜNGER
• ... IST TOT
• BLEISTIFT
• GUTES FRÜHE
NEUES JAHR

RESEARCH REPORT 2021 – 2023

Growth and Change

PREFACE

On Growth and Change

ESI in its original conception ("ESI 1.0") worked for a decade, first in the old building and subsequently in the fantastic new building since 2018/2019. The intellectual focus was on visual neuroscience, with particular emphasis on research on nonhuman primates. Over the last three years (let's call it "ESI 1.5"), the institute has gone through a major transition, with both the addition of junior research groups and a cognitive neuroscience department as well as the departure of a department. The empirical scope has significantly broadened, the institute has grown in terms of number of scientists, and the infrastructure continues to be optimized to facilitate the best possible research.

Change is exciting, but it can be hard. Change that comes with the opportunity for growth should be seen as a thrilling chance to develop the research, mentorship, and outreach in novel directions. We are now in the phase of constructing ESI 2.0. This is our shared opportunity to define the goals, aspirations, and hopes for the next chapter of science, training, and public engagement that we accomplish at ESI.

From connectomics to principles of wiring in the brain, from the neurophysiological foundations of vision, balance, and foraging to new ideas on neural coding, from working memory to language – a wide range of questions and approaches has been embraced by the PIs at the institute. **Research** on these topics will continue, but it is also a major goal for ESI to grow, both by recruiting new departments and directors and by hiring new junior research groups, to complement and expand the areas of investigation. Scientific efforts will increase on areas such as computation, cognition, and communication. By being more thoughtfully embedded in the landscape of Frankfurt neuroscience and capitalizing on our location on the medical school campus – and immediately adjacent to the new cooperative brain imaging center CoBIC – ESI can and should play a central role in developing systems, computational, and cognitive neuroscience in the Frankfurt and Rhein-Main region – and, of course, nationally and internationally.

ESI has a growing number of pre-doctoral and post-doctoral trainees. These early-career scientists bring new ideas, fresh energy, fewer preconceptions, and the promise of embracing the edgiest theories, techniques, and approaches to address the foundational questions of the brain and cognitive sciences. ESI must become an institution of first-rate **teaching and mentorship**, and the leadership of the institute is committed to further developing this critical aspect of a leading research establishment.

Finally, we want ESI's contribution to be known, locally and globally. The institute has begun to offer **more public outreach and service**, and the success of the events – the conferences, concerts, and workshops – have provided participants a chance to enjoy and celebrate the science, the people, and the opportunities the institute makes possible. We will continue to think creatively about how to connect with the public, ranging from young school kids to mature audiences eager to experience the fabulous work done at ESI.

David Poeppel

140

2 On Growth and Change
6 Insights

ESI

8 The ESI Story
12 Core Scientific Mission
14 Future Goals
16 Frankfurt Networks
18 Partnerships and Cooperations
20 Facts and Figures
22 Organization

OUR LABS*

26 Cuntz Lab
36 Havenith & Schölvinck Lab
52 Laurens Lab
62 Poeppel Department
80 Rademaker Lab
96 Schmidt Lab
108 Singer Senior Research Group
122 Vinck Lab

* as of January 2024

24

SERVICE GROUPS

140 Scientific Core Facility
142 Technical Group
144 Animal Facility
Facility Management
145 Administration
146 Public Relations &
Information Management

EVENTS & OUTREACH

148 ESI SyNC, ESImeets,
Girls'Day, CuttingGardens

148

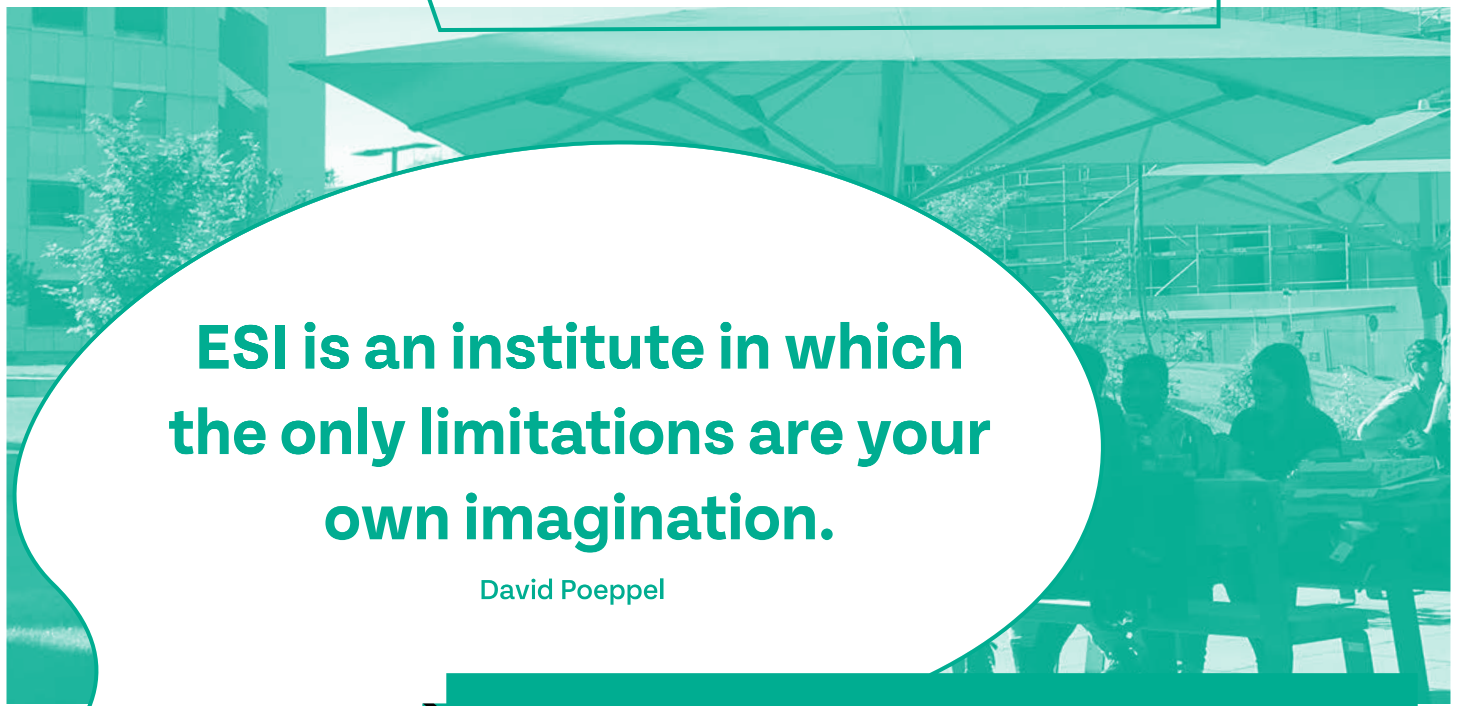
PUBLICATIONS

152 2021
154 2022
156 2023

158 Imprint

I like that there are so many different nationalities and people of backgrounds coming together to bring neuroscience forward.

Alisha Crider



ESI is an institute in which the only limitations are your own imagination.

David Poeppel

What makes the ESI unique, is that we have such a diversity of different labs inside of this institute.

Robert Taylor

It's all about electricity!

Athanasia Tzanou

It's the brain that creates the mind.

Wolf Singer

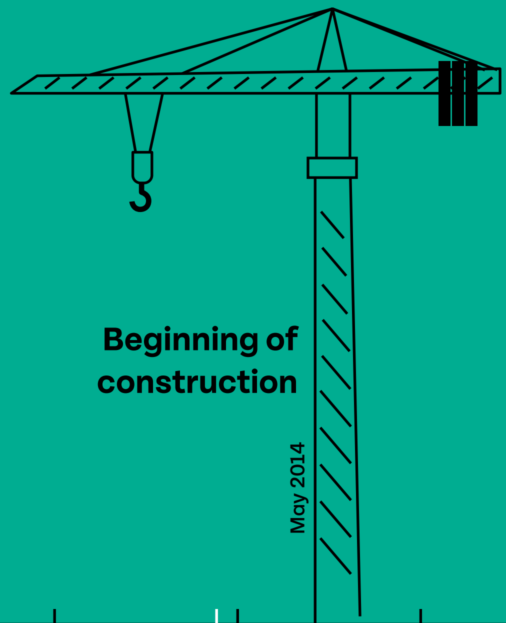
One of our big goals is to show that science can be done in a lot of different ways.

Martha Havenith

HOW WE CAME TO BE

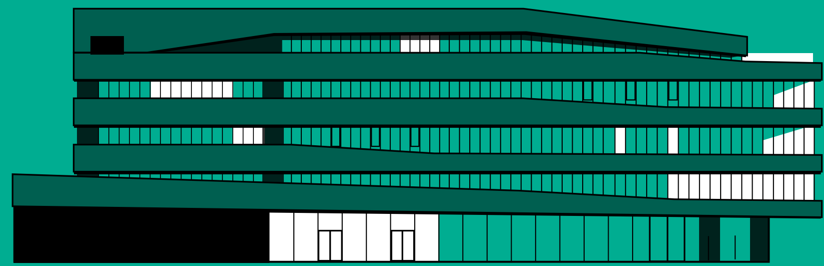
THE ESI STORY

Parcel size:
11.302 m²
Office (& lab) space:
2846,7 m²



Beginning of construction

May 2014



2008

12. September 2008

Dr. Andreas and Dr. Thomas Strüngmann **found** the Ernst Strüngmann Institute (ESI) for Neuroscience.

27. November 2013

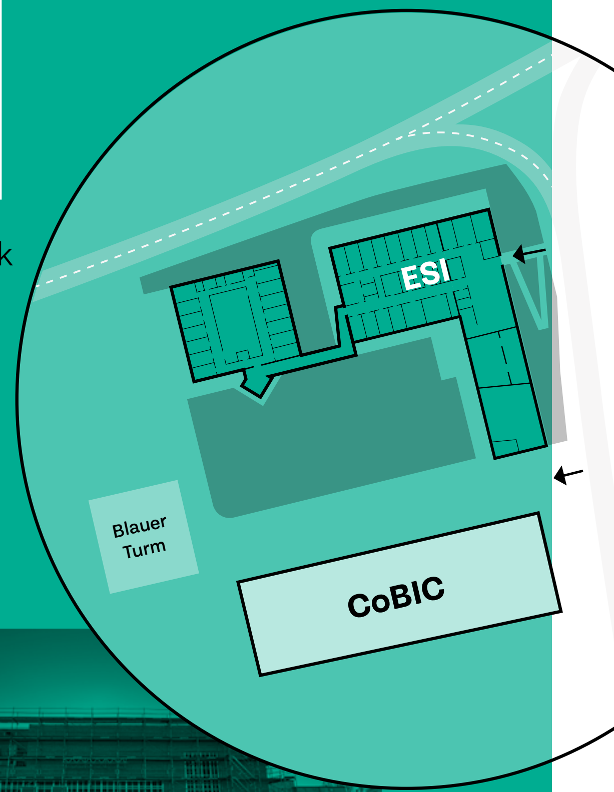
The state of Hesse transfers the **property to ESI for 99 years** (Erbbaurecht).

March 2018

Move-in date for the new institute building

End of 2020

Construction work starts for the **Cooperative Brain Imaging Center (CoBIC)** adjacent to the south of the ESI.



HOW WE CAME TO BE

THE ESI STORY

In September 2008, Dr. Andreas and Dr. Thomas Strüngmann founded the Ernst Strüngmann Institute (ESI) for Neuroscience. The institute is named after their father, Dr. Ernst Strüngmann, who died in 2005. In memory of his guidance and advice, the family established the Ernst Strüngmann Foundation, which funds the institute.

The ESI has the legal form of a “gemeinnützige Gesellschaft mit beschränkter Haftung (gGmbH)”, i.e. a non-profit corporation, with the Strüngmann brothers as “Gesellschafter” (partners) and a “Stiftungsrat” (board) guiding the work. The Chief Executive Officer serves at the pleasure of the board and is a scientific member of the Max Planck Society.

In order to capitalize on the expertise of an organization with substantial history of running basic research institutes, the foundation partnered with the Max Planck Society. This type of public-private partnership in research is rare in Germany, and the “Ernst Strüngmann Institute for Neuroscience in Cooperation with the Max Planck Society” was designed to **combine the flexibility of private funding with the research excellence of an established organization.**

ESI’s founding director was Prof. Wolf Singer, and the institute started its work in the former building of the Max Planck Institute for Brain Research in Frankfurt. In 2009, Prof. Pascal Fries joined to become ESI’s first managing director. In 2011, when Prof. Singer assumed emeritus status at the Max Planck Institute for Brain Research, he joined ESI as Senior Research Group leader.

Over the next several years, research group leaders joined ESI (and some moved on to new positions). In 2018, the new home was ready and the institute moved into the terrific research building at Deutschordenstrasse 46. In 2021, David Poeppel joined ESI as managing director. Between 2021 and 2023, ESI consisted of two departments, one senior research group, and six independent research groups. This size, roughly, will be maintained in the future. ESI 2.0 strives to host three departments run by directors and seven or more research groups run by independent group leaders.

WHAT WE DO

CORE SCIENTIFIC MISSION

The mission of ESI is to conduct fundamental brain research.

The focus to date has been on the systems neuroscience level: the research seeks to understand how the neurons of the brain work together to bring about our experiences and behavior, ranging from (simple seeming) aspects of perception to (straightforward seeming) components of cognition to the not-so-clear-seeming foundations of conscious experience.

To this end, researchers at ESI develop new concepts and theories and craft new recording and analysis methods to test these ideas, often in collaboration with national and international partners. New insights and methods are disseminated through publications, lectures, workshops, conferences, and teaching activities.

The training and mentorship of students and postdocs through transfer of knowledge and techniques is an integral component of ESI's mission. Moreover, ESI supports the translation of insights and methods from fundamental research to applications, in particular for clinical purposes.

Finally, it is an important goal to embrace public outreach and service, to make the research understandable and available to broader communities.

The scientific mission of the institute is accomplished by a diverse group of scientists at different career stages.
(The research programs of the groups are described in subsequent sections of the report.)

Between 2021 and 2023, ESI comprised the following research teams:

- Department of Prof. Fries
- Department of Prof. Poeppel
- Senior Research Group of Prof. Singer
- ESI Research Group of Prof. Martin Vinck
- ESI Research Group of Dr. Hermann Cuntz
- Max Planck Research Group of Dr. Jean Laurens
- joint Max Planck Research Group of Dr. Martha Havenith and Dr. Marieke Schoelvinck
- Max Planck Free Floater Group of Dr. Rosanne Rademaker
- Max Planck Otto Hahn Award Group of Dr. Helene Schmidt

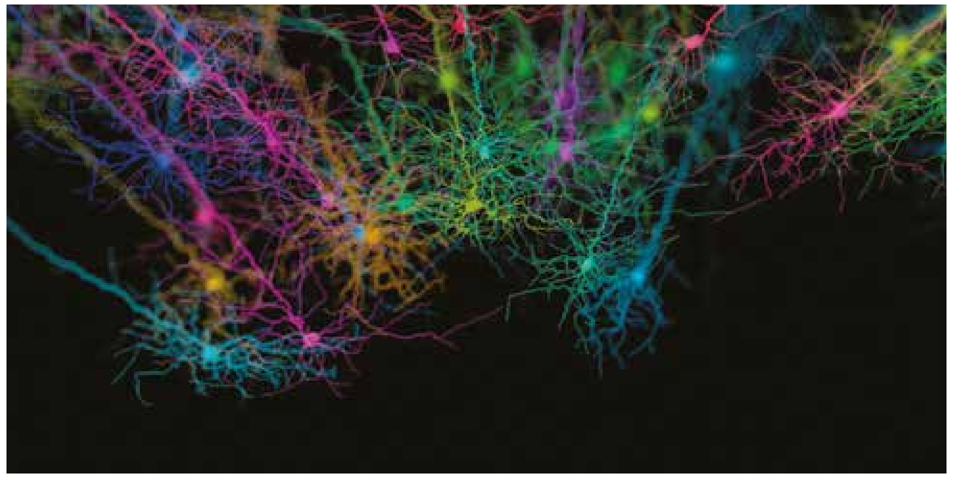
These groups constitute the extended faculty of ESI.

WHAT WE DO

FUTURE GOALS

The scientific mission of ESI will continue to be basic research in neuroscience. **The scope of research, however, will broaden over the next years,** and the institute will place its focus on fundamental research in the brain and cognitive sciences, encompassing systems neuroscience, computation, and cognition. The emphasis will remain on studying higher-order processes, from navigation to foraging, from memory to language. In that sense, the ESI stands apart from related institutes that focus on cellular and molecular neurobiology.

With the levels of investigation spanning systems, computational, and cognitive neuroscience, the methods and model systems also become more varied: the research will continue to include non-human primates and humans and other approaches (from rodents – and maybe robots? – to bats – and maybe birds?). **Of particular interest is work that links neural mechanisms with theoretically well-motivated and computationally well-characterized behaviors.** One might think of the goal as connecting the intellectual 'spirit of neuroethology' with current experimental techniques and computational approaches to understand the mechanisms that form the basis for perception and cognition.



The combination of the research agenda of ESI and the physical location of the institute motivates two additional goals. First, the ongoing and planned work should connect seamlessly to approaches in computational neuroscience, machine learning, artificial intelligence, biologically inspired computing, and related areas of investigation – because these are active domains of interest for many of our local partners that can enhance the research of ESI. Second, in light of the fact that the institute is in the middle of the medical school campus, in particular the large neurology, neurosurgery, and psychiatry community, ESI should capitalize more effectively on the opportunities afforded by the adjacent clinical neuroscience work.

To achieve these goals, i.e., broadening the empirical scope of the research, ESI will revitalize and implement the plan for recruiting two more departments, with **the explicit goal of increasing the diversity of the institute leadership.** Likewise, research group leaders with the ambition to pursue these lines of research for some years will be actively recruited.

WHERE WE ARE

FRANKFURT NETWORKS

The local network for ESI 2.0: Local partner institutions in Frankfurt that study the brain and cognitive sciences

The location of ESI in Frankfurt – its proximity to neighboring institutions that focus on closely related scientific challenges – makes it obvious to develop and strengthen these relationships.

Two Max-Planck Institutes are directly relevant: the **MPI for Brain Research**, a world-class center for cellular and circuit-level neuroscience, will be a partner on scientific projects as well as a close collaborator on crafting a new graduate neuroscience program, a project that has commenced. The **MPI for Empirical Aesthetics** has a department (and in the future maybe more) dedicated to human neuropsychology and will be a partner on brain imaging initiatives in the new **Cooperative Brain Imaging Center (CoBIC)**.

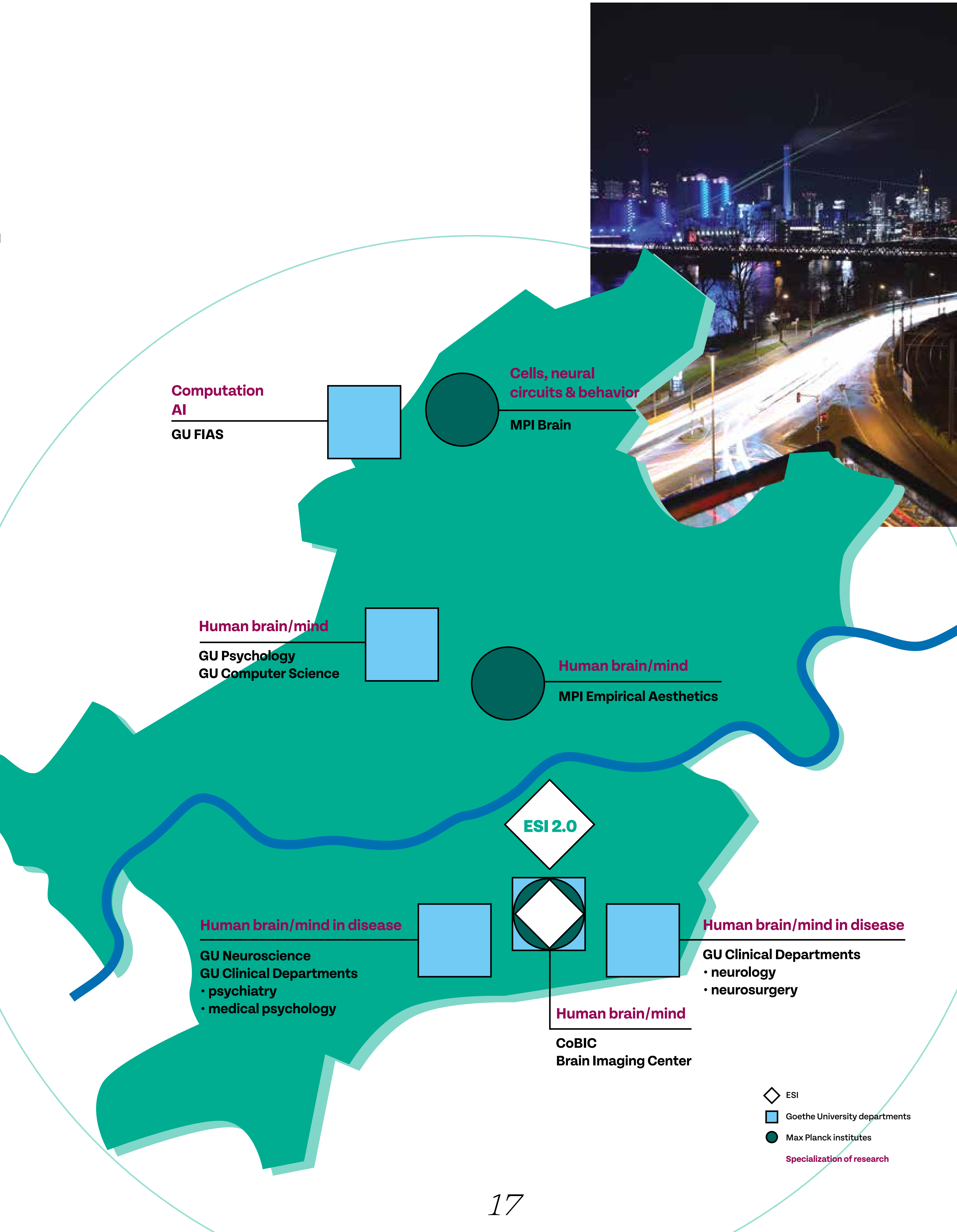
Goethe University has a number of departments that are integral to strengthening the local brain and cognitive science community. The **Frankfurt Institute for Advanced Studies (FIAS)** houses first-rate computational neuroscience. The university's computer science and psychology departments are pursuing research directly relevant to ESI, ranging from biologically inspired computing to cognitive neuroscience. And ESI's immediate neighbors are the medical school departments directly relevant to human neuroscience: neurology, neurosurgery, neuroradiology, psychiatry, and medical psychology.

The spatial embedding of ESI makes one feature clear: there is tremendous local expertise in human neuroscience and cognitive science. Given the commitment of ESI to have its intellectual focus on perception and cognition, it stands to reason that ESI 2.0 can and should be a hub for systems and cognitive neuroscience, for example with a focus on dynamics and computation. More broadly, ESI and its immediately adjacent institutional neighbors can be a hub for the study of human neuroscience, making Frankfurt a location with a more well-delineated mission.

In order to support each other institutionally in the region, and in order to solve problems best addressed as a group of stakeholders with political clout, a number of institutions recently formed the **"Frankfurt Alliance". This includes Goethe University, the Max Planck Society, Fraunhofer, Leibniz, and other partners – including ESI.** This alignment allows better sharing of resources, dealing with hiring complexities, lobbying, and other tasks best handled by a group representing thousands of local scientists, staff, and students.

The relevance and quality of other neighboring institutions should also not be forgotten. The **TU Darmstadt**, **Mainz University**, **Giessen University**, and **Marburg University** are strong academic partners with excellent relevant research programs. ESI is already partnering with these institutions, for example in the context of the new and large collaborative LOEWE center grant DYNAMIC, on network foundations of psychiatric diseases.

ESI will play a central role in further establishing systems neuroscience across levels in the region, with one goal being to lead an effort towards cutting-edge human neuroscience as a hallmark of the Frankfurt neuro-landscape.



WHO WE WORK WITH

PARTNERSHIPS & COOPERATIONS

Participants at the Ernst Strüngmann Forum exchanging ideas during a break.

The neighborhood

Of the many significant partnerships and cooperations that ESI has, the closest ones are with our local “siblings” and “cousins.” The institute’s sibling is the **Ernst Strüngmann Forum**, an independent entity that runs a scientific workshop series with major international visibility and impact. The Forum fosters the growth of knowledge by providing a discussion environment for researchers to scrutinize high-priority problems from multiple perspectives. The goal is not (necessarily) to achieve consensus but to identify gaps in our knowledge – and recommend ways of addressing these gaps in future research. Like ESI, funding is provided by the Ernst Strüngmann Foundation. Going forward, these events will be held at ESI, and a substantial proportion of the workshop topics will relate to the brain and cognitive sciences, broadly construed.

ESI’s immediate neighbor is, likewise, a close relative. The **Cooperative Brain Imaging Center (CoBIC)** is a neuroimaging facility run by Goethe University, ESI, and the Max Planck Society. The new and expanded imaging center opens in the spring of 2024 and houses a 7T MRI scanner (Terra), two 3T MRI systems (Prisma), whole head MEG (CTF), EEG, and other key technologies for human neuroscience. ESI and CoBIC now constitute the nucleus of a neuroscience campus.

One persistent challenge for independent research institutes such as Max Planck Institutes and ESI is the ability to graduate PhD students. However, in addition to partnering with universities directly on a case-by-case basis to confer degrees, ESI is a member of the **Max Planck School of Cognition**, which provides infrastructure to grant PhDs to our students.

The region

ESI is increasingly well embedded in the regional networks of institutions and initiatives relevant to systems, computational, clinical, and cognitive neuroscience. For example, we are active members of the **Rhine-Main-Neuroscience network (rmn2)** and participate in the **Interdisziplinäres Zentrum für Neurowissenschaften Frankfurt (IZNF)** at Goethe-Universität to support local interaction and shared grant applications. ESI is also an active partner in the newly formed **Frankfurt Alliance**, which joins the local institutes in Frankfurt (Max Planck, Fraunhofer, Leibniz, Goethe University) to support each other with infrastructure needs, hiring challenges, and other topics that can best be solved using joint policy approaches.

One example of an exciting new development is that ESI plays a key role in the newly approved **LOEWE DYNAMIC** program, a multi-year research center funded by the state of Hessen to understand psychiatric disorders in the context of dynamic network analyses.

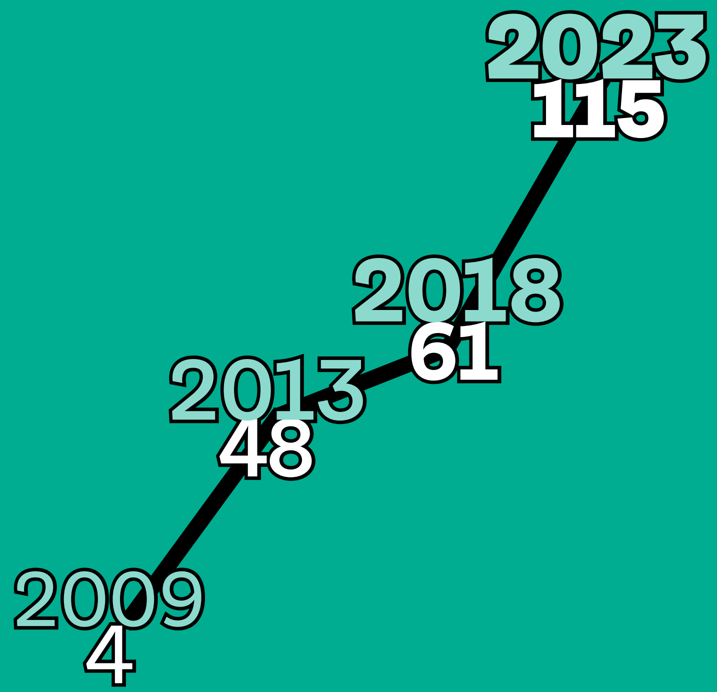
The world

Virtually every PI at the Institute has local, regional, and international research collaborations. Indeed, ESI researchers have joint students and grants in **20 countries**. In light of the increasing focus on human neuroscience and higher cognition, one international initiative will be developed more systematically: the **ESI-NYU Center for Language, Music, and Emotion (CLaME)**. With initial seed funding by the Max Planck Society and NYU, this center generated an enormous amount of research and training, and the ability to develop these areas in a combined international setting will amplify the research ambitions because of what each of the two institutions can independently contribute to these foundational questions.

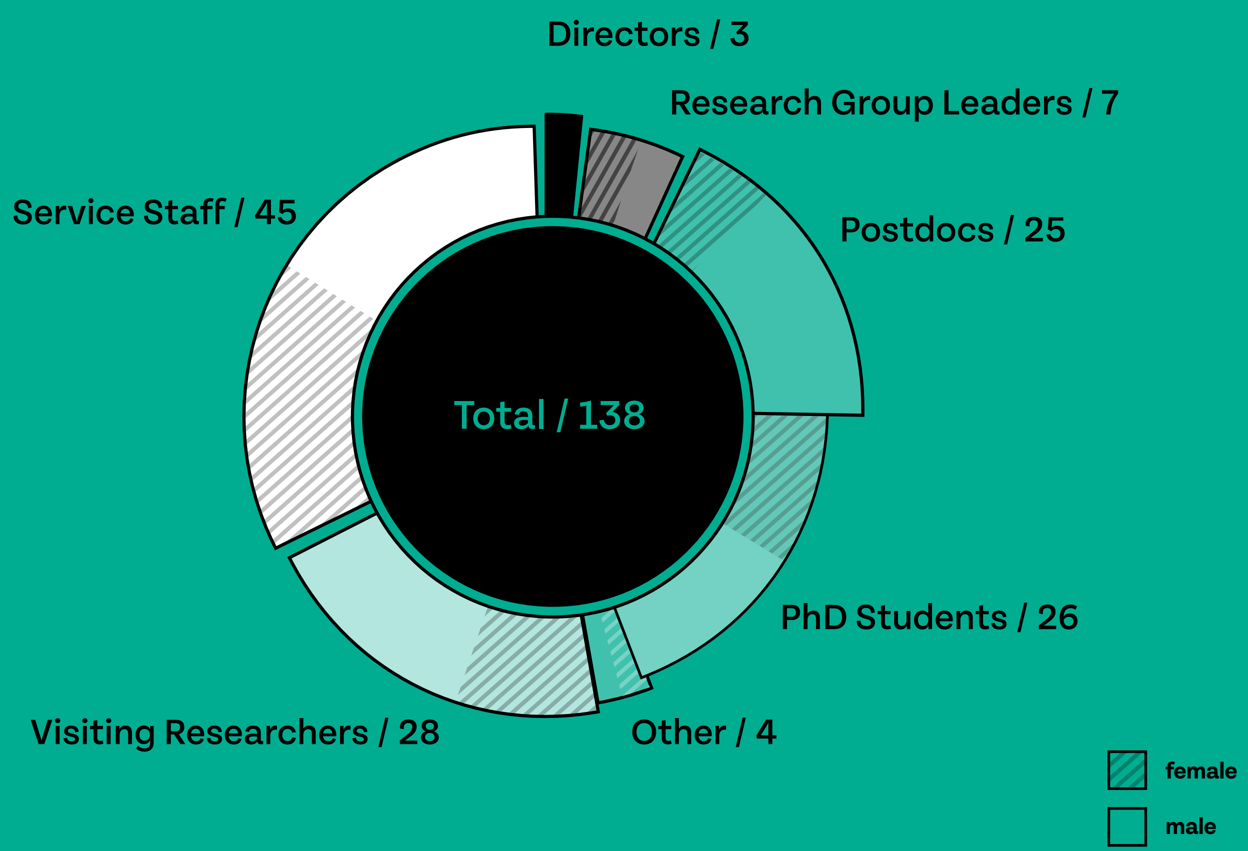
The Cooperative Brain Imaging Center (CoBIC) opens in spring of 2024.

WHO WE ARE

PEOPLE



Number of employees over the years



Number of employees per function

Number of employees per gender

Home countries of all employees

WHO WE ARE

ORGANIZATION

DIRECTOR

David Poeppel

CONSULTATIVE BOARD

The consultative board of the Ernst Strüngmann Institute (ESI) for Neuroscience is a central element in linking the institute to the public and society. It is composed of representatives of regional politics, the university, economy and media.
The members are:

POLITICS

Ayse Asar State Secretary in the Hessian Ministry of Science and Art
Dr. Ina Hartwig Stadträtin of the Magistrat Frankfurt am Main

UNIVERSITY AND UNIVERSITY MEDICAL CENTER

Prof. Dr. Jürgen Graf Medical Director, University Medical Center, Frankfurt
Prof. Dr. Enrico Schleiff President of University of Frankfurt
Prof. Dr. Stefan Zeuzem Dean of the Medical School of University of Frankfurt

ECONOMY AND BANK

Friedrich von Metzler Partner of the B. Metzler seel. Sohn & Co. KgaA
Dr. Kersten von Schenk Lawyer, retired notary and author of legal publications

MEDIA

Ina Dahlke Hessischer Rundfunk
Jürgen Kaube Frankfurter Allgemeine Zeitung
Dr. Regina Oehler Science Department of Hessischer Rundfunk, retired

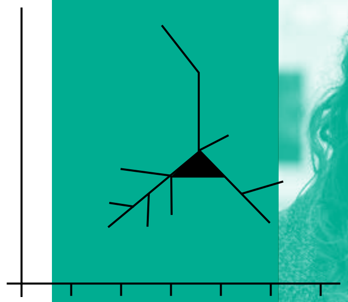
ESI BOARD OF TRUSTEES

From left to right: Patrick Cramer, President MPS / Wolf Singer, ESI Board of Trustees / Özlem Türeci, ESI Board of Trustees / Herbert Jäckle, ESI Board of Trustees / Asifa Akhtar, Vice President MPS, Chair ESI Board of Trustees / David Poeppel, CEO ESI / Erwin Neher, ESI Board of Trustees / Andreas Strüngmann, ESI Board of Trustees / missing in picture: Prof. Dr Rudolf Steinberg, former President of the Goethe University, Frankfurt am Main
(as of December 31, 2023)

SCIENTIFIC ADVISORY BOARD (SAB)

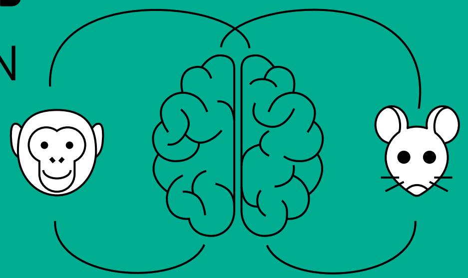
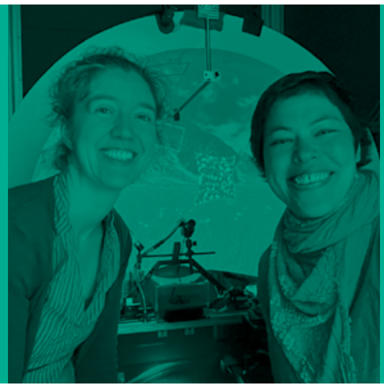
Prof. Dr. Alain Destexhe Paris-Saclay Institute of Neurosciences, ICN Integrative & Computational Neuroscience, CNRS – Université Paris-Sud
Prof. Dr. Jean-René Duhamel Institute Of Science Cognitives – Marc Jeannerod, Bron
Prof. Dr. Joachim Gross University of Münster
Prof. Dr. Sonja Hofer The Sainsbury Wellcome Centre, University College London
Prof. Dr. Christopher Moore Brown University, Providence
Prof. Dr. Anthony J. Movshon New York University, New York
Prof. Dr. Anna Christina Nobre Yale University, New Haven
Prof. Dr. Friedrich Sommer University of California, Berkeley

OUR RESEARCH LABS



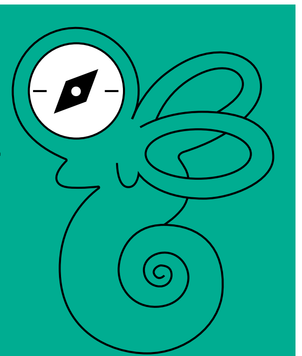

CUNTZ LAB

COMPUTATIONAL NEUROANATOMY

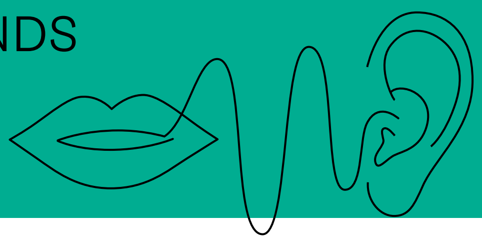
HAVENITH & SCHÖLVINCK LAB

THE ZERO NOISE BRAIN

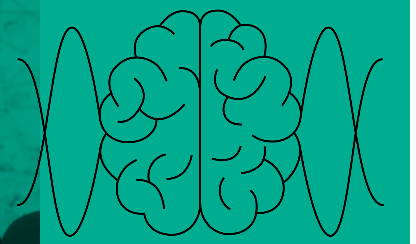
LAURENS LAB

SYSTEMS NEUROSCIENCE OF NAVIGATION AND MOTION



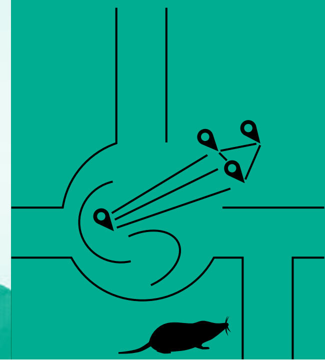

POEPPEL DEPARTMENT

HUMAN MINDS AND BRAINS AND SOUNDS

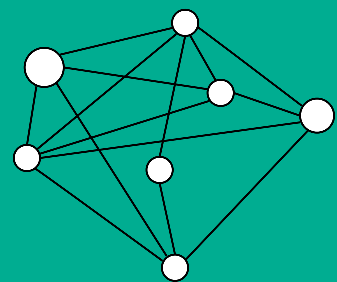
RADEMAKER LAB

THE VISUAL BRAIN AND HUMAN THOUGHT

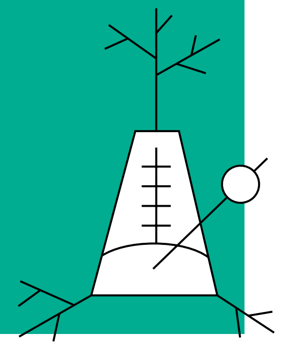
SCHMIDT LAB

CONNECTOMICS OF NAVIGATION




SINGER SENIOR RESEARCH GROP

THE CEREBRAL CORTEX: A DYNAMIC SYSTEM

VINCK LAB

PRINCIPLES OF NEURAL CODING AND INTER-AREAL INTERACTIONS

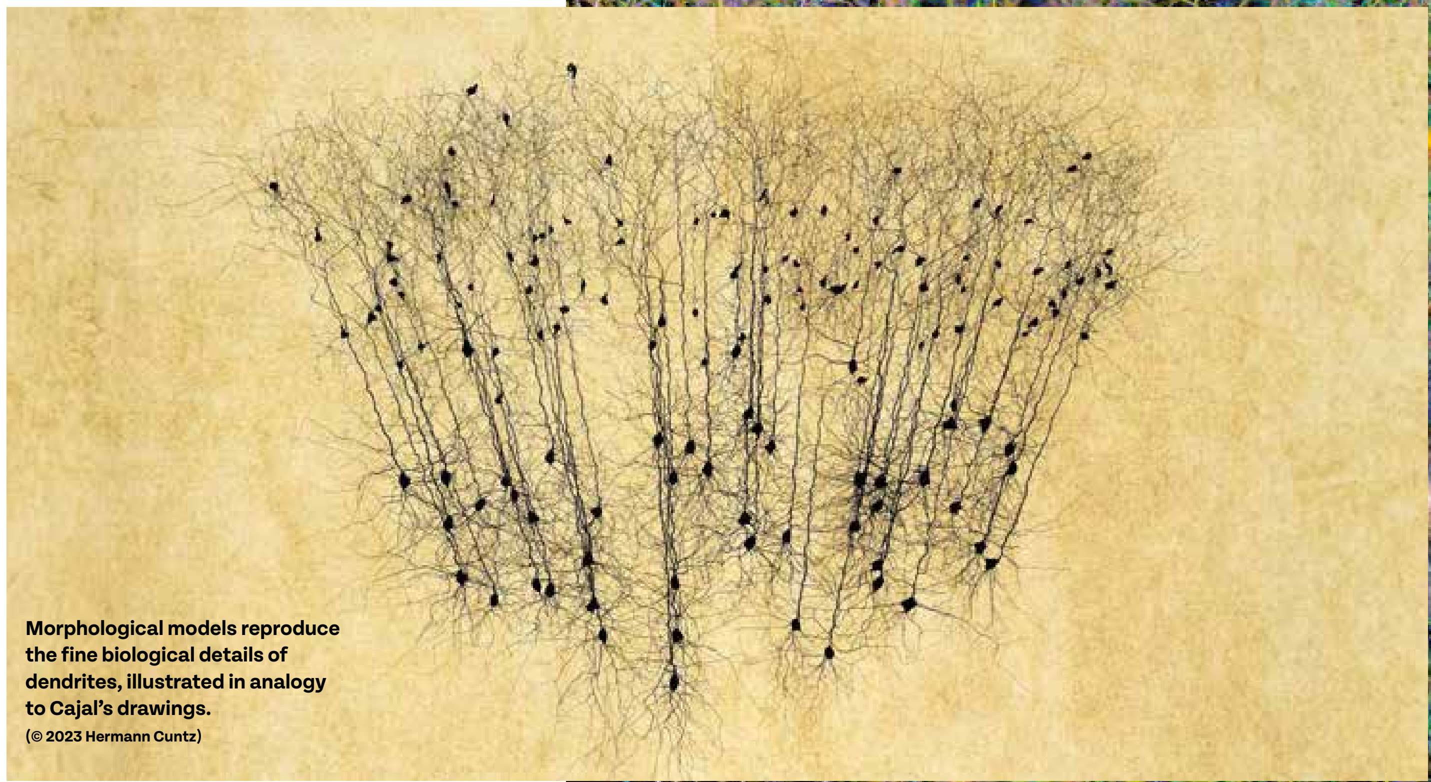
CUNTZ LAB

COMPUTATIONAL NEUROANATOMY

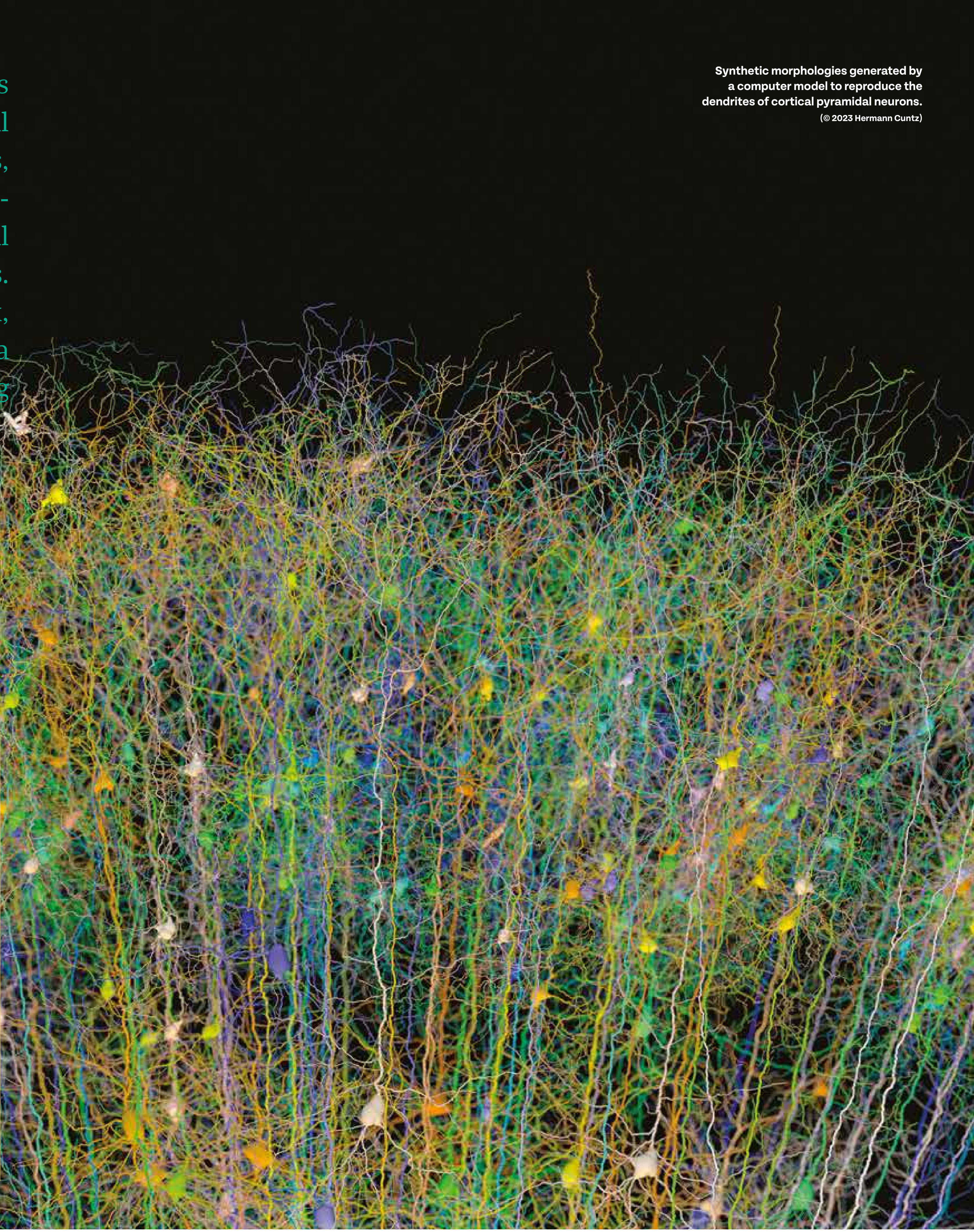
Principal Investigator Hermann Cuntz / Co-PI Peter Jedlicka (Giessen University) / Associated Researchers Alexander Bird, André Ferreira Castro, Moritz Groden (PhD, 2022), Martin Mittag, Nicholas Hananeia, Christian Ebner / Students Andrea Stolz (BSc, from 2023), Bassem Hermila (MSc, 2023), Sophie Schmidt-Hamkens (MSc, 2022), Verena Haas (MSc, 2021), Lukas Frank (MSc, 2021), Benjamin Fani Sani (BSc, 2021) (as of December 2023)

"We would like to understand the biophysics of neural computation and information processing as a function of single cells and circuits."

CUNTZ LAB How do neurons connect to form the sophisticated circuits that allow the brain to function? Our research employs computational methods for the direct generation of synthetic neuronal morphologies, guided by constraints related to wiring, computation, and network context. This approach, coupled with analytical tools, has yielded crucial insights into both neuronal function and the anatomy of circuits. Furthermore, it has resulted in the development of the TREES toolbox, an extensive open-source software package for neuroanatomical data management and modelling, boasting thousands of users and receiving hundreds of citations.

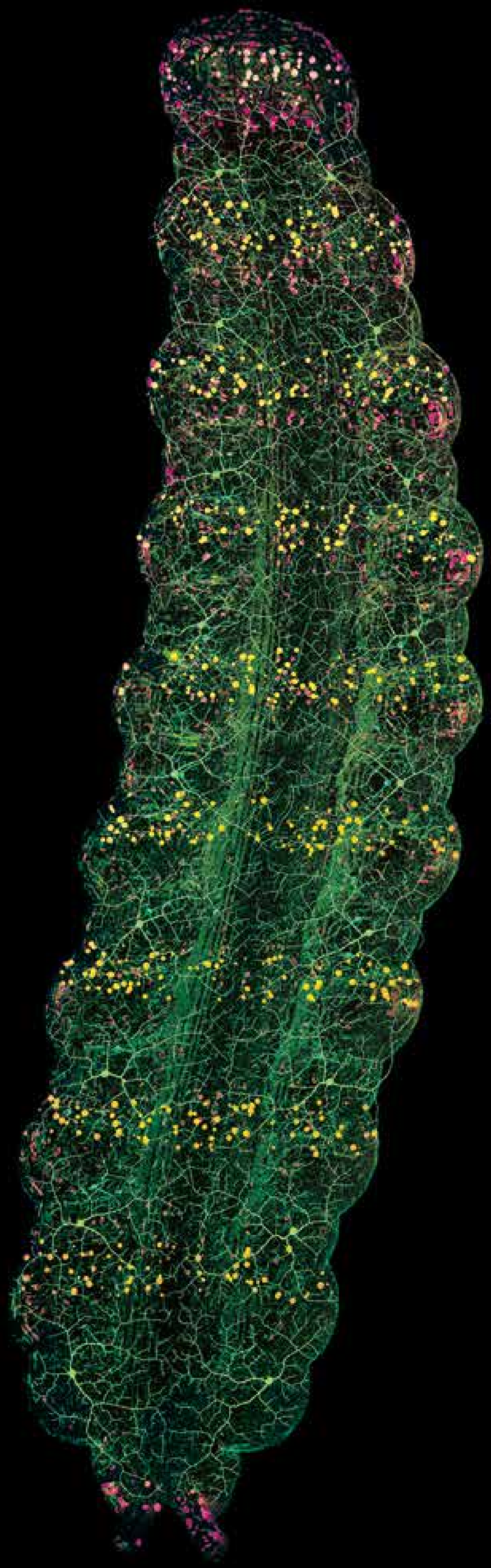


Morphological models reproduce the fine biological details of dendrites, illustrated in analogy to Cajal's drawings.
(© 2023 Hermann Cuntz)



Synthetic morphologies generated by a computer model to reproduce the dendrites of cortical pyramidal neurons.
(© 2023 Hermann Cuntz)

CUNTZ LAB



Maturation of model Class IV da dendrites in the fly larva.
(© 2023 Hermann Cuntz)

In Cajal's footprints **Recent advances in neuroscience have led to innovative techniques for dissecting neural circuits and constructing connectomes. Inspired by Santiago Ramón y Cajal's century-old idea of deciphering brain blueprints through neuron morphology, our research addresses this challenge using modern computational techniques.**

Despite the increasing prominence of neural networks in fields like machine learning and artificial intelligence, our understanding of their biological counterparts remains poor. Specific connectivity rules, developmental processes, and genetic underpinnings are poorly characterised, despite their critical relevance to brain function. Leveraging -omics techniques such as connectomics and transcriptomics, extensive datasets of network structure are made available but these *big data* are hard to interpret. Our models, elucidating the selforganisation of connectivity and structure, demonstrate predictive power for such complex data, potentially aiding in the discovery of their molecular foundations. These models also constitute a vital cornerstone for advancing neuromorphic computing approaches.

In the course of the last three years we have perfected the tools for morphological modelling and expanded them to include the developmental dynamics. In addition, we have explored the structure-function relationship using our models leading to a number of surprising findings.

> *Computer modelling* helps us dissect the precisely timed growth programs that lead to different dendrite types.

1 Optimal circuits

Watching a circuit as it forms

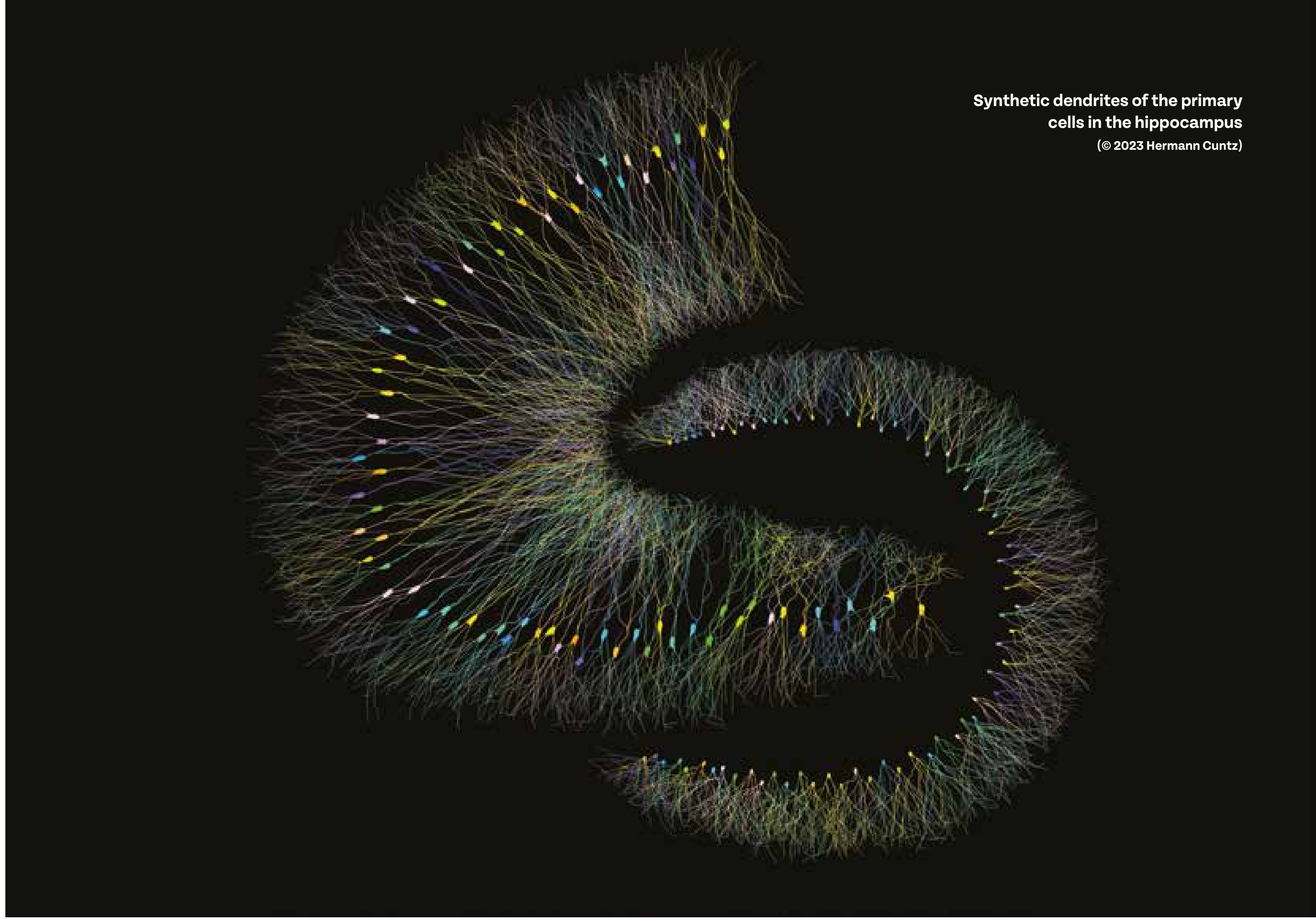
How does biology implement neural wiring? We reconstruct a neuron's path during development, its integration into an existing circuitry and how it adapts to an altered circuitry.

→ Baltruschat L, Tavosanis G, Cuntz H **A developmental stretch-and-fill process that optimises dendritic space filling.** *bioRxiv*.)

→ Stürner T, Ferreira Castro A, Philipps M, Cuntz H+, Tavosanis G+ (2022) **The branching code: a model of actin-driven dendrite arborisation.** *Cell Reports*, 39(4):110746.

→ Ferreira Castro A, Baltruschat L, Stürner T, Bahramid A, Jedlicka P, TavosanisG+, Cuntz H+ (2020) **Achieving functional neuronal dendrite structure through sequential stochastic growth and retraction.** *eLife*, 9:e60920.

To understand the biological underpinnings of neural circuit formation, we employ time-lapse anatomical data, high-resolution microscopy, and molecular techniques. This necessitates novel quantitative tools for consecutive reconstructions, for example by studying developing fly neurons in an extensive collaboration with Gaia Tavosanis. Our investigations have revealed that biological dendrite growth ensures optimal wiring and space filling throughout development, yielding significant functional implications. Diverse molecular programs appear to govern customised morphological shapes. In collaboration with Jonathon Howard, we now focus on elucidating the molecular biophysics of this process.



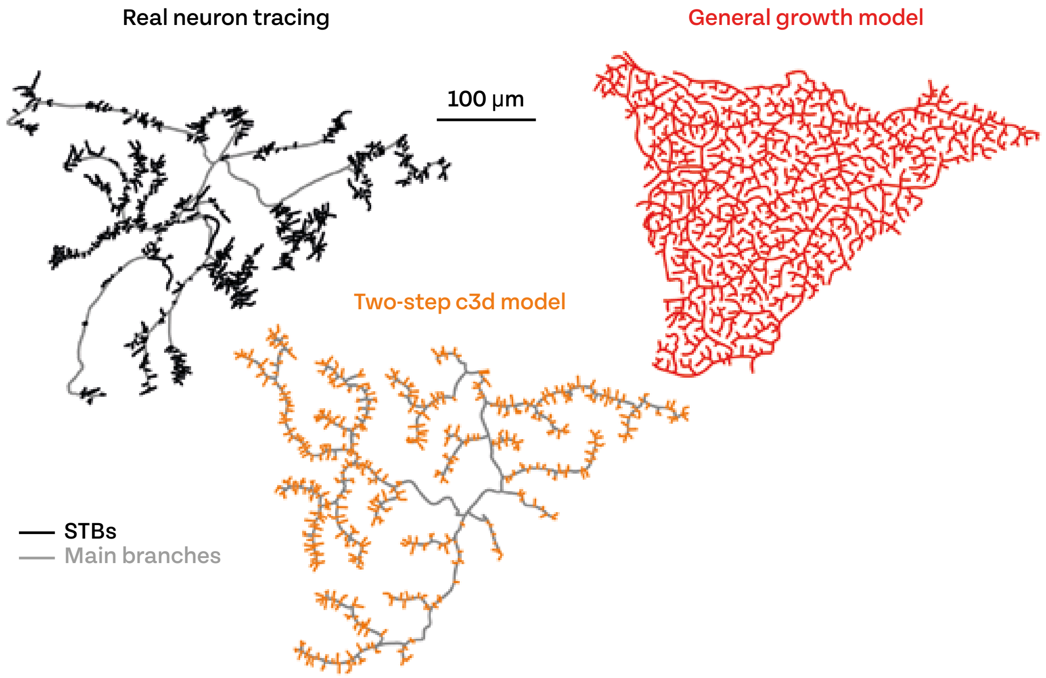


Figure 1: Morphological model of Class III da dendrites with their specialised small terminal branches. *Modified from Stürner et al., 2022.*

A branching code for neuronal dendrites

Dendrites are the beautifully branched input structures that shape a neuron's connectivity and the underlying computation on its inputs. We are working with computer models that describe the morphology from simple optimal wiring criteria: The dendrite collects inputs from other neurons in a way to minimise the required material and the conduction delays in the circuit. One question is whether this type of optimisation should also lead to space-filling trees and which developmental growth program might be responsible for this.

Recently, we introduced a regularity index *R*, based on average nearest neighbour distances to vary the input organisation in our models. Interestingly, the input regularity R_{Input}, which could be measured and modelled during dendritic maturation and in EM-based connectomes, could be read out in the regularity of a dendrite's branching point distribution but not in the value for termination points that were more randomly spread. Most importantly, R_{Input} in different cell types could be fundamentally different such as in fly dendritic arborisation (da) neurons or rather similar such as in fly lobula plate tangential cells.

In response to these insights and efforts, we formulated a novel theory of dendrite growth based on detailed developmental experimental data in Class IV da neurons in the fly. These dendrites optimise wiring and space filling. Synthetic dendrites generated from scratch using growth rules based on optimisation principles followed the dendritic development observed in these cells.

Having identified the Class III da neuron for its irregular space filling because of its specialised small terminal branches (STBs, Fig. 1, Black) we found that for these cells the general space filling growth model obtained in Class IV da neurons (Fig. 1, Red), did not perform well. Modelling Class III da neurons interestingly required a second step that confined STBs in a close range to the main branches (Fig. 1, Orange). A more regular space filling was partly recovered in actin regulatory protein mutants indicating the importance of these proteins in a secondary growth program step for STB formation. Overall, computer modelling helps us dissect the precisely timed growth programs that seem to lead to the diversity of dendritic trees that we observe in the brain.

CUNTZ LAB

2 Optimal computation

The big structure–function question

What are the consequences of single neuron morphology on neural computation? Using our morphological models we explore the consequences of wiring rules onto cell types and neural function.

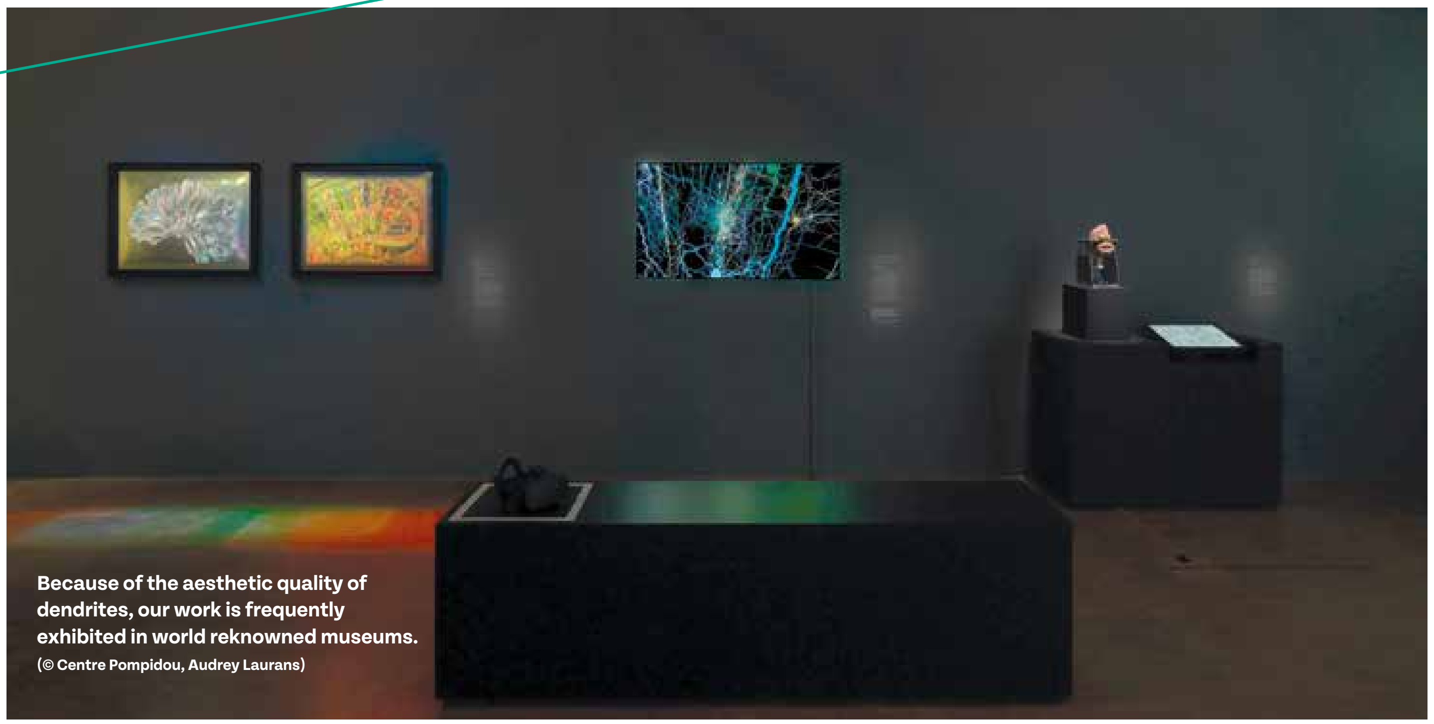
Our research employs morphological models to establish scaling properties of neuronal morphology and electrophysiology. Remarkably, neural electrophysiology proves robust to morphological changes driven by connectivity requirements. We further explore passive measures, including synaptic integration, integration time constants, dendritic filtering, and synaptic plasticity in compartmental models.

→ Cuntz H, Bird AD, Mittag M, Beining M, Schneider M, Mediavilla L, Hoffmann FZ, Deller T+, Jedlicka P+ (2021) **A general principle of dendritic constancy – a theory of neuronal size and shape-invariant excitability.** *Neuron*, 109(22):3647-3662.

→ Schneider M, Bird AD, Gidon A, Triesch J, Jedlicka P+, Cuntz H+. (2023) **Biological complexity facilitates multi-objective tuning of cellular parameter space.** *PLoS Computational Biology*, 19(7):e1011212.

→ Bird AD, Jedlicka P, Cuntz H. (2021) **Dendritic normalisation improves learning in sparsely connected artificial neural networks.** *PLoS Computational Biology*, 17(8):e1009202.

Watch this beautiful *visualisation of classical music by pianist Jimin Oh-Havenith* with our dendrites.


Because of the aesthetic quality of dendrites, our work is frequently exhibited in world reknowned museums.
(© Centre Pompidou, Audrey Laurans)

Dendritic constancy/normalisation

In the 1960s, Wilfrid Rall successfully applied equations from cable theory to neurons. It meant that he could calculate the propagation of currents in dendritic trees, the input structures of neurons. Until then, the contribution of dendrites to neuronal function had been largely ignored. But Rall could show that electrical signals from individual inputs across the dendrites attenuated dramatically and could interact in sophisticated ways – a turning point for our understanding of neural computation. We explored a feature of cable theory that seems to generalise across diverse dendritic trees: instead of following the impact of single inputs, we considered synaptic activity when it distributes across the whole or parts of the dendritic tree. Interestingly, the cable then appears to collapse to a single point, making the neuron's responses independent of the dendrite's shape or size. This means that the input-output function of neurons may conveniently not change during development or in the context of neurological diseases when dendrites undergo massive structural changes.

So in a way, neurons are more equal than one may think. Importantly, however, dendritic constancy does not diminish the importance of the large palette of synaptic learning rules and local computations in dendrites that make neurons unique and are sure to keep neuroscientists on their toes for times to come. Nevertheless, we believe that seeing how dendrites can behave equally across scales will contribute to a better understanding of general principles in neuronal function. Intriguingly, in a recent follow-up study we have shown that the normalisation of synaptic input weights based on the dendritic constancy mechanism improves learning performance in artificial neuronal networks. Thus, dendritic constancy may be of interest not only for neuroscience but also for the machine learning community.


The user interface of our own software package, the TREES Toolbox, allows to reconstruct dendrites from microscopy image stacks but also to browse large collections of reconstructed or modelled morphologies.
(© 2023 Hermann Cuntz)

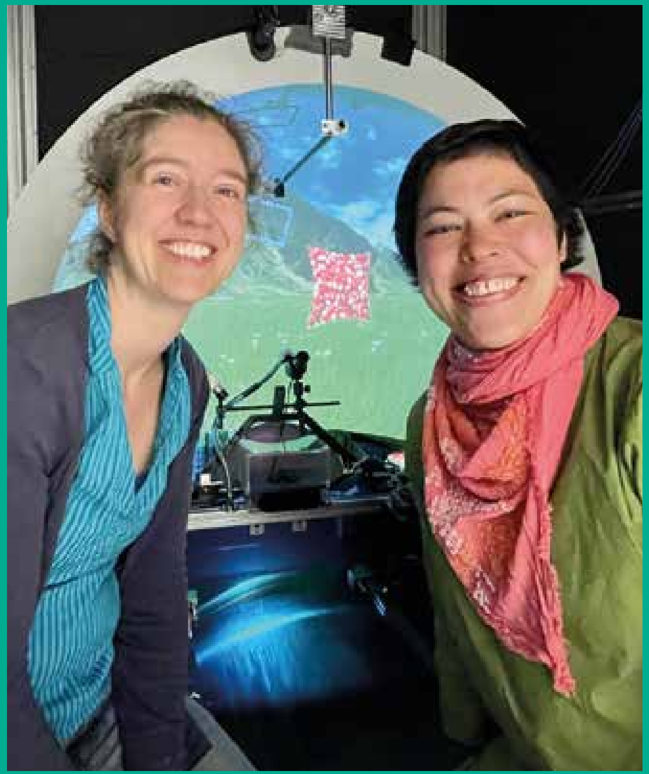
HAVENITH & SCHÖLVINCK LAB

THE ZERO NOISE BRAIN

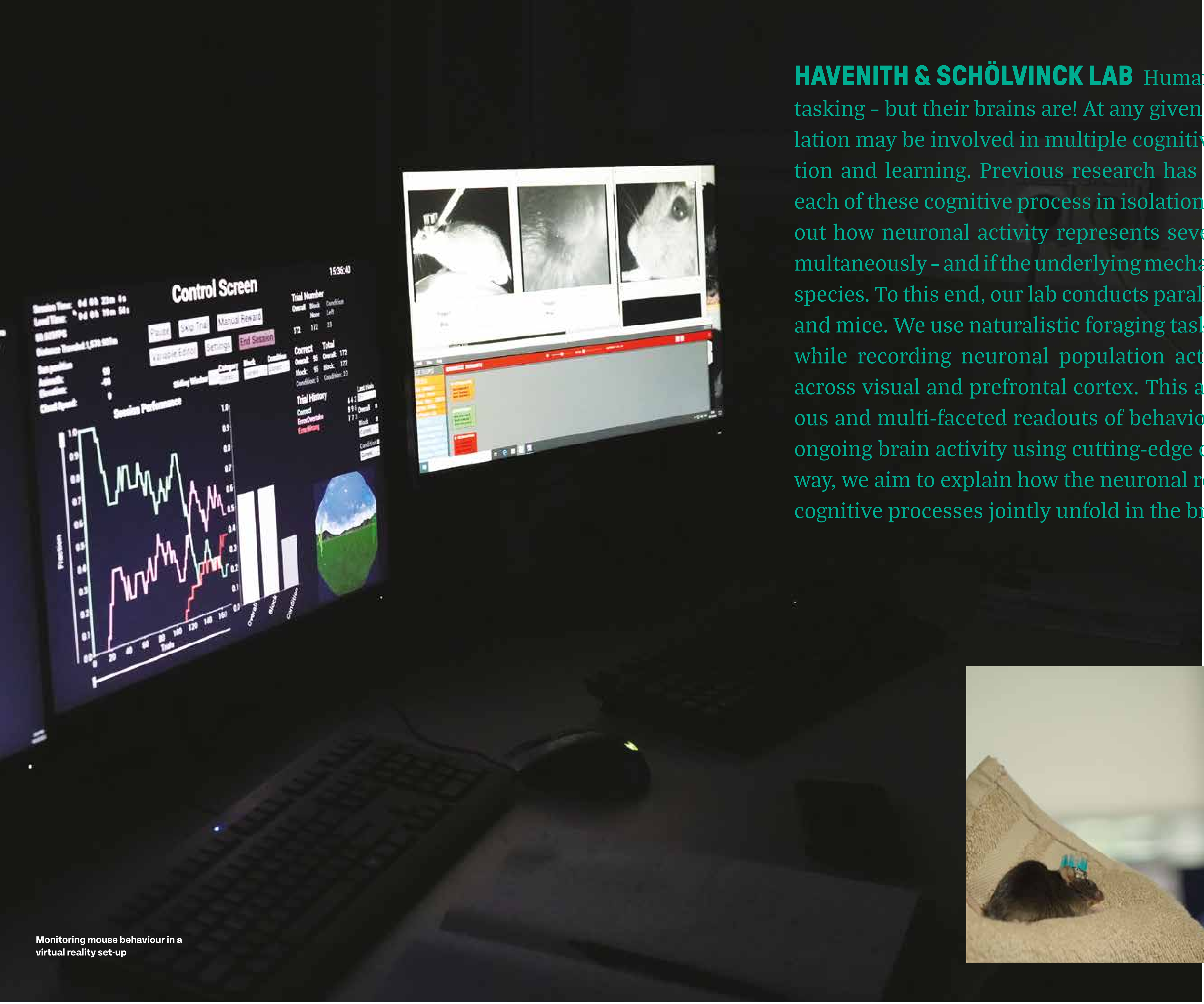
MOUSE // PI Martha Havenith / Postdoc Muad Abd El Hay / PhD Student Robert Taylor
MONKEY // PI Marieke Schölvinck / Postdoc Katharine Shapcott / PhD Student Pierre-Antoine Ferracci* / Computation Alejandro Tlaie Boria, Iuliia Glukhova / Technical Assistants Olga Arne, Marvin Weigand*, Tim Schröder* / MSc students Iuliia Glukhova, Regina Khamatnurova, Alisha Crider, Eva Petersen, Berkutay Mert

(as of December 2023)

*Alumni



"We probe superimposed cognitive processing during naturalistic foraging in mice, monkeys, and humans."



Monitoring mouse behaviour in a virtual reality set-up

HAVENITH & SCHÖLVINCK LAB Humans may not be good at multitasking – but their brains are! At any given moment, a neuronal population may be involved in multiple cognitive processes, such as attention and learning. Previous research has almost exclusively studied each of these cognitive process in isolation. In contrast, we aim to find out how neuronal activity represents several cognitive processes simultaneously – and if the underlying mechanisms are preserved across species. To this end, our lab conducts parallel experiments in monkeys and mice. We use naturalistic foraging tasks in a virtual environment, while recording neuronal population activity in homologous areas across visual and prefrontal cortex. This allows us to obtain continuous and multi-faceted readouts of behaviour, which we then relate to ongoing brain activity using cutting-edge computational tools. In this way, we aim to explain how the neuronal representations of universal cognitive processes jointly unfold in the brain in real time.

HAVENITH & SCHÖLVINCK LAB

Recording behaviour and neuronal activity from a mouse in a virtual reality environment

The Zero-Noise Lab was founded in March 2020 under the joint leadership of Marieke Schölvinck and Martha Havenith. Its work is based on the premise that under natural circumstances, the interaction between an organism and its environment is an incredibly dynamic process.

Neither sensory stimuli, nor internal perceptual and cognitive processes, nor behavioural responses, ever stand still. Despite this, most studies in systems neuroscience investigate one specific cognitive process in isolation, and average over large numbers of trials to filter out 'noise', i.e. ongoing and context-dependent dynamics.

While the practice of cross-trial averaging has revealed important aspects of brain function, we have recently shown that averages are at best somewhat, and in many experimental contexts, barely relevant for ongoing brain computations and behaviour. More generally, even though this reductionist approach is widely practiced in systems neuroscience, it excludes integral features of neuronal processing. This includes the inherent closed-loop nature of sensory experience and behaviour, as well as the fact that under natural circumstances, multiple cognitive processes (e.g. attention and learning) simultaneously shape neural activity, often in the same brain area, in order to respond flexibly to external challenges. We aim to find out how neuronal activity represents such cognitive processes simultaneously at any given moment. What's more, we investigate if the solutions to this fundamental challenge of brain computation are evolutionarily preserved, or diverge across species.

→ Tlaie A, Shapcott KA, Van der Plas T, Rowland J, Lees R, Keeling J, Packer A, Tiesinga P, Schölvinck ML, Havenith MN. **What does the mean mean? A simple test for neuroscience.** *Under review at PLoS Computational Biology.*

To study these questions, our lab conducts exactly mirrored experiments in two prominent model species of systems neuroscience: monkeys and mice - an approach that is to our knowledge unprecedented. Specifically, we use intuitive foraging tasks in a highly immersive virtual reality (VR) environment to examine naturalistic, visually guided behaviour in monkeys and mice. Simultaneously, we record the activity of large neuronal populations in multiple cortical areas along visual processing and decision making pathways that are preserved across mammalian species. This approach uniquely allows us to obtain multi-faceted moment-by-moment readouts of behaviour, which we then map onto different aspects of ongoing brain activity using cutting-edge computational tools.

To pursue this goal, we have developed a tightly interlinked lab structure, whereby lab members focus either on experiments in one species, or on cross-species computational analyses. While PhD projects generally zoom in on one cognitive process in order to keep the scope of the project manageable, these individual analyses are then subsumed in an overarching computational framework of superimposed cognitive processing across species, spearheaded by the three postdoctoral researchers of the lab. In the following sections, we first describe the general experimental set-up, followed by five sections on the interlinked research directions we are currently pursuing.

We use naturalistic foraging tasks in a virtual environment, while recording neuronal population activity in visual and prefrontal cortex.

Experimental Approach

To create an optimally immersive VR environment, we have built two large spherical domes with the animals placed in the centre, on the inside of which we project a highly naturalistic VR using a spherical mirror (Fig. 1A). The spherical dome extends to 25 degrees visual angle, creating an immersive experience for the animals by covering both their central and peripheral vision. Mice traverse the VR by running on a spherical treadmill suspended by air, whereas the monkeys move a trackball with their hands. As such, while input devices cannot be replicated exactly across species, both preserve the closed-loop nature of visual perception (movement = visual flow).

→ Schroeder T, Taylor R, Abd el Hay M, Franca ASC, Battaglia F, Tiesinga P, Schölvinck ML, Havenith MN. **A surgical protocol for safe, fast and recoverable chronic implants of silicone probes in mouse cortex.** In preparation.

To optimize the physical setup, we have created several new hardware designs, including customized bases for the spherical treadmill and trackball; a modular head fixation system for mice that is miniaturized, comfortable for the animals and compatible with electrophysiological implants; and a 3D-printable system for liquid reward. These designs have been open-sourced on the platform Zenodo and described in a methods paper that is currently in preparation for JoVE.

One central reason why superimposed cognitive processing has so far evaded study is that classical behavioural paradigms in neuroscience typically generate extremely simple readouts, such as correct/incorrect trial classifications and reaction times. Such limited behavioural metrics make it impossible to track the dynamics of several cognitive processes evolving in parallel. To overcome this obstacle, our analyses integrate an unprecedented range of behavioural markers. The trackball movement through the VR is being recorded with two computer mice and translated into movement trajectories within the VR. From the turns of direction in these trajectories, reaction time is calculated; this is the thesis work of MSc student Berkutay Mert. The eye data for the monkeys and humans are generated by an iRec camera and include the [x,y] position as well as pupil size, for mice they are extracted from video footage using DeepLabCut. Lastly, we use several high-resolution cameras filming the animals' faces, eyes, paws and whole body.

→ Shapcott KA, Weigand M, Glukhova I, Havenith MN, Schölvinck ML. **DomeVR: Immersive virtual reality for primates and rodents.** Under review in Plos One.

While simplified VR environments are used more frequently in neuroscience, VR environments featuring truly naturalistic visual scenes are far less common. To be able to flexibly create elaborate visual scenes featuring naturalistic objects, we developed a new toolbox called DomeVR, based on the Unreal gaming engine. This toolbox was specifically developed for this project by one of our postdoc alumni, Marvin Weigand. DomeVR combines a logging and synchronization system for ultra-precise timing control, an interactive GUI, an immersive dome projection, and support for a broad range of behavioural interfaces, allowing it to be applied across different species. It provides our lab members with a simple, flexible and intuitive way of designing new behavioural paradigms, as well as a GUI that grants the experimenter full control over relevant task parameters at all times (Fig. 1B). The DomeVR toolbox has been made available to the scientific community on BioRXiv and Github, and is currently under review in PLoS One.

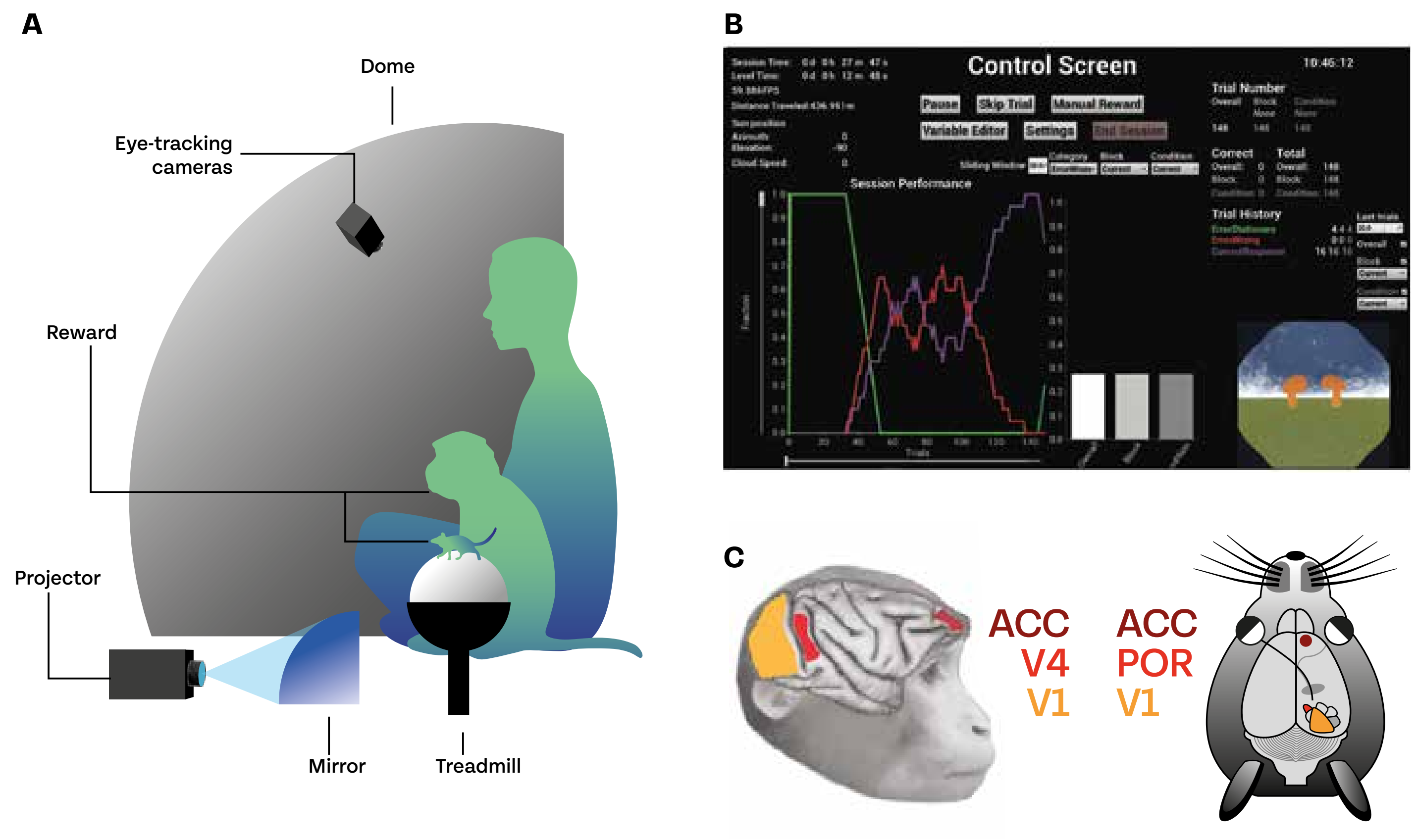
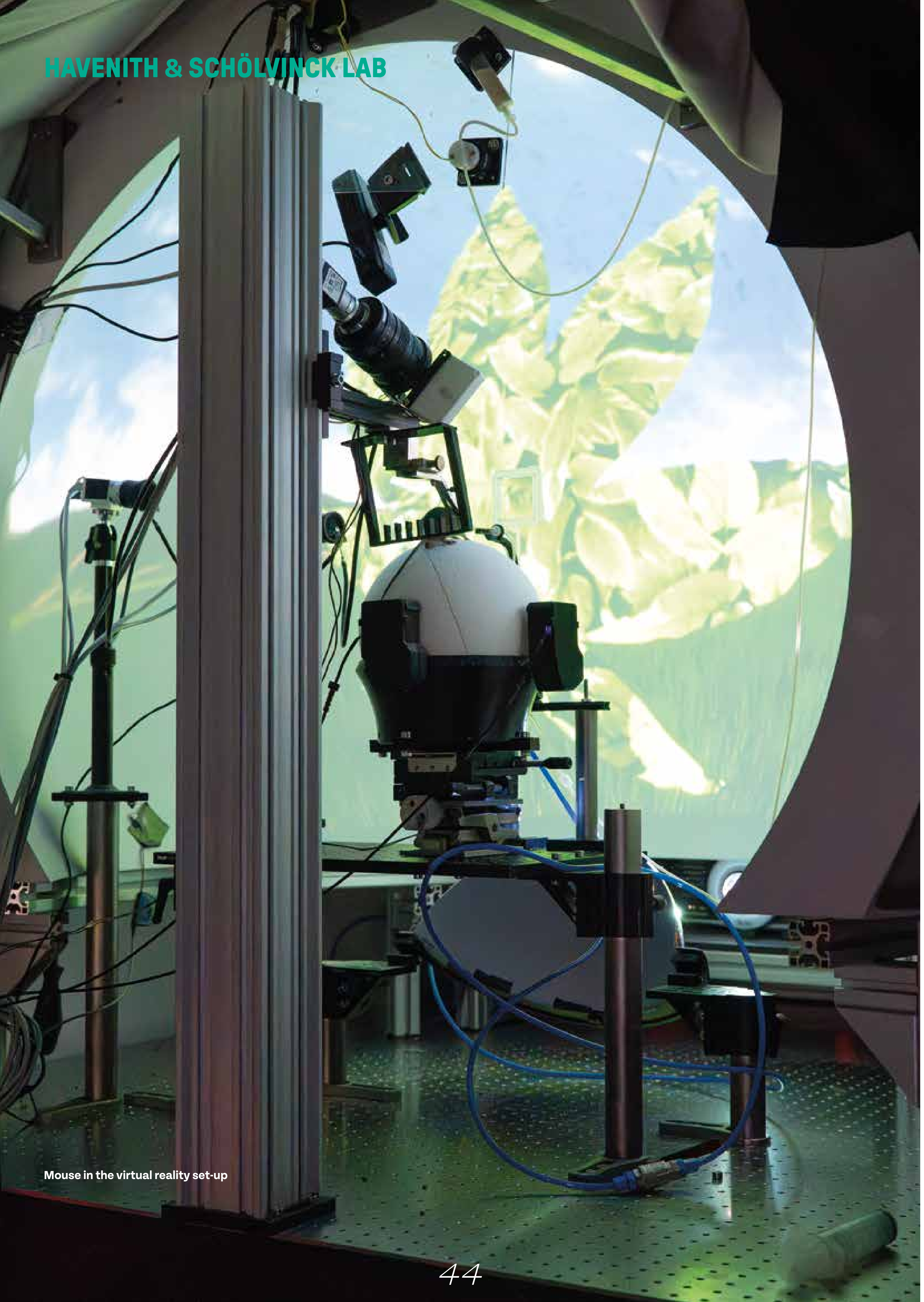


Figure 1. Experimental set-up. (A) VR dome with mice, monkeys, and humans in centre. **(B)** Control screen of DomeVR, toolbox developed for our VR. **(C)** Targeted homologous areas for neuronal recordings.

To compare the neuronal dynamics of cognitive processing across species as directly as possible, we are simultaneously recording spiking activity and local field potentials from three cortical areas that have been shown to be homologous across mammalian species (Fig. 1C). Specifically, we record from primary visual cortex (V1, processing basic visual features); higher visual cortex (POR in mice and V4 in monkeys, processing higher-order visual features as well as their behavioural relevance); and anterior cingulate cortex (ACC, returning behavioural feedback to visual areas). To be able to characterize neuronal interactions across different time scales including fast perceptual decisions at the millisecond level, attention fluctuations at the scale of minutes and learning processes over hours and days, we use high-density, chronically implanted electrodes in both species.

For monkeys, we implant several Floating Micro-electrode Arrays (FMAs), comprising 36 rigid platinum/iridium electrodes of individually customizable length, to pick up individual action potentials as well as local field potentials. We already implanted six of these arrays in our first monkey Cosmos, and are about to implant six arrays in our second monkey Karl. The array connectors are housed in custom-designed casings implanted on the other hemisphere, which have been of great interest to other groups working with FMA arrays. For mice, we rely on multiple 64-channel silicone probes (Cambridge Neurotech), which are chronically implanted within a wearable Faraday cage with in-built head-fixation, using flexible electrode drives to be able to adjust recording location (3Dneuro).

Neuronal data are being analysed using SyNCoPy, which is a Python-based package developed at ESI for analysing electrophysiological data. We extract a wide range of continuous parameters of neuronal population activity, including those previously associated individually with cognitive processes such as sensory decision making, attention or learning: LFP response amplitude, LFP coherence, LFP spectral power, spike-LFP phase locking, population firing rates and relative spike timing. These neuronal features then form the basis



Mouse in the virtual reality set-up

for modelling the neuronal correlates of superimposed cognition at the microcircuit level.

With this setup, we create foraging-based visual discrimination tasks that are applicable across species. Our approach aims to mimic central features of naturalistic visual processing, yet ensure precise experimental control. To do so, we teach animals to forage for visual items associated with varying rewards in a naturalistic VR environment. Specifically, monkeys and mice are given the exact same task: approaching differently shaped leaves in a natural environment that yield different amounts of reward (soy milk or juice) once they have been reached (Fig. 2A). This allows us to preserve three fundamental properties of visual processing in the wild: 1) visual scenes are generally cluttered, i.e. relevant objects are surrounded by a multitude of other visual signals, 2) perception and action operate in a closed loop, such that sensory stimulation is constantly modulated by the animal's own behaviour, and 3) associations between stimuli and behavioural outcomes vary – the same location may be a food source or not depending on context, and updating such associations flexibly is a prerequisite for survival. By featuring a rich set of stimuli and behavioural choices, this task inherently creates a context in which different cognitive processes can dynamically overlap and intersect. For instance, by requiring animals to continuously decide between naturalistic stimuli of different perceptual difficulties, while the reward associations of these stimuli shift dynamically over time, we are engaging several processes: visual detection of stimulus differences, sustained attention to process stimuli upon their appearance, memorization of a learned reward association, as well as flexible adaptation to changes in that association.

This addresses one of the core ambitions of the lab: to study cognitive processes not in isolation, but in natural, continuous interaction with each other. Finally, the task also enables us to tap into innate foraging instincts that are preserved across species, requiring minimal training and allowing us to observe the brain doing what it was designed to do.

Research topic 1: natural perception

Are humans better at discriminating natural objects than artificial gratings commonly used in visual neuroscience? Psychophysical experiments in our VR setting suggest they do: they discriminate fine differences between two fish better and faster than between two gratings.

A prerequisite for studying naturalistic visual processing is understanding how the visual system processes natural visual stimuli. We therefore developed a psychophysics experiment investigating the discriminability between naturalistic looking objects. This project was the thesis work of MSc student Alisha Crider. Classical psychophysics experiments typically include black and white grating stimuli on a solid, gray background meant to maximize contrast and facilitate discrimination. However, the human visual system evolved to differentiate between natural shapes, colors, and textures, like those common in flora and fauna. Our experiments therefore investigated discriminability at varying levels of 'naturalness'. We designed three conditions: a classical grayscale grating, a grating consisting of a texture of natural stripes, and a completely natural fish morphing into another fish. All three conditions were presented on two backgrounds, a uniform grey background and a realistic mountainous landscape. Healthy human participants completed a two-alternative forced choice (2AFC) discrimination task, during which they chose between two simultaneously presented visual objects of varying degrees of similarity in each trial.

Results showed that the participants could distinguish better and faster between the morphed natural fish, than the grayscale or the natural gratings. The two different backgrounds had no quantifiable effect on performance. These results are currently being written up for publication.

→ Crider A, Shapcott KA, Glukhova I, Havenith MN, Schölvinck ML. **Discriminability of natural stimuli.** In preparation.

HAVENITH & SCHÖLVINCK LAB

Research topic 2: spontaneous attention

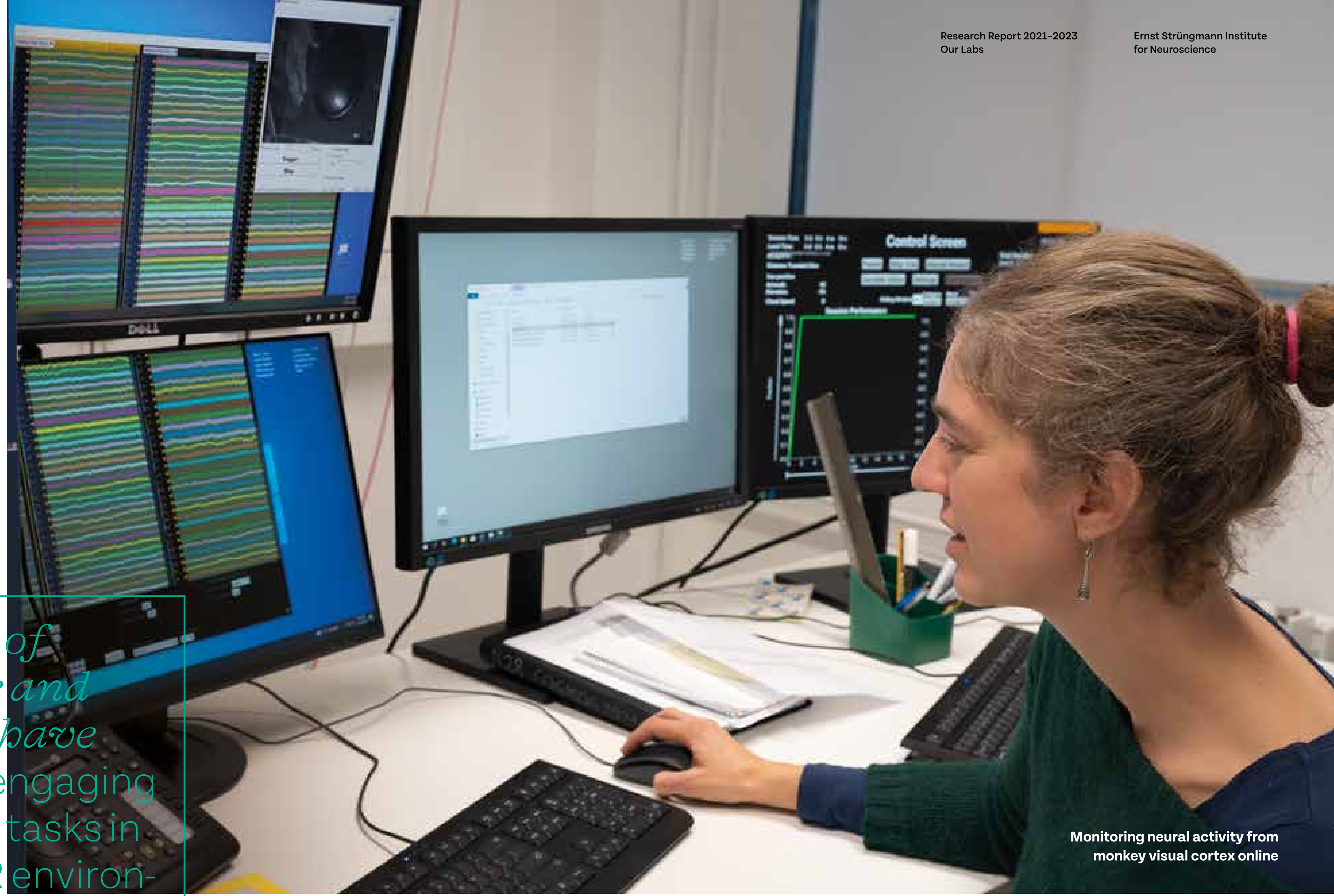
So far, attention has mostly been examined in artificial, over-trained task paradigms, which diverge widely between species. Through our natural VR task and neural recordings in homologous areas, we are uniquely able to compare the behavioural and neural dynamics of attention directly across species.

So far, neuroscience has not yet been able to identify neural markers that reliably predict attentional states moment by moment, nor to point to reliable solutions to attentional deficits. This may be due to previous studies ignoring two important features of attention "in real life": it is an innate ability, and it is highly conserved across species. In everyday life, the orientation of attention is usually spontaneous, whereas laboratory tests of attention require extensive training and instruction, lasting for weeks and months to years. The result is that the animals become "experts" – giving highly accurate automated responses that require little conscious decision-making. This process is called overtraining and not only leads to behaviour that arguably does not reflect natural attention in a dynamic environment – it also dramatically alters the neural connections involved in this behaviour.

Attention in the wild (e.g. to monitor predators or food sources) follows similar principles across species. In contrast, in the laboratory, attention is measured completely differently in different species, making it impossible to compare results. For example, the best-known attention test for rodents is the simple five-choice row reaction time task (5CSRTT). In this test, animals must monitor five potential stimulus positions for stimulus appearance, and attention is estimated by the proportion of stimuli missed. In comparison, sustained attention experiments in primates typically feature extremely rigorous and highly controlled experimental designs, including eye fixation, head fixation and short reaction time windows.

To compare how attention fluctuates spontaneously in different species, we have collected behavioural data from mice, monkeys and humans performing identical versions of the core foraging task. With this approach, we aim to reveal mechanisms for the activation of innate, "effortless" attention and highlight similarities and differences in attentional mechanisms in three species that perform exactly the same naturalistic attention task. So far, we have found that when speed and accuracy of performance are both taken into account, the temporal dynamics of attention are surprisingly similar across all three species (Fig. 2B). We also find that there are distinct behavioural 'attractor states' along the performance space of speed and accuracy that all three species frequent in similar ways. This is particularly unexpected since mice have so far generally been thought to have shorter attention spans and overall poorer attentive performance than primates. This potentially indicates that such findings may be more due to the nature of the attention tasks given to rodents, rather than genuine differences in attentional processing. This work is spearheaded by our PhD student Iuliia Glukhova.

Our approach of allowing mice and monkeys to behave naturally, by engaging them in intuitive tasks in an immersive VR environment, and analysing the neurobehavioural responses moment by moment, aims to study cognitive processes as they interact in real life.



Monitoring neural activity from monkey visual cortex online

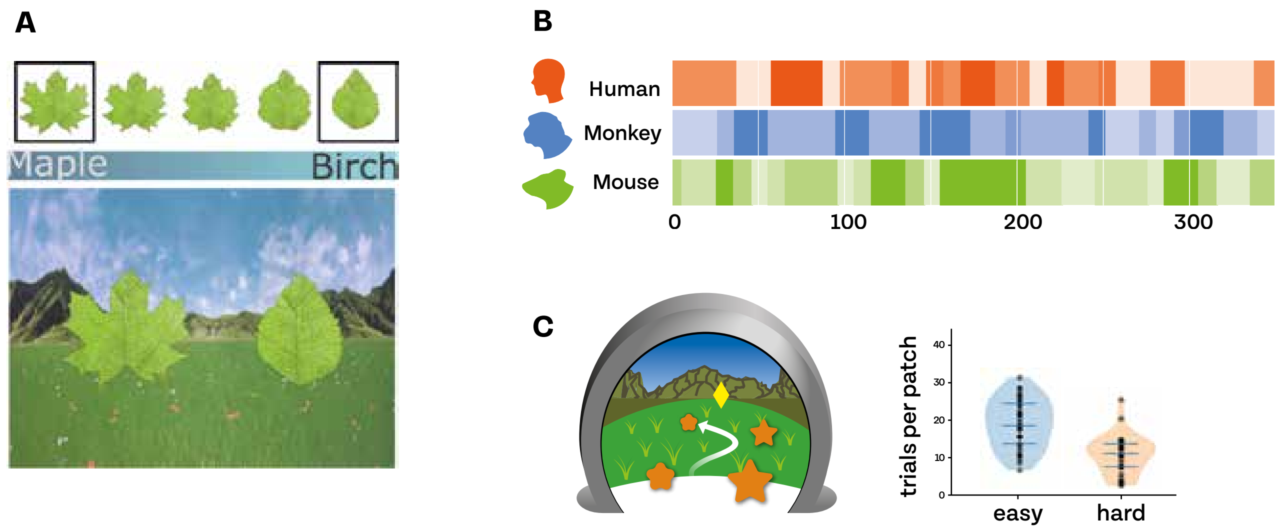


Figure 2. Task and experimental data. (A) Morphing stimuli for perceptual decision task. **(B)** Similar attentional fluctuations in humans, monkeys, and mice. **(C)** Foraging paradigm (left) and behavioural data (right).

HAVENITH & SCHÖLVINCK LAB


Monkey engaged in a naturalistic task in the virtual reality

To this end, we combine all three types of behavioural variables captured by our VR setup: videos of the face and hands (monkeys) or full body (mice), trackball movement, and eye data.

Research topic 3: flexible learning

In the wild, animals quickly learn from their environment; in the lab, flexible rule learning can be a nigh impossible process. By employing rule updating schemes directly borrowed from natural foraging situations, we are able to elicit flexible learning of rule shifts in humans, monkeys and mice.

To study flexible learning across species, we employ a variation on the core VR task described above, in which a central comparison stimulus is rewarded compared to Stimulus A, but not rewarded compared to Stimulus B. As such, animals have to learn to evaluate the same stimulus differently depending on its stimulus context. In addition, the visual similarity between stimuli is varied gradually via stimulus morphing (Fig. 2A). This approach has allowed us to establish one-trial rule switching in a visual task in mice. We are currently analyzing the neuronal and behavioural signatures that predict successful and unsuccessful rule switches on a trial-by-trial basis. Specifically, we have found that systematic differences in saccading patterns before and after stimulus appearance predict switching success. This is especially exciting finding since mice were long thought to not show deliberate, task-related saccades. The work characterizing the neurobehavioural dynamics of flexible learning is led by our PhD student Robert Taylor.

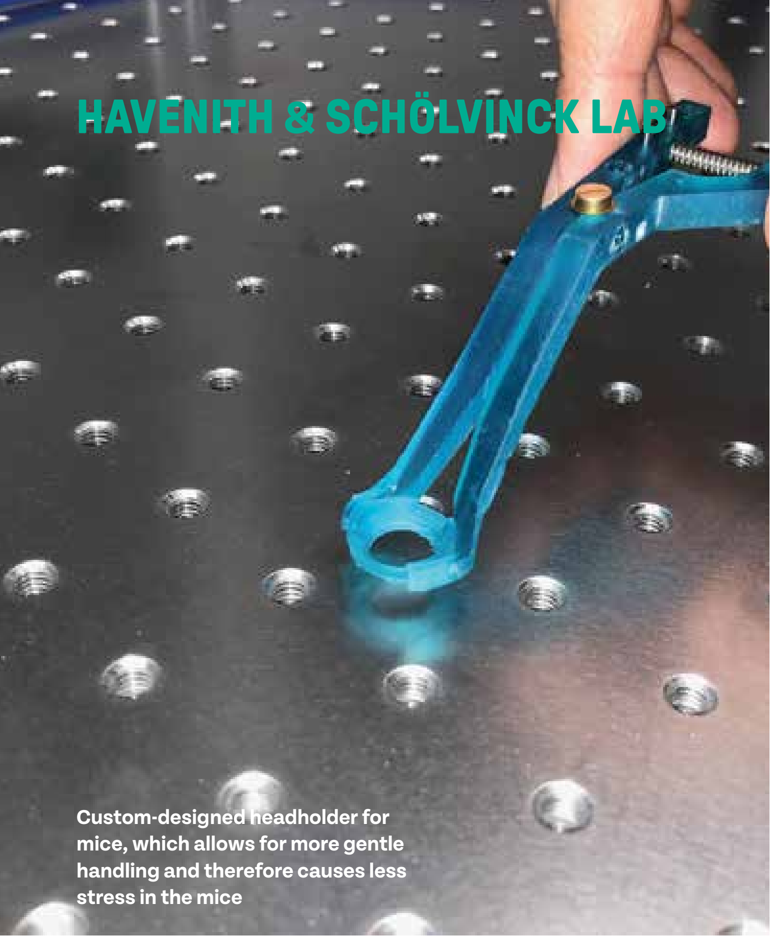
As an extension of this basic paradigm, we probe the effect of psychedelic compounds on cognitive flexibility in mice. Psychedelic substances such as psilocybin have proven to be very effective in treating mental disorders such as depression, anxiety and post-traumatic stress disorder (PTSD) in humans. They are thought to act through two main mechanisms: acute neuropsychological 'reset' during exposure, and sustained rewiring of neuronal connectivity. Our project aims to provide a careful characterization of the neuronal and behavioural signatures of psychedelic experience by tracking and analyzing the behaviour and neuronal activity of freely moving mice under the influence of psilocybin, and then linking these acute neurobehavioural motifs to subsequent changes of cognitive flexibility in our VR foraging tasks. This project is led by our postdoc Muad Abd El Hay.

Research topic 4: internally driven decision-making

In the wild, foraging for food is subject to varying levels of success. We mimic this situation in our VR environment to study the neural and behavioural dynamics of foraging in monkeys.

Second, we use the core task to study the behavioural dynamics of foraging. Foraging is commonly studied in laboratory settings as the 'patch-leaving problem', which simulates foraging in an environment with food items distributed in sparse patches. As foraging within a patch continues, local resources diminish, and the time required to find a new food item increases, reducing the rate of food intake. As a result, the benefits of diminishing resources must be balanced against the cost of searching for a new patch. This paradigm has been abstracted by many neuroscience experiments as a task where on each trial, the subject can choose to perform an immediate task that

HAVENITH & SCHÖLVINCK LAB



Custom-designed headholder for mice, which allows for more gentle handling and therefore causes less stress in the mice

diminishes in reward, or perform a more costly task that restores reward to its original value.

By featuring self-motion translated by a trackball, our VR environment lends itself to a foraging task that highly resembles a real-life setting, since moving the trackball to cross large distances in the VR also requires a substantial energy expenditure. We have therefore implemented a naturalistic VR patch-leaving task, where subjects need to choose between two objects close by, only one of which is rewarded (Fig. 2C). Rewards can either be high or low, with the probability of a high reward decreasing with every target choice. Choices between adjacent objects thus constitute a 'patch'; the participant can decide at any time to move to a new patch by approaching a third object located in the distance. Reaching this third object does not by itself yield any reward, but instead restores the reward probabilities for the two close-by objects. This project was carried out mostly by a PhD student on the monkey side, Pierre-Antoine Ferracci, and has now been taken over by another PhD student in the lab, Shivangi Patel.

Research topic 5: superimposed cognition

Identifying superimposed cognitive processes forms the core aim of our work. To this end, we harness deep-learning algorithms to extract hidden states from behavioural read-outs, and then relate the overlapping cognitive processes to underlying neural activity from visual and prefrontal cortex.

Our lab's drive to characterize superimposed cognitive processes is implemented via two complementary pathways. First, we are currently developing a large neurobehavioural model in which behavioural variables like attentional state, rule prediction and spontaneous decision shifting defined in the research topics 1-4 (see above) are linked to a large variety of neuronal variables. The framework for this analysis has been established by our computational postdoc Alejandro Tlaie-Boria, and will be further developed in collaboration with Paul Tiesinga's lab from the Donders Institute for Brain, Cognition and Behaviour (NL). This model will establish which behavioural processes are most closely related with which aspects of neuronal activity. The approach is clearly hypothesis-driven, since behavioural variables are defined based on widely accepted concepts like attention. As such, our findings can be directly compared to the extensive existing literature on these concepts. However, basing our definitions of cognitive processes on human concepts of cognition will also limit our analysis and interpretations.

Therefore, our second approach infers superimposed cognitive processes from behaviour in an agnostic way. To this end, we combine all three types of behavioural variables captured by our VR setup: videos of the face and hands (monkeys) or full body (mice), trackball movement, and eye data. Video recordings are analysed using Deep LabCut, an open-source toolbox for markerless pose estimation of behaving animals. To extract ongoing cognitive states agnostically from these variables, we use a combination of hidden state models and sensorimotor models, called a Markov-Switching Linear Regression (MSLR) model, to infer underlying cognitive dynamics from behaviour (Fig 3). Briefly, for both mice and monkeys, their facial features can be well captured by a surprisingly similar and small number of states. These states are predictive of reaction times and correlated with certain task outcomes (hit, wrong, miss), indicating that they reflect genuine performance states. Analysis of the most predictive facial features suggests that during incorrect trials, animals may be focused on the 'wrong' sensory input – giving more weight e.g. to olfactory or auditory input than visual signals. The paper describing these findings is currently in the final stages of preparation.

As this model has a time resolution of one trial, we are now developing a second model to make moment-by-moment predictions of the trajectory that monkeys and mice take through the virtual world. This project is headed by our computational postdoc Alejandro Tlaie-Boria, and developed in collaboration with Jonathan Pillow's lab at Princeton University.

→ Tlaie A, Shapcott KA, Taylor R, Abd El Hay M, Glukhova I, Ferracci PA, Mert B, Pillow JW, Havenith MN, Schölvinck ML. **Thoughtful faces: inferring internal states across species using facial features.** In preparation.

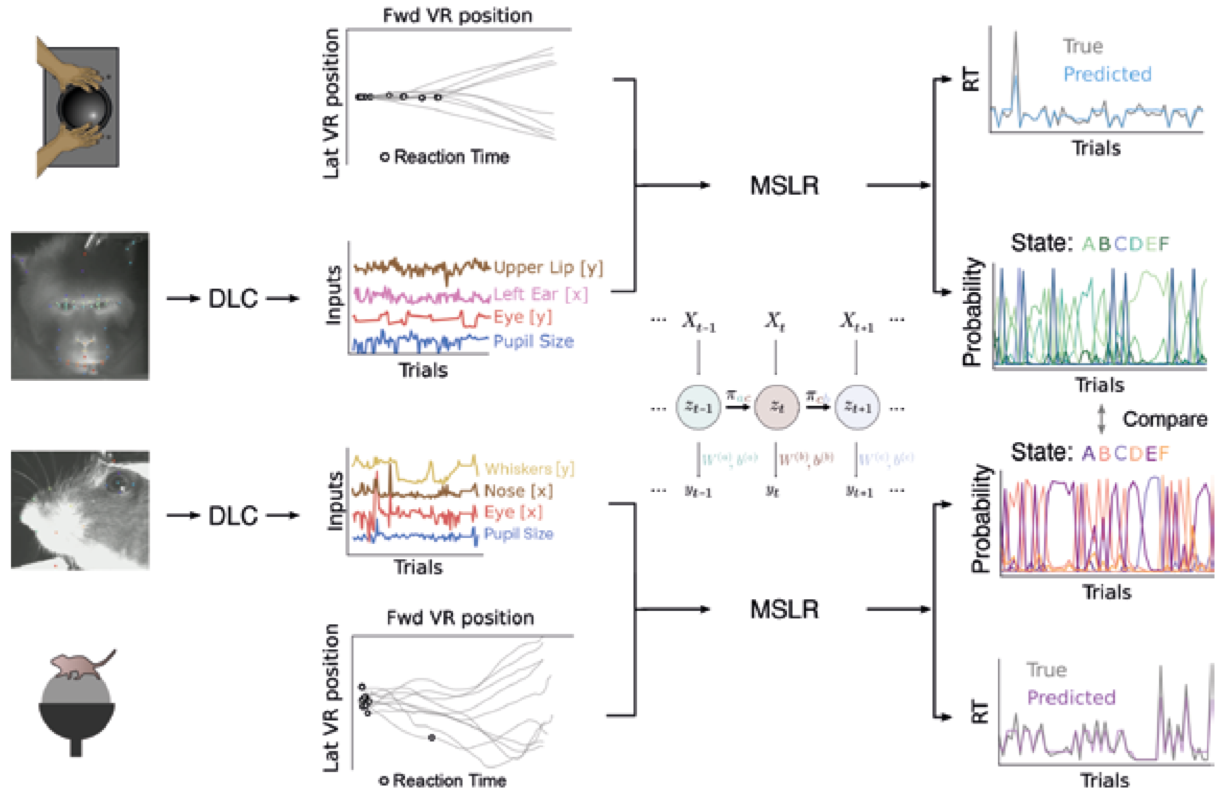


Figure 3. Extracting cognitive states. The videos and trackball movement (left) provide a large amount of behavioural variables (middle), which are combined into several cognitive states using an MSLR model (right).

Conclusions

Typical neuroscience experiments study the brain's cognitive processes in isolation, by recording neuronal activity from animals that are severely restricted in their sensory input and behavioural repertoire. Our approach of allowing mice and monkeys to behave naturally, by engaging them in intuitive tasks in an immersive VR environment, and analysing the neurobehavioural responses moment by moment, aims to study cognitive processes as they interact in real life. This work is far from completed – yet significant milestones, such as establishing the importance of single-trial analysis in capturing the information content of neuronal dynamics; acquiring high-quality and directly comparable behavioural and neural data from both species; and extracting internal states from behaviour in a data-driven way, have been reached. Others, like the dynamic linking of neuronal dynamics to superimposed cognitive processes, are well on their way. We are excited to continue our endeavour in the coming years!

LAURENS LAB

SYSTEMS NEUROSCIENCE OF NAVIGATION AND MOTION

Principal Investigator Jean Laurens / Post-doc Francesca Lanzarini, Nada El Mahmoudi / Graduate Student Deepak Surendran, Farzad Zaie Nezhad / Lab Manager Colleen Illing

(as of December 2023)

"Our lab pioneers 'natural neuroscience', where experiments are integrated in the animals' daily routines. We establish a novel ethical paradigm for neuroscience studies in non-human primates that acknowledges and respects the animals aiding our discoveries."

LAURENS LAB Imagine a squirrel in a tree, leaping from branch to branch with ease and precision. Its brain coordinates posture, balance, motor and navigation skills to pilot it through the treetop. Humans may not seem as agile, but in fact we have many similar abilities: we explore and navigate through complex environments; hike on uneven or slippery terrain, and with some training we can race down slopes on mountain bikes or alpine skis.

How does the brain control the body? And how do diseases, age or brain injuries affect these abilities? This is what my research group is investigating. We combine the recording of neuronal activity, measurements of motor and navigation behaviors and mathematical modeling. Our research is based on experiments on rats and monkeys. Acknowledging our ethical responsibility, we develop new techniques for the planning and ethical conduct of experiments on animals, for improving the 3Rs (Reduce, Replace, Refine), and promoting a culture of care and respect for our animals.

A camera for analysing the motion of the animals blends into a surrounding of plants and posters.

Innovating neuroscience: natural conditions in the lab and ethical animal research

Over the past two decades, groundbreaking technologies and concepts have ushered in a new era for experimental brain research on animals. Modern brain implants now contain hundreds of electrodes to record large populations of neurons. Miniature electronics enable wireless recordings in freely moving animals. The widespread application of 3Rs and of a culture of care for the animals has made Europe a champion of ethical, respectful animal research.

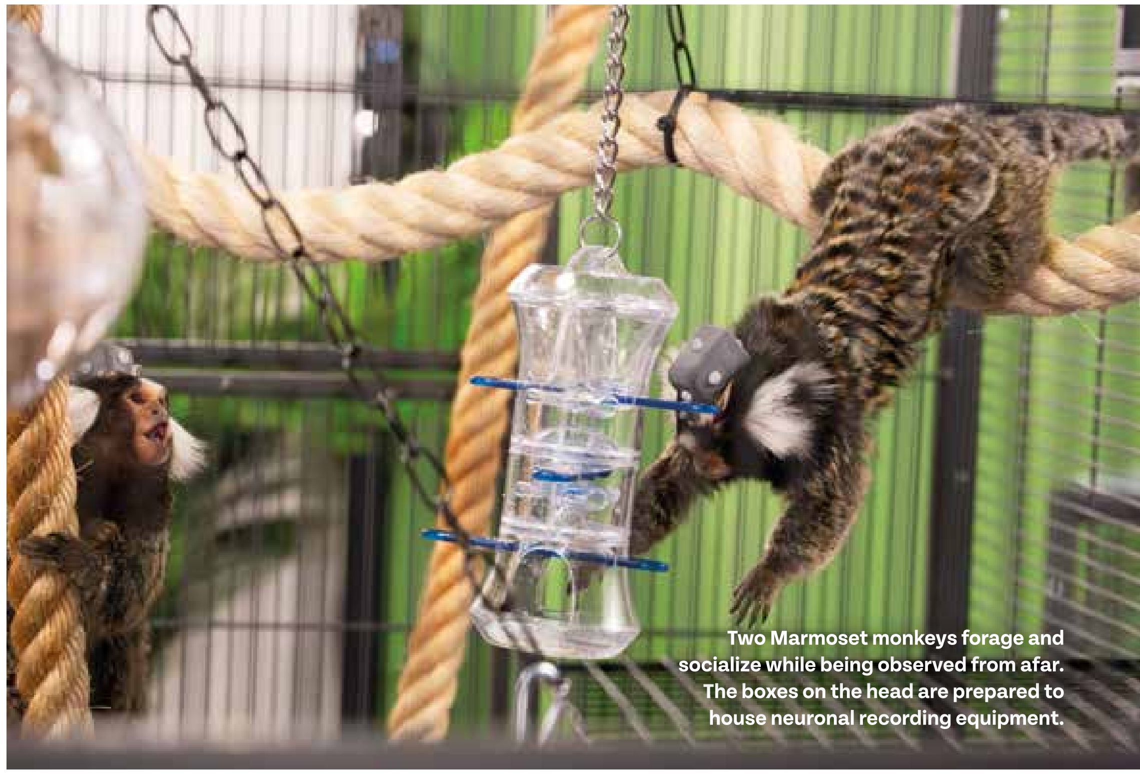
Building on these advancements, our lab is pioneering innovative experimental paradigms. Guided by the principle of "natural neuroscience," we strive for integrating our lab's experiments into the animals' daily routines. We've designed our lab to mimic natural environments, blending experimental tasks of spatial navigation and memory with the animals' innate foraging activities. To ensure the well-being of our marmosets, we are also constantly improving our procedures and equipment - this includes training protocols, transport cages, ergonomic primate chairs and, above all, promoting a culture of positive interaction between laboratory staff and animals.

We have already developed and published innovative statistical methods for the design and analysis of experiments on non-human primates. These ensure that the results are meaningful and robust, which in turn ensures that the maximum scientific benefit is achieved with each experiment - in line with the ethical requirement of reduction. Recognizing the ethical concerns about animal research, we place great importance on transparent communication with the public. We believe that openness fosters both understanding and trust.

In summary, our lab not only pushes the boundaries of neuroscience techniques, but also pioneers an ethical paradigm for neuroscience studies in non-human primates that recognizes and respects the animals that enable our discoveries.

→ Laurens, Jean. 2022b. **The Statistical Power of Three Monkeys.** *preprint. Neuroscience.* doi: 10.1101/2022.05.10.491373.

The widespread application of 3Rs and of a culture of care for the animals *has made Europe a champion of ethical animal research.*



Two Marmoset monkeys forage and socialize while being observed from afar. The boxes on the head are prepared to house neuronal recording equipment.

LAURENS LAB

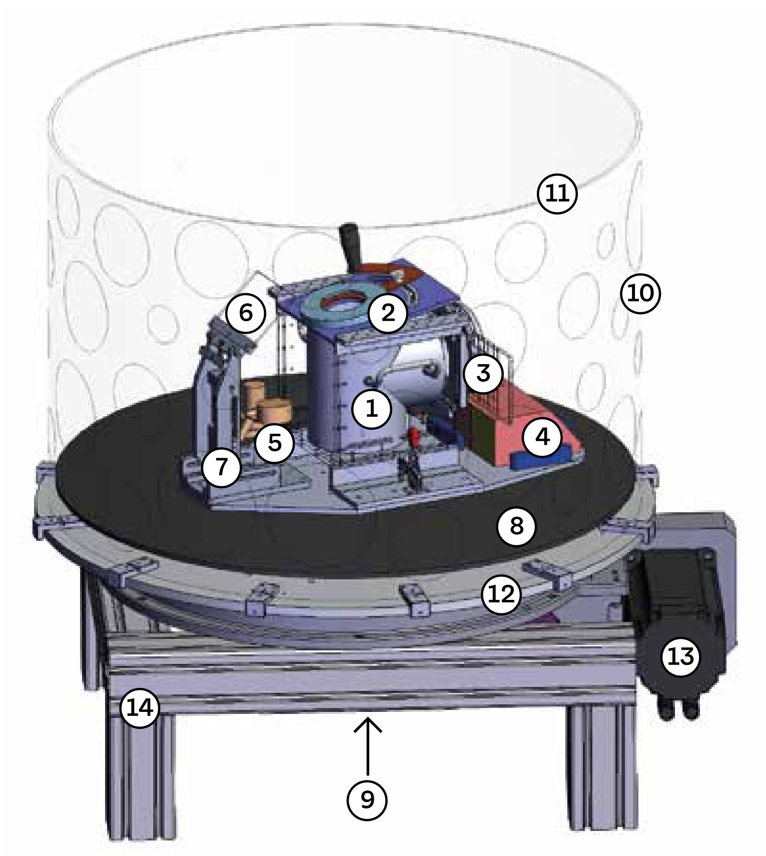
The sense of motion

We also possess a brain system for sensing our body motion: the vestibular system, named after its relation to the balance organ in the inner ear (the vestibular organ).

My research group focuses on theoretical modeling of the vestibular system, and establishing marmosets as an animal model for vestibular function and neurophysiological research on central vestibular pathways. We have recently expanded a mathematical model to simulate the clinical consequences of inner ear lesions. Concurrently, we have constructed a vestibular rotator to administer classical vestibular function tests in marmosets. We are preparing further experiments focused on postural control in freely moving animals. Our vision is to establish the Marmoset monkey as a pivotal model for both translational and basic research into human postural control and vestibular function across health, disease, and aging.

→ Laurens, Jean. 2022a. **The Otolith Vermis: A Systems Neuroscience Theory of the Nodulus and Uvula.** *Frontiers in Systems Neuroscience* 16:886284. doi:10.3389/fnsys.2022.886284.

→ Angelaki, Dora E., and Laurens, Jean. 2021. **Two Functionally Distinct Purkinje Cell Populations Implement an Internal Model within a Single Olivo-Cerebellar Loop.** 2021.05.09.443096.



1 Chair body
2 Neckplate
3 Entrance door
} Marmoset chair

4 Reward dispenser

5 Eye tracking camera
6 Infrared Mirror
7 Camera positioning mechanism

8 Inner platform

9 Inner assembly motor (hidden)

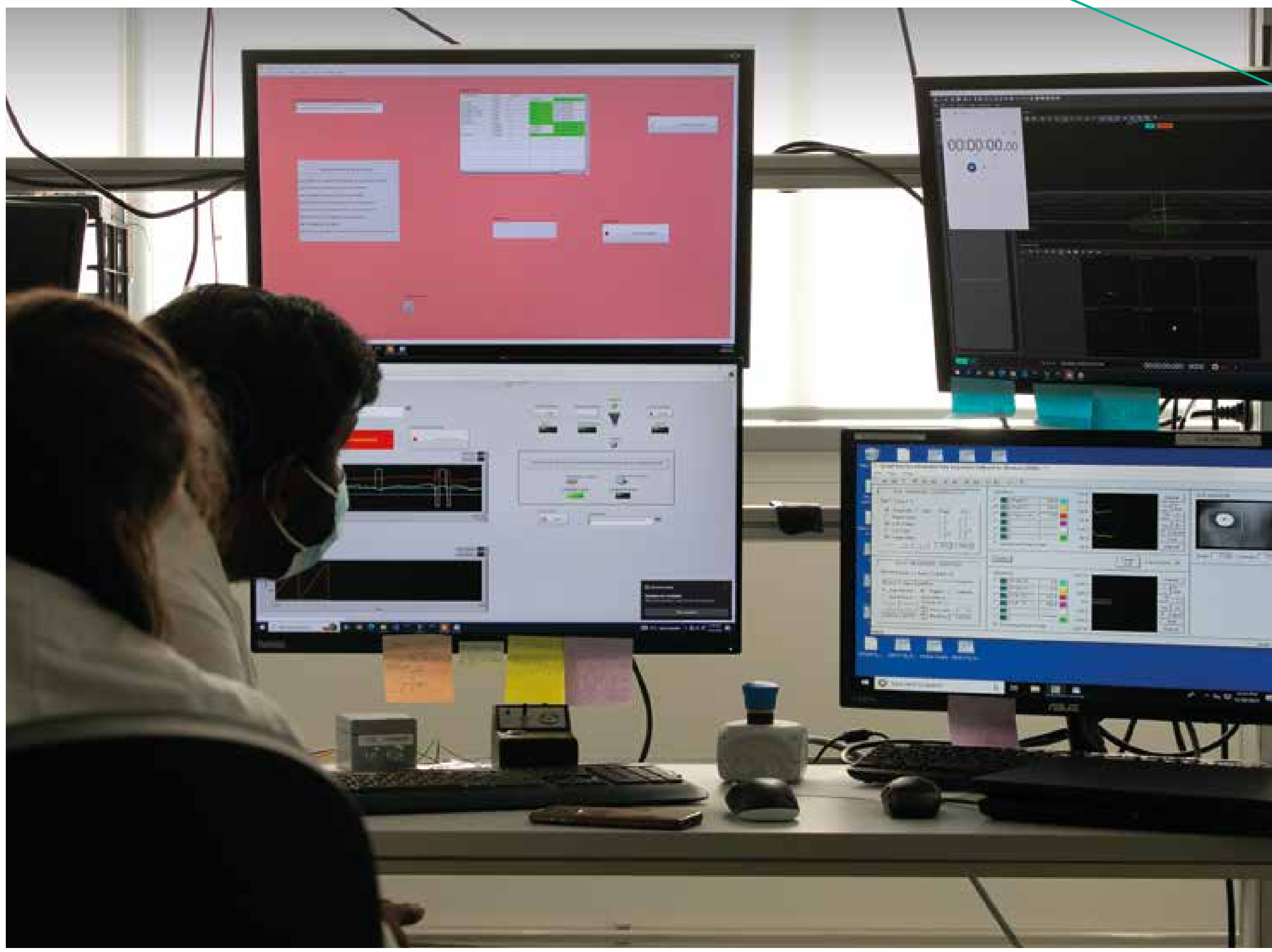
10 Circular wall (white with black dots)
11 LED illumination
12 Outer platform

13 Outer assembly motor

14 Base structure

What do we learn by putting monkeys on rotating chairs?
Discover it here:

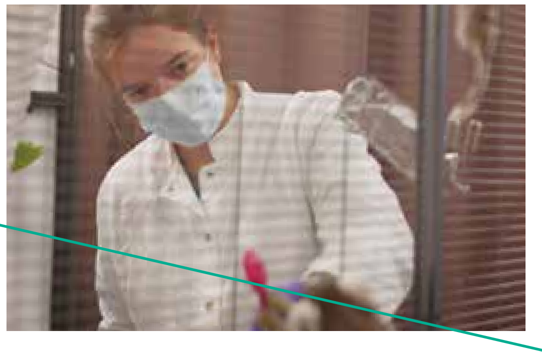
Eye movements recordings during a Marmoset rotation experiment



LAURENS LAB

Suppose you decide to walk from your bedroom to your kitchen. How long do you need to think about your route? Probably not very long. Can you mentally retrace your everyday route to work? Yes? We owe these abilities to the brain's navigation system. My lab studies a particular component of this system: the head direction cells system, also known as the 'brain compass'.

We investigate various facets of this brain compass. We aim to understand how it functions in three-dimensional space and how it updates itself in relation to visual landmarks or in the dark. To achieve this, we train rats and marmoset monkeys to forage in natural conditions, or to solve custom-made mazes. We are also developing wireless neuronal recording systems that will enable us to probe directly the activity of head direction cells during these tasks.



Watch us on Youtube:
"Testing Ground – A Documentary about Animal Research at the ESI"

1 Main cage
2 Remote-controlled food dispenser
3 Proximal cues (also providing enrichment)
4 Distal surround cues
5 Retroflective markers (on demonstration puppet)
6 Marmoset monkey with head implant and markers
7 3D motion capture camera (top) and high-speed video camera (bottom)
8 Monitoring computers

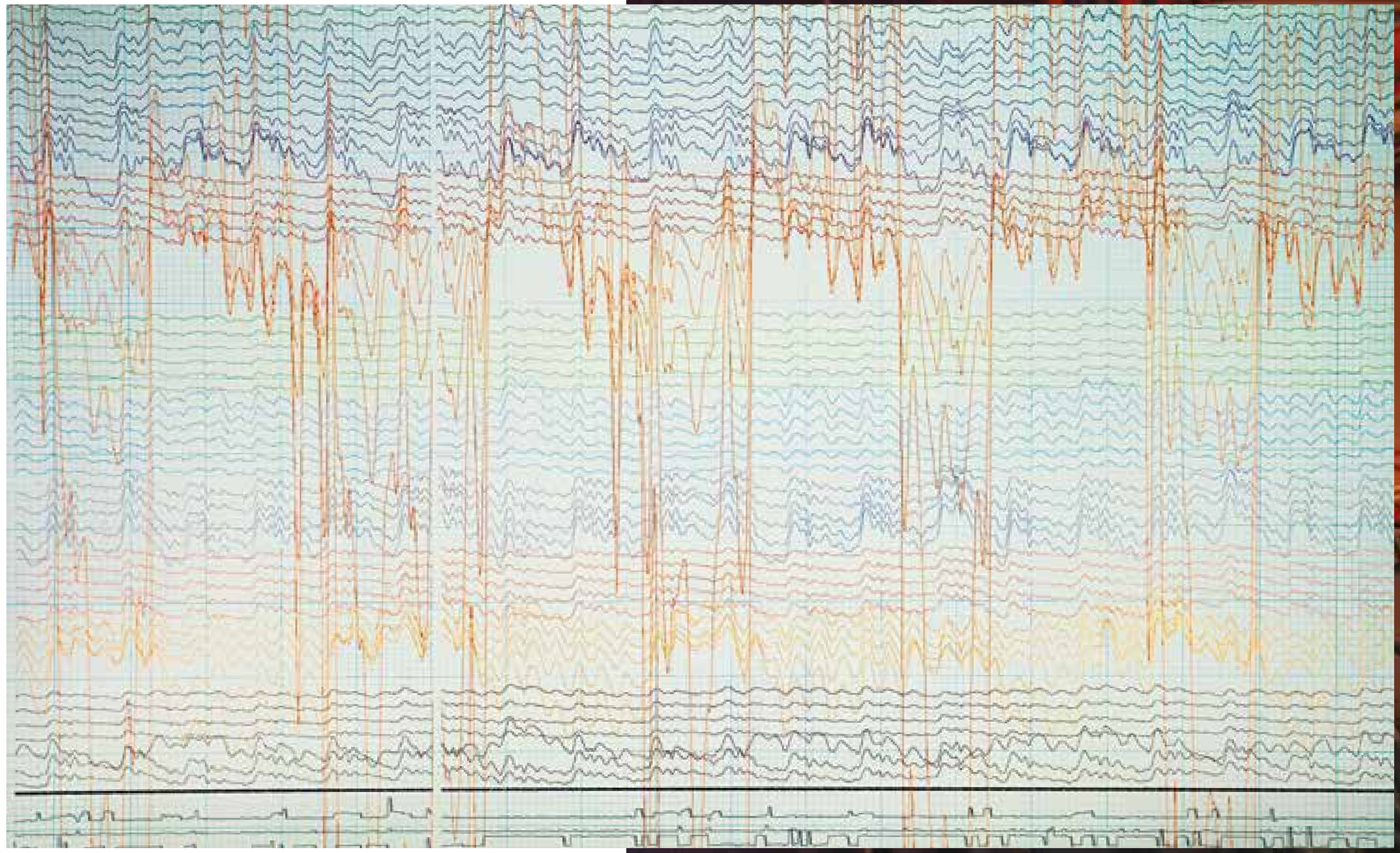
HUMAN MINDS AND BRAINS AND SOUNDS

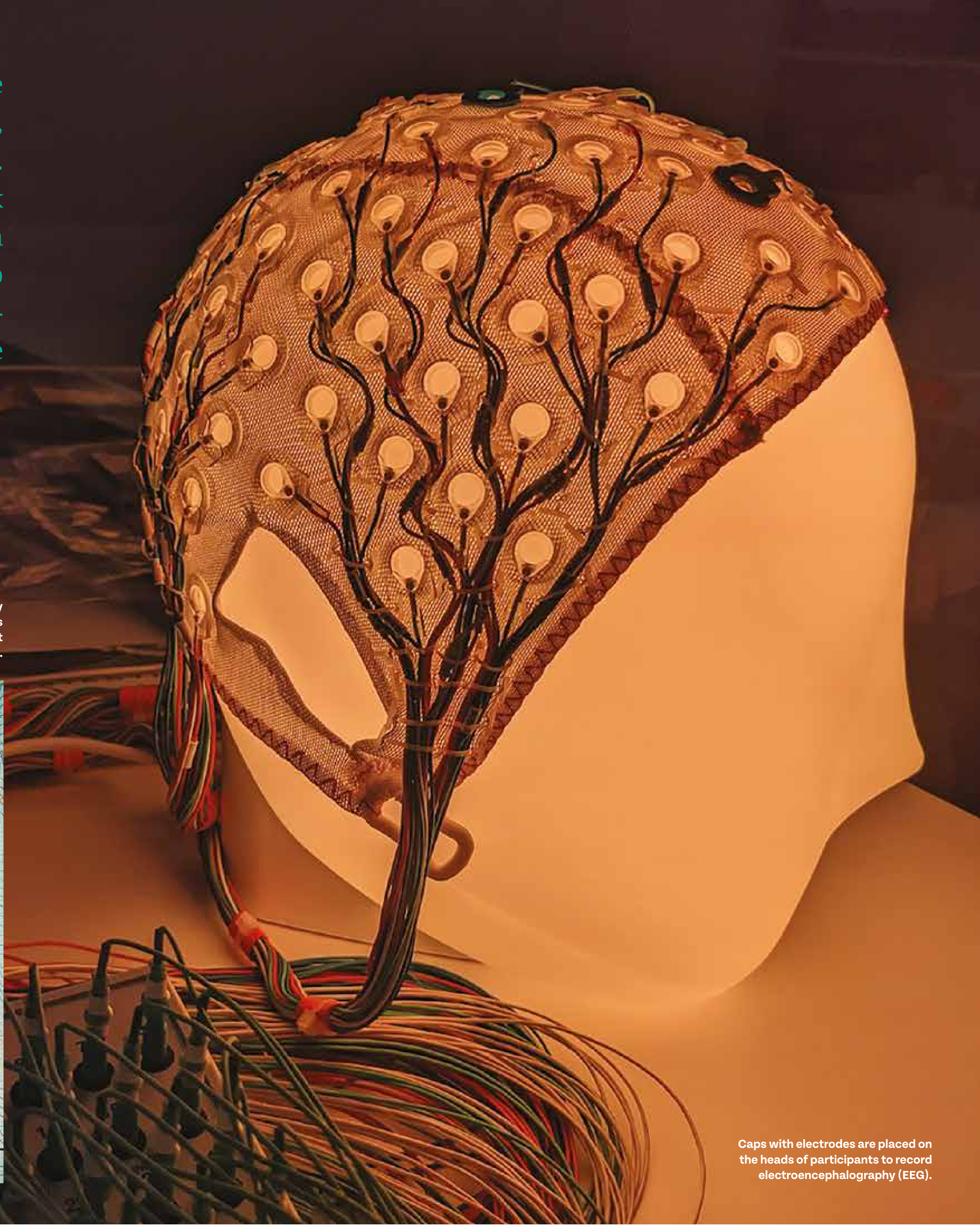
Director Prof. David Poeppel PhD / Assistants Cordula Ullah, Anja Tydecks, Renata Vajda / Postdocs Peter Donhauser, Francisco Garcia Rosales, Matthias Grabenhorst, Saskia Helbling, Natalie Schaworonkow, Yue Sun / PhD Students Federico Adolfi, Berfin Bastug, Martina Vilas (GU), Leonardo Zeine / MTA Tracia Webster-Kreis / MRI engineer Sean Lee / Ernst Strüngmann Visiting Professors Prof. Dr. Oded Ghitza (Boston University), Prof. Nina Kazanina Ph.D. (University of Geneva). (as of December 2023)

"The techniques we use to study human neuroscience have the right temporal resolution and (ever increasing) spatial resolution – but we really are struggling with the right 'conceptual resolution.' What are the best possible approaches to develop compelling linking hypotheses between neuro-biology and cognition?"

POEPPEL DEPARTMENT The lab is new at ESI – in fact, it is the newest research group. In a substantial reorganization of the institute, in April 2021 David Poeppel joined ESI as a scientific director and CEO. While several members of the team from the previous Max Planck Institute joined ESI, the majority of the team is new and has now been assembled. The lab has been able to take advantage of existing lab equipment for the moment (e.g., an EEG system, psychophysics facilities, a brain imaging laboratory shared with the university), while we wait for the laboratory to be completed at ESI in the course of 2024.

Each trace shows brain activity recorded at individual sensors that measure neural dynamics at different locations.





Caps with electrodes are placed on the heads of participants to record electroencephalography (EEG).

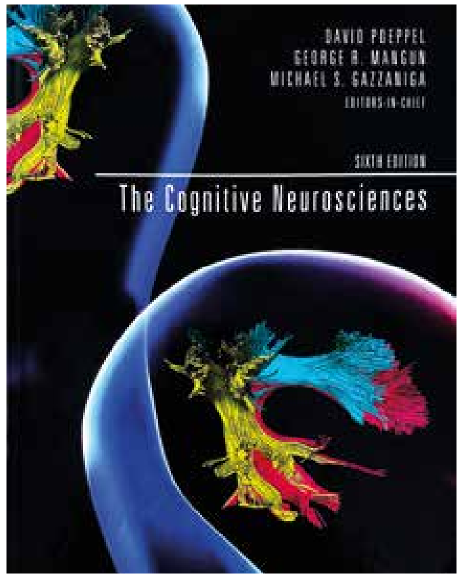
POEPPEL DEPARTMENT

The lab focuses, broadly speaking, on the relationship between neurobiology and cognition. The lab members primarily work on the neural foundations of *speech perception and language processing, on auditory cognition and music, on the temporal structure of perceptual experience, and on questions concerning how to analyze and interpret the signals we record from the human brain*. The main methods we employ to study the human brain include electrophysiological recordings using magnetoencephalography (MEG), electroencephalography (EEG), and electrocorticography (ECoG), as well as imaging studies that use structural and functional magnetic resonance imaging (MRI). Importantly, studying perception and cognition in a neuroscience context draws as much on behavioral work as it does on currently available techniques for recording from the human brain. Our studies include a wide range of behavioral and psychophysical approaches to characterizing a function – that is to say, to linking the representations and computations that form "the stuff of thought" to the neurobiological infrastructure that constitutes "the stuff of brain."

The researchers seek to identify linking hypotheses that bridge behavioral (or functional or computational) characterizations and neurobiological characterizations. The approach taken is one of methodological pluralism; that is to say, we use whichever methodological angle is most suited to investigate a given theoretically motivated question, and we embrace convergent evidence arising from different techniques. A guiding conceptual framework that informs the research is well articulated by arguments advanced by David Marr in his work in the 1970s on computational vision. A complex system – such as vision or language or music – can be studied productively at the implementational, algorithmic, and computational levels. Marr pointed to the inadequacy of a narrowly implementation-level approach to understanding. His objection to trying to understand the brain by focusing too restrictively and exclusively on implementation was that this leads primarily to descriptions, not explanations. Describing brain activity and neural connections is not the same as knowing how they underwrite perception, cognition, emotion, decision making, linguistic communication, etc. Inspired by this line of reasoning, research in the lab aims to be sensitive to the complexity of what should be considered descriptions of the brain as it performs the range of tasks that we study and what can be considered an explanation of complex behavior.

The research is wide in scope, with areas of experimental work ranging from low-level auditory perception to high-level language or music processing. The team members embrace (or at least generously tolerate) an interdisciplinary stance, while being aware of the dangers that come with it. In the end, the proof is in the pudding (an expression perhaps not ideally suited in the context of brain science …). In light of the care, experimental creativity, and quantitative rigor that the lab group has consistently demonstrated, the researchers that constitute the team have made significant contributions to the field(s).

→ Poeppel, D., Mangun, G. R., & Gazzaniga, M. S. (Eds.). (2020). **The Cognitive Neurosciences**. *MIT Press*.



A magnetoencephalography (MEG) machine captures brain activity using hundreds of detectors housed inside what looks like an old fashioned hair dryer. This device measures the magnetic fields elicited by neuronal currents and is one of the most sensitive machines to study human brains.

POEPPEL DEPARTMENT

We need oscilloscopes and plenty of other devices to set up and execute experiments, from bats to humans.

A. Speech, Language, and their Neural Foundations

Spoken language comprehension and production require processing systems that align the demands of auditory perception and speech-motor control (the sensorimotor interfaces), on the one hand, with the representational and computational requirements of the language system, on the other. The seeming effortlessness and automaticity of the perceptuomotor and linguistic processes as we experience them belie the number and complexity of the bottom-up and top-down operations that jointly constitute the perception of speech and comprehension of language. Developing a theoretically motivated, computationally explicit, and neurobiologically realistic understanding of this system remains a foundational challenge for cognitive neuroscience. The research the lab carries out draws on neuroscience, linguistics, psychology, computation, and other relevant domains of inquiry. The bread and butter of the lab consists of experiments on the neural basis of speech perception. Several example studies from the recent project period serve to illustrate the kinds of questions the lab continues to pursue.

Spoken language is of a continuously-varying acoustic signal, but listeners experience it as sequences of discrete speech units which are assembled to recognize discrete words. To examine how the brain sequences speech, we recorded two-hours of MEG data from participants listening to narratives. The analyses reveal that the brain encodes the three most recently heard speech sounds in parallel and maintains this information well past its dissipation from the sensory input. Each speech sound representation evolves over time, jointly encoding both its phonetic features and the amount of time elapsed since onset. Consequently, this dynamic neural pattern encodes both the relative order and the phonetic content of the speech sequence. The data show how phonetic sequences in natural speech are represented at the level of neuronal populations and provide insight into what intermediate representations exist between sensory input and (sub-)lexical units.

→ Gwilliams, L., King, J. R., Marantz, A., & Poeppel, D. (2022). **Neural dynamics of phoneme sequences reveal position-invariant code for content and order.** *Nature Communications*, 13(1), 6606.

There is steady progress on the question of the processing of discrete speech units. But how does a listener segment information that is 'packaged' in larger units? Building on both neuroimaging (structural and functional MRI) and neurophysiological (EEG, MEG) experiments, we have investigated, for example, the interaction between syllable-level and word-level processing (using MEG), as well as testing the widely discussed issue of how statistical information at the phoneme and syllable levels is extracted by learners (using fMRI).

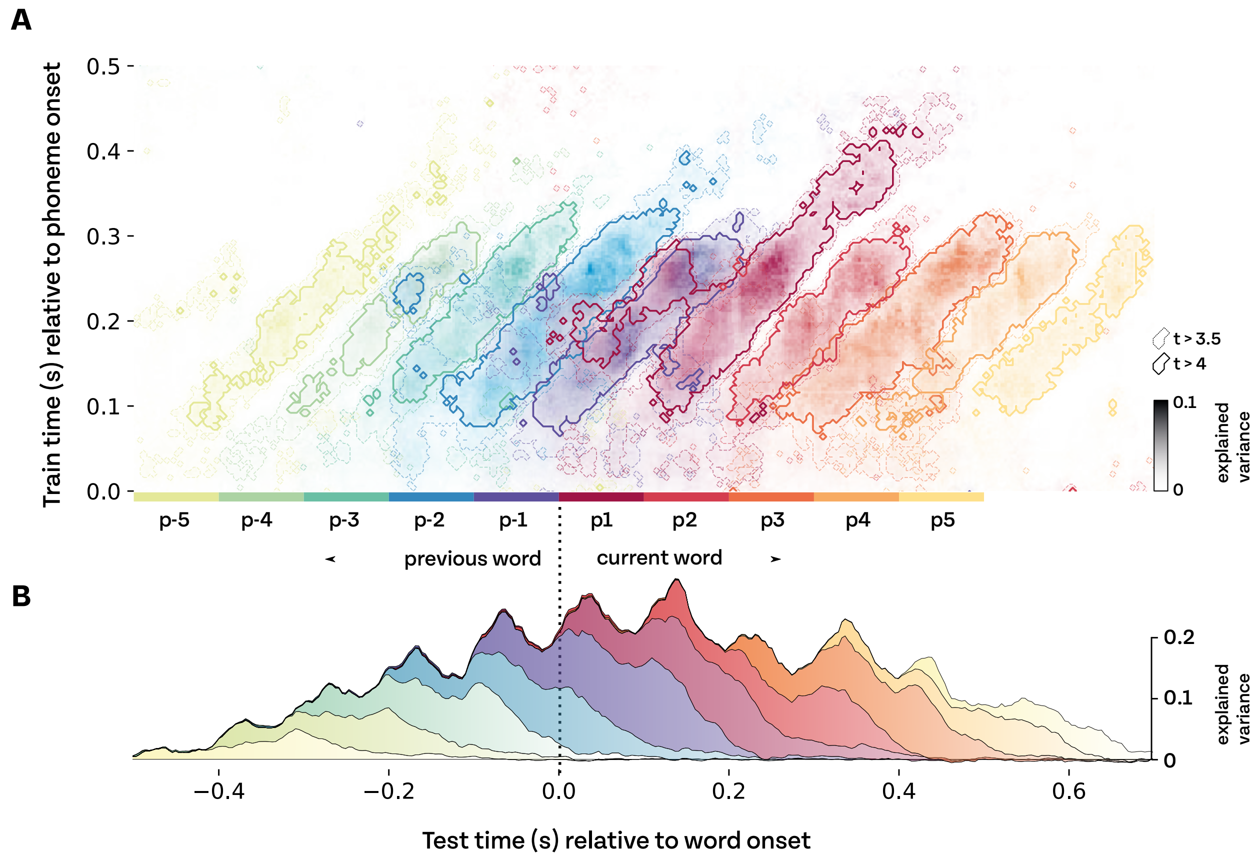


Figure 1: Phonetic feature processing across the sequence Accurate sequencing is central for speech comprehension: auditory inputs are transient and unfold rapidly, but the meaning they convey is constructed over longer timescales. We show that the brain does not process and discard inputs at the rate with which new inputs are received. We find that the phonetic representations of the three most recently heard phonemes are maintained in parallel. **(A)** Temporal generalisation (TG) results from MEG data, superimposed for 10 phoneme positions. Results represent decoding performance averaged over 14 phonetic features. From the first phoneme in a word (P1, dark red) moving forwards, and the last phoneme in a word (P-1, dark blue) moving backwards. The result for each phoneme position is shifted by the average duration from one phoneme to the next. The y-axis is the time that the decoder was trained, relative to phoneme onset. The x-axis represents the time that the decoder was tested, relative to word onset. Contours represent t-value threshold of 4 (dark lines) and 3.5 (light lines). **(B)** Decoding performance of the diagonal axis of each phoneme position (where train times are equal to test times). The visualization represents when phonetic information is available, regardless of the topography which encodes it. We use a stack plot, such that the variance explained by different phoneme positions is summed along the y-axis.

In behavioral experiments, participants typically sit in recording booths and execute perceptual or cognitive tasks.

It is remarkable to work in a field in which we know *so little about something so important* as the human mind/brain.

Oscillation-based approaches suggest that low-frequency auditory cortex oscillations track syllable-sized acoustic information and therefore emphasize the relevance of syllabic-level acoustic processing for speech segmentation. How syllabic processing interacts with higher levels of speech processing remains unclear. We investigated lexical and sublexical processing as well as their interaction with (acoustic) syllable processing using a frequency-tagging paradigm. Participants listened to disyllabic words presented at 4 syllables/sec. Lexical content (native language), sublexical syllable-to-syllable transitions (foreign language), or mere syllabic information (pseudo-words) were presented. We showed that syllable-to-syllable transition information activated a bilateral superior, middle temporal and inferior frontal network. Lexical content resulted, additionally, in increased neural activity. However, evidence for an interaction of word- and acoustic syllable-level processing was not conclusive. The results highlight how subtle and sensitive syllable-to-syllable transition information for word-level processing is.

→ Rimmele, J. M., Sun, Y., Michalareas, G., Ghitza, O., & Poeppel, D. (2023). **Dynamics of functional networks for syllable and word-level processing.** *Neurobiology of Language*, 4(1), 120-144.

How do listeners learn what units to track to begin with? Listeners across the lifespan show the ability to detect and learn patterns in seemingly random stimuli. This is referred to as statistical learning (SL), a process especially important when learning language. In an imaging study, capitalizing on individual differences in speech auditory-motor synchronization, we demonstrate that recruitment of a specific neural network supports SL from speech. While the analysis (ICA) of fMRI data revealed that a network of auditory and superior pre/motor regions is universally activated in the process of learning, a frontoparietal network is additionally and selectively engaged by some individuals (so-called high auditory-motor synchronizers). Activation of this frontoparietal network correlates with increased learning performance, and interference with this network via articulatory suppression (i.e., producing irrelevant speech during learning) equalizes performance across the entire sample. The experiment provides new evidence for the specific cortical networks underlying statistical learning in speech, and, in addition, draws attention to the advantage of factoring in individual differences for a precise characterization of such cognitive phenomena.

→ Orpella, J., Assaneo, M. F., Ripollés, P., Noejovich, L., López-Barroso, D., Diego-Balaguer, R. D., & Poeppel, D. (2022). **Differential activation of a frontoparietal network explains population-level differences in statistical learning from speech.** *PLoS Biology*, 20(7), e3001712.

→ Poeppel, D., & Assaneo, M. F. (2020). **Speech rhythms and their neural foundations.** *Nature Reviews Neuroscience*, 21(6), 322-334.

3D-printed heads and headcasts are both fun to look at and necessary to optimize how data are recorded and analyzed from human brains.

POEPPEL DEPARTMENT

→ Raccah, O., Doelling, K. B., Davachi, L., & Poeppel, D. (2023). **Acoustic features drive event segmentation in speech.** *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 49(9), 1494.

→ Poeppel, D. and Idsardi, W. (2022). **We don't know how the brain stores anything, let alone words.** *Trends in Cognitive Sciences.*

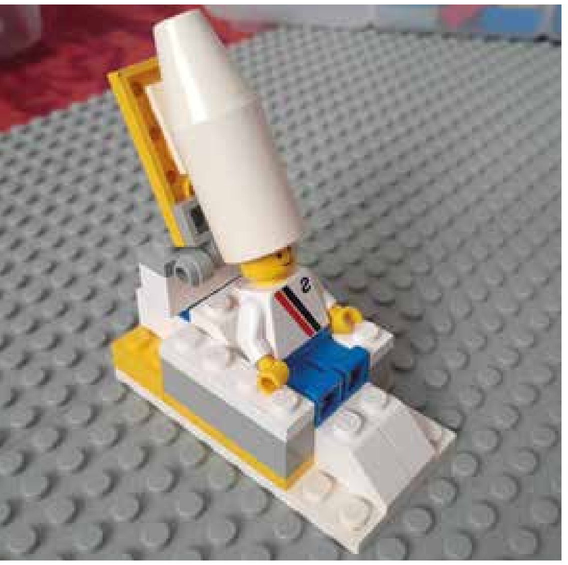
→ Sun, Y., & Poeppel, D. (2023). **Syllables and their beginnings have a special role in the mental lexicon.** *Proceedings of the National Academy of Sciences*, 120(36), e2215710120.

Much of the research in this domain is addressed to language processing questions, for example, the questions of statistical learning or segmentation or parsing. But there is, of course, an equally profound set of mysteries about storage. These can be called mysteries, rather than just problems, because the fact of the matter is that we do not have the faintest idea about how the 'atoms of language' are stored. There is a long tradition of research in linguistics and psycholinguistics on the mental lexicon, but elementary questions remain unsolved. In this domain, too, we are trying to make incremental progress. In one new study, we build on the intuition that beginnings of words are, in some sense, special. This intuition is widely shared, for example, when playing word games. Not apparent is whether this is substantiated empirically – and what the underlying organizational principle(s) are. We answer this simple seeming question using a quantitative approach. We test the hypothesis that the distribution of information in words is governed by a hypothesized computational unit for online speech perception and production: syllables. By analyzing twelve languages, we demonstrate that there is a compelling asymmetry between syllable beginnings (onsets) versus ends (codas) in their involvement in distinguishing the words stored in the lexicon. Specifically, we show that the functional advantage of syllable onset reflects an asymmetrical distribution of lexical informativeness within the syllable unit, rather than an effect of a decay of informativeness from the beginning to the end of a word. The converging finding across typologically different families supports the theory that the syllable unit, while known to be a critical primitive for both speech perception and production, is also a key organizational constraint for lexical storage.

→ Sun, Y., & Poeppel, D. (2023). **Syllables and their beginnings have a special role in the mental lexicon.** *Proceedings of the National Academy of Sciences*, 120(36), e2215710120.

→ Chen, P., Poeppel, D., & Zuanazzi, A. (2023). **Meaning creation in novel noun-noun compounds: humans and language models.** *Language, Cognition and Neuroscience*, 1-18.

The rapid development of large language models has, unsurprisingly, also motivated new experimentation. There is no question that such artificial neural network models are very useful tools, including for cognitive neuroscience. A different question is to what extent these models exhibit parallels to human performance that motivate the conclusion that they provide mechanistic insight into the brain and cognitive sciences. One of the hallmark features of human language is productivity, a property closely aligned with compositionality, and in comparing human performance, for example with novel compounds, one can identify which attributes do and do not reflect parallels between artificial neural networks and human cognitive performance. Likewise, ANN performance on automatic speech recognition is remarkable. It does not follow, however, that the underpinnings of large language models used for recognition can be used to explain human speech recognition. Here, too, there are fascinating parallels as well as principled differences.



Small prototype versions of recording setups (Thank you, Lego MEG!) help us design labs – and entertain smaller, younger lab visitors.

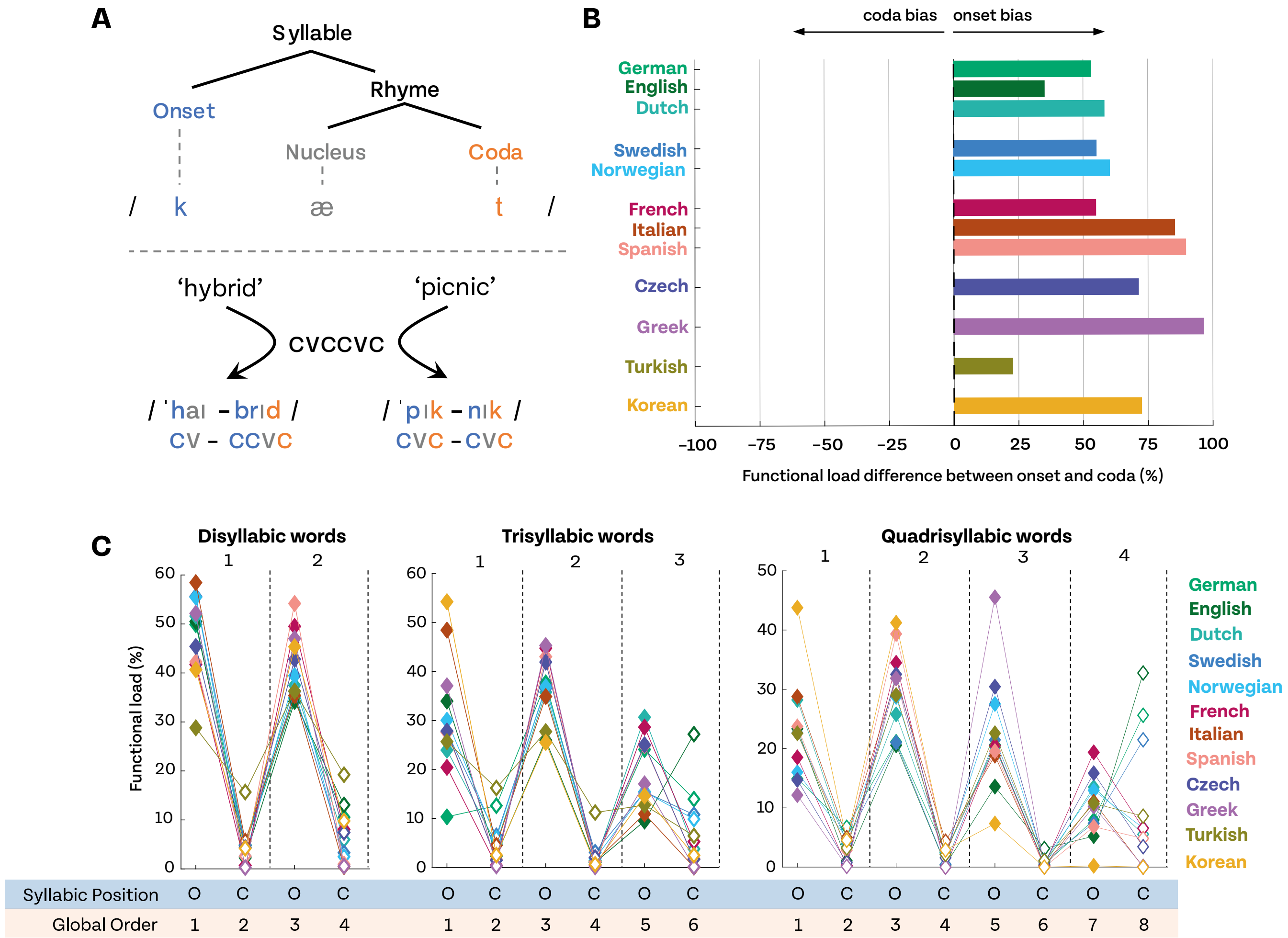


Figure 2: (A) Syllables and syllabification. Subunits and internal structure of syllables with the illustration of the word 'cat' (/kæt/-/CVC/). A syllable is typically composed of a vowel as nucleus (i.e., /æ/) that can be preceded and followed by one or more consonants. The consonants before the vowel are referred to as onset (i.e., /k/), those after the vowel as coda (i.e., /t/). Bottom panel: syllabification provides chunking to the phoneme sequence of words. While the phonological wordforms 'hybrid' and 'picnic' have the same sequence of consonants (C) and vowels (V), the two sequences are decomposed into syllables of different structures following syllabification rules of English. The figure illustrates that each phoneme of a word occupies a dedicated position within the corresponding syllable. Syllabic position impacts the robustness with which each phoneme is processed during speech production and perception. In general, consonants at syllable onsets are more robustly processed during speech perception and production than consonants at syllable coda. **(B)** Difference in functional load (in percentage) between syllable onset and coda in 12 languages. Languages are grouped according to typological criteria. Higher functional load indicates greater importance of a syllabic position in distinguishing words. Our results show higher load for syllable onset than syllable coda in all examined languages. **(C)** Variation of functional load across the onset and coda positions of each syllable in words with multiple syllables (disyllabic: left; trisyllabic: middle; quadrisyllabic: right). Filled diamonds indicate the functional load of the onset of each syllable and open diamonds indicate the functional load of the coda of each syllable. The numbers on top indicate the position of each syllable within the corresponding multisyllabic words. Dashed lines show the boundaries between syllables. Individual syllabic positions (labelled accordingly as O: onset; C: coda, indicated in the blue row of the x-axis) are also given a second label based on the global order of these position within the corresponding multisyllabic words (indicated in the orange row of the x-axis). The decreases of functional load mainly occur within syllables, supporting the view that syllables are organizational units for the modulation of functional load. In particular, the rebound of functional load from the coda of a syllable to the onset of the following syllable reject the idea of an effect of global decay of lexical informativeness from the beginning to the end of words, as has been claimed.

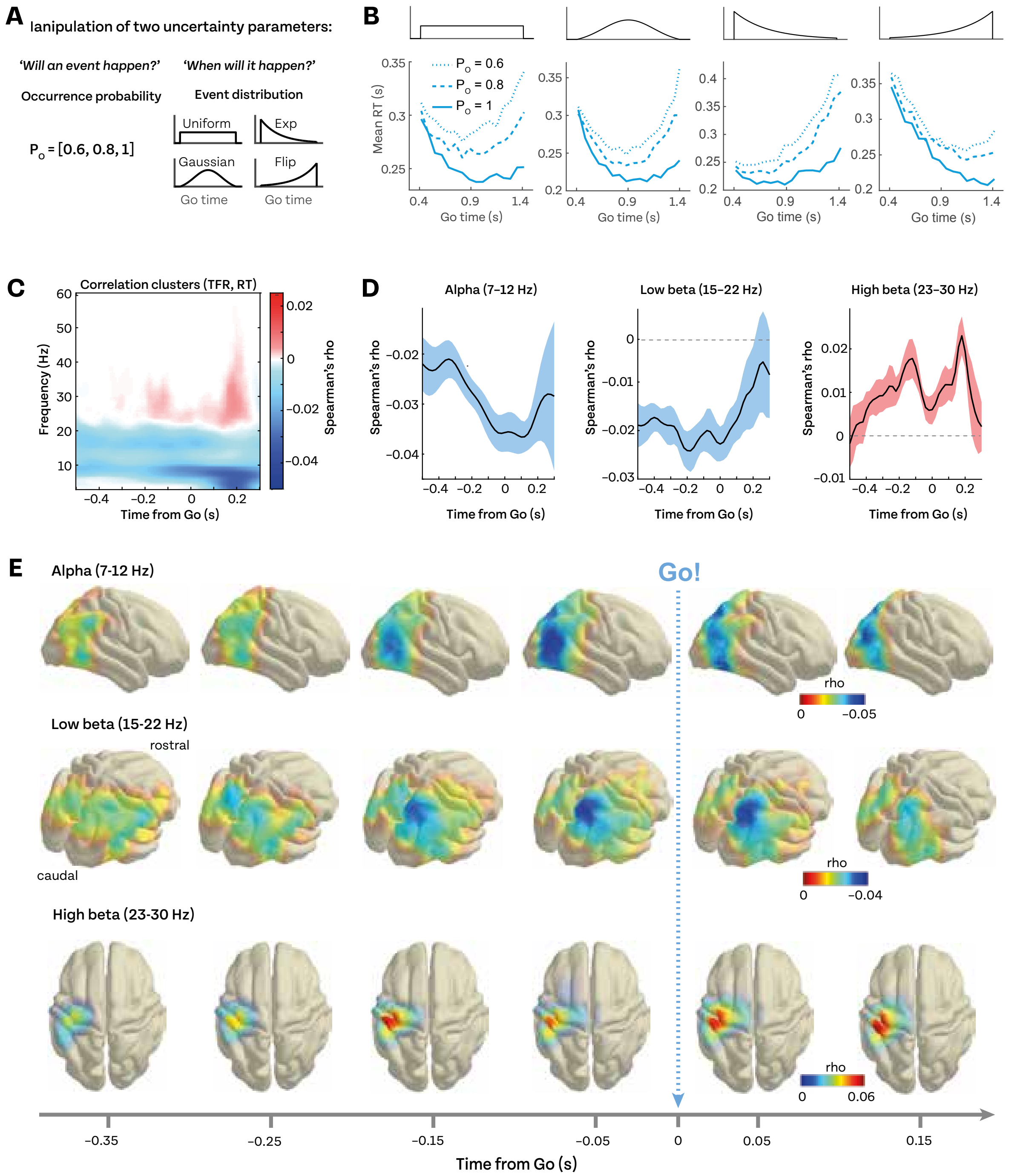


Figure 3: **(A)** We investigated temporal event anticipation in behavior by separately manipulating the event occurrence probability (PO) and the event distribution over time. **(B)** Reaction time curves, as a proxy for anticipation, were independently modulated by event occurrence probability and event distribution over time, suggesting independence of the representation of the two sources of uncertainty (Grabenhorst et al., PNAS, 2021). **(C)** Using magnetoencephalography, we investigated the neural correlates of temporal anticipation in audition and vision (Grabenhorst et al., under review). Reaction times to events distributed in time (exponential and flipped exponential "Go"-cue distributions) were correlated with spectral power in the alpha (7–12Hz), low beta (15–22Hz) and high beta (23–30Hz) bands (cluster test on Spearman's rho). **(D)** Correlation dynamics in the three frequency bands before the sensory event suggest a functional relationship between power modulation and temporal anticipation. **(E)** Modeling and source-level correlation analysis demonstrates that the probability distribution of sensory events is represented in three distinct neural signals prior to the anticipated event: 1) in inferior parietal lobule and posterior middle temporal gyrus (alpha), 2) in superior parietal lobule (low beta), and, 3) in left sensorimotor cortex (high beta). These results directly link the probability distribution of sensory events to cortical dynamics and demonstrate a supra-modal role of posterior parietal and posterior middle temporal areas in a fundamental cognitive function: the anticipation of events in time.

Our lab, too, is not immune to the seductive allure of studying human linguistic interaction in more naturalistic contexts or with more naturalistic materials. The majority of research in the area of inquiry is executed with carefully crafted and controlled experimental materials, in order to allow for restrictive interpretations of the results. On the other hand, there is growing appetite for understanding naturalism, context, and the ecologically valid features of human perception and action. Building on earlier experiments recording EEG from multiple participants at the same time, we will continue to study different features of human perception and cognition by recording from interacting participants concurrently. A growing body of evidence suggests that synchronized neural activity across people is a useful non-invasive proxy for joint attention and can even indicate better learning. Similarly, we have made progress on investigating - even very subtle - acoustic modulations in real speech that reflect emotion or differing semantic interpretations. Listeners are typically remarkably good at perceiving conveyed emotion even in brief nonspeech vocalizations; and, perhaps in part culturally conditioned, listeners apprehend nuanced communicative intentions like irony.

→ Dikker, S., Michalareas, G., Oostrik, M., Serafimaki, A., Kahraman, H. M., Struiksma, M. E., & Poeppel, D. (2021). **Crowdsourcing neuroscience: inter-brain coupling during face-to-face interactions outside the laboratory.** *NeuroImage*, 227, 117436.

→ Holz, N., Larrouy-Maestri, P., & Poeppel, D. (2021). **The paradoxical role of emotional intensity in the perception of vocal affect.** *Scientific Reports*, 11(1), 9663.

→ Holz, N., Larrouy-Maestri, P., & Poeppel, D. (2022). **The variably intense vocalizations of affect and emotion (VIVAE) corpus prompts new perspective on nonspeech perception.** *Emotion*, 22(1), 213.

→ Larrouy-Maestri, P., Kegel, V., Schlotz, W., van Rijn, P., Menninghaus, W., & Poeppel, D. (2023). **Ironic twists of sentence meaning can be signaled by forward move of prosodic stress.** *Journal of Experimental Psychology: General.*

A shortcoming of the research program will continue to be the large distance between neural mechanisms at the cellular or circuit levels and the measurements we can make in the human brain (with the exception of certain clinical interventions). To be sure, there are components of language processing that are not accessible to study with other systems. However, the sensorimotor interfaces, that is to say the perceptual analysis of complex signals, as well as vocal-motor control, can be sensibly studied in animal models. One promising approach that links human cognitive neuroscience to systems neuroscience is to work with marmosets. These animals are highly social and highly vocal, and marmoset neurophysiology stands to enable an appropriate mechanistic understanding of the auditory and motor interfaces for human speech perception and production.

→ Kiai, A., Clemens, J., Kössl, M., Poeppel, D., & Hechavarría, J. (2023). **Flexible control of vocal timing in Carollia perspicillata bats enables escape from acoustic interference.** *Communications Biology*, 6(1), 1153.

B. The Temporal Structure of Perceptual Experience

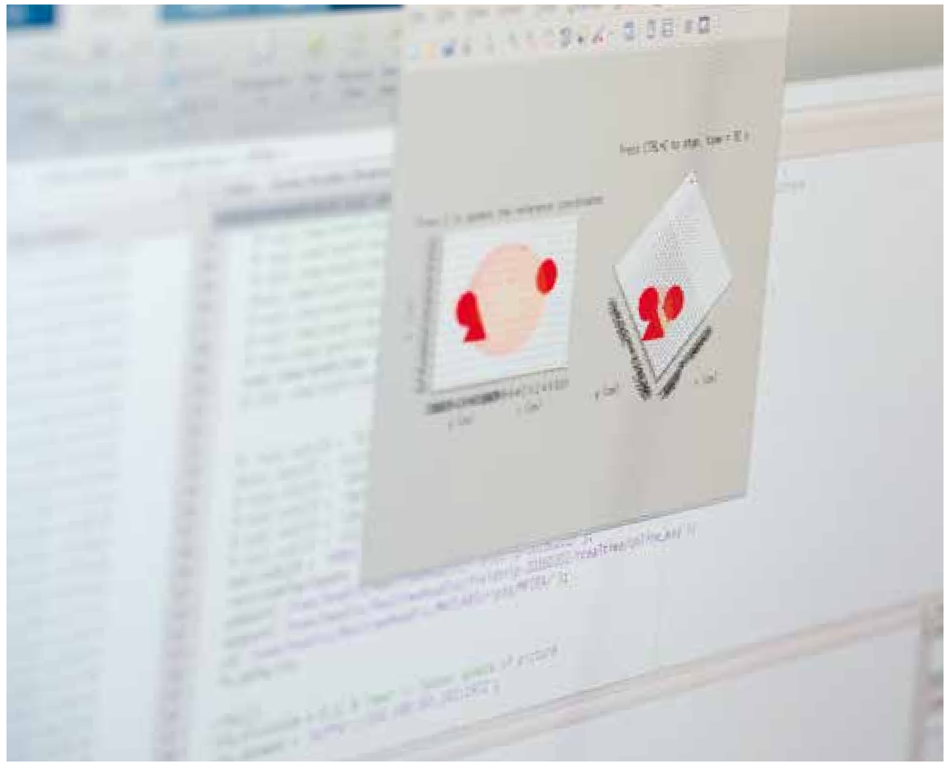
One foundational topic that connects many projects in different areas across the lab concerns the extent to which temporal structure - in the broadest sense, including timing properties of stimuli, aspects of neural processing, and attributes of experimental tasks - conditions our experience. One way the lab has approached this question is to identify the basic building blocks of temporal experience. Because the nervous system consists of a finite number of building blocks (neurons, dendrites, spines, ensembles, etc.) subject to biophysical constraints, one can imagine the existence of a set of basic temporal computations, i.e., an inventory of time-based processes that underpin many different functions. Oscillations are one neurophysiological substrate that may support such operations, but there are other attributes that add to our list of elementary building blocks.

→ Sun, Y., Michalareas, G., & Poeppel, D. (2022). **The impact of phase entrainment on auditory detection is highly variable: Revisiting a key finding.** *European Journal of Neuroscience*, 55(11-12), 3373-3390.

→ Sierra, F., Poeppel, D., & Tavano, A. (2022). **Two attentive strategies reducing subjective distortions in serial duration perception.** *Plos One*, 17(3), e0265415.

→ Sierra, F., Muralikrishnan, R., Poeppel, D., & Tavano, A. (2022). **A perceptual glitch in serial perception generates temporal distortions.** *Scientific Reports*, 12(1), 21065.

POEPPEL DEPARTMENT



The analysis of human brain data requires many approaches to analysis and visualization, from sketches of ears and noses to reconstructed gyri and sulci.

One very fundamental phenomenon that cuts across virtually all domains of experience – and that is especially salient in the processing of music, speech, and other dynamic events – is how we treat 'the future.' We have known for a long time that we make remarkably good predictions, not only about when an event will happen in the future, but sometimes even what the event will be. How this is achieved has been the topic of both psychophysical and neurobiological experimentation, and we have pursued that path as well, arguing against the widely endorsed concept of hazard rate as the only or main mechanistic concept. The environment is shaped by two sources of temporal uncertainty: the discrete probability of whether an event will occur at all and – if it does occur – the continuous probability of when precisely it will happen. These two types of uncertainty are fundamental to every form of anticipatory behavior from learning to decision-making to motor planning. How the brain models these uncertainty parameters and how they interact in anticipation is not known. It is typically assumed that the discrete probability of whether an event will occur has a fixed effect on event expectancy over time. In contrast, we demonstrate that this pattern is dynamic and monotonically increases across time. Remarkably, this behavior is independent of the continuous probability of when an event will occur. The effect of continuous probability on anticipation is commonly proposed to be driven by the hazard rate (HR). We show that the HR fails to account for behavior and propose a model of event expectancy based on the (simpler to compute) probability density function of events. The results we show hold for vision and audition, suggesting independence of the representation of the two uncertainties from the respective sensory input modality. Our data on this issue has enriched understanding of fundamental anticipatory processes and also has provocative implications for aspects of behavior and its neural underpinnings.

→ Grabenhorst, M., Maloney, L. T., Poeppel, D., & Michalareas, G. (2021). **Two sources of uncertainty independently modulate temporal expectancy.** *Proceedings of the National Academy of Sciences*, 118(16), e2019342118.

C. Oscillations and other Signal Challenges

Neuronal oscillations are argued to play a role in many perceptual and cognitive tasks, including attention, navigation, memory, motor planning, and – most relevant in the context of our research – spoken-language comprehension, music perception, and other dimensions of auditory cognition. The specific computational functions of neuronal oscillations are uncertain – and vigorously debated. Our experiments over the years have aimed to clarify how these neurophysiological phenomena may or may not contribute to speech, language, memory, sequencing and music processing. For example, in order to segment a naturalistic input signal (e.g., a speech signal) into usable pieces for subsequent computation (e.g., concatenation, combinatorics, composition), it has been suggested that one mesoscopic-level mechanism is "temporal windowing," or chunking, which could be implemented as low-frequency brain oscillations. Dynamically changing auditory signals (as well as visual stimuli, including signs) contain critical information required for successful decoding that is carried on multiple temporal scales (e.g., slower intonation-level information, syllabic information, and rapidly changing featural

information). These different aspects of signals (slow and fast temporal modulation, frequency composition) must be analyzed to achieve successful recognition. Insofar as oscillations constitute a useful neuronal substrate for entrainment, it is impor-tant to have a deep understanding of what can be analyzed on the basis of such signals. The combination of neurophysiological experimentation using MEG with psychophysics and a variety of cutting-edge analysis approaches converge on the hypothesis that there is temporally discretized processing, supported by oscillatory activity in different frequency regimes.

Three areas of inquiry arise in the context of this line of research. First, we need to have a solid grasp on the measurement problem itself: what is the best way to acquire and describe such neural data? Second, the most sensitive and robust data-analytic approaches need to be developed, tested, and applied to a wide range of relevant data. Set, we need concurrently to think about the issue of underlying sources, that is to say which neural structures elicit the activity we measure and theories about. A particular relevance is the opportunity to get spatial resolution at the level of laminar, cortical organization, with noninvasively recorded MEG data.

The intricate patterns of oscillatory activity, in studies across species, are usually characterized in terms of frequency and amplitude. In this study, oscillations from the bat frontal and auditory cortices were examined on a cycle-by-cycle basis, focusing on their characteristic waveform shape. The waveform shape of oscillations relates closely to local physiology and is informative about the nature of the dynamically changing states. However, how waveform shape differs across structurally distant but functionally and anatomically connected and related cortical regions is not well understood. Here we

→ Schaworonkow, N., & Voytek, B. (2021). **Enhancing oscillations in intracranial electrophysiological recordings with data-driven spatial filters.** *PLOS Computational Biology*, 17(8), e1009298.

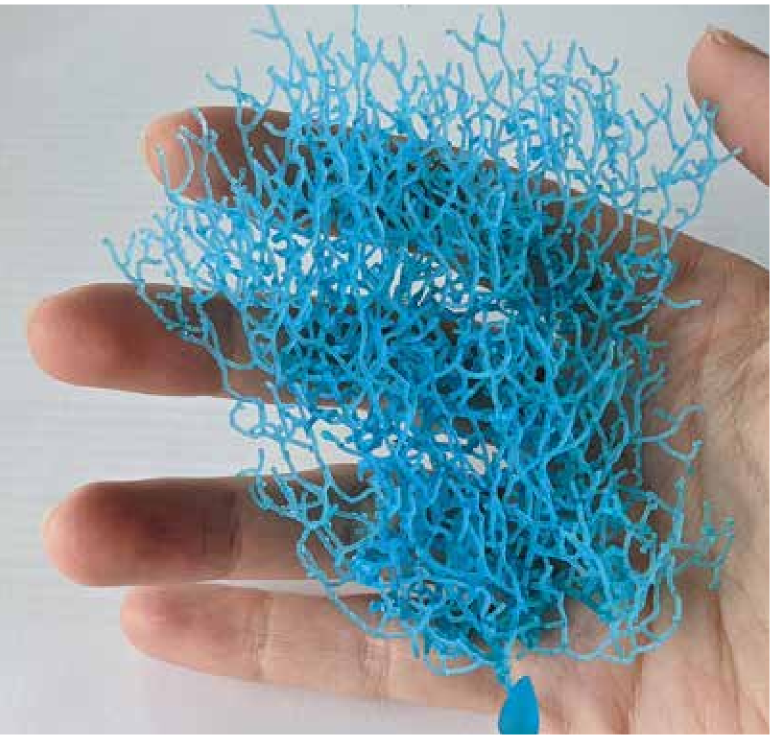
→ Schaworonkow, N., & Nikulin, V. V. (2022). **Is sensor space analysis good enough? Spatial patterns as a tool for assessing spatial mixing of EEG/MEG rhythms.** *Neuroimage*, 253, 119093.

→ Tavano, A., Rimmele, J. M., Michalareas, G., & Poeppel, D. (2023). **Neural oscillations in EEG and MEG. In Language Electrified: Principles, Methods, and Future Perspectives of Investigation** (pp. 241-284). New York, NY: Springer US.

→ Helbling, S. (2023). **Inferring laminar origins of MEG signals with optically pumped magnetometers (OPMs): a simulation study.** *bioRxiv*.

→ García-Rosales, F., Schaworonkow, N., & Hechavarria, J. C. (2023). **Oscillatory waveform shape and temporal spike correlations differ across bat frontal and auditory cortex.** *Journal of Neuroscience*.

Old didactic posters and old devices with cable salad can inspire new ideas and unexpected experiments.



A 3D-printed representation of a neuron highlights both the intricacy and aesthetic beauty of brain cells.

capitalized on simultaneous recordings of local field potentials (LFPs) in the auditory and frontal cortices of awake, male Carollia perspicillata bats. We describe, on a cycle-by-cycle basis, waveform shape differences across these cortical regions. The waveform shape differs markedly in the fronto-auditory circuit, even for rhythmic activity that is correlated in comparable frequency ranges (e.g., in the delta and gamma bands) in the context of spontaneous neural activity. We report consistent differences between regions in the variability of waveform shape across individual cycles. The model we envision predicts higher spike-spike and spike-LFP correlations in regions with more asymmetric shape, a phenomenon that is supported by observations in the data: spike-spike and spike-LFP correlations were higher in frontal cortex. These results suggest that oscillatory activity in frontal and auditory cortex possess distinct dynamics related to the anatomical and functional diversity of the fronto-auditory circuit of which they are a critical part. What is particularly noteworthy about this project is that it constitutes a genuine collaboration between analytic approaches developed a human neuroscience and data from animal neurophysiology. Gaining a deeper understanding of the mesoscale of neural activity that likely underpins important aspect of perception and cognition benefits tremendously from the close alignment between animal neurophysiology and human cognitive neuroscience.

D. Conceptual Foundations of the Field(s)

→ Poeppel, D. and Idsardi, W. (2022). **We don't know how the brain stores anything, let alone words.** *Trends in Cognitive Sciences.*

→ **The ESI Foundations Institute Workshop: Beyond Associations** (October 2022). *https://www.tfi.ucsb.edu/events/all/2022/how-it-possible-store-concepts-and-propositions-minds-and-brains*

→ Bowers, J.S., Malhotra, G., Dujmović, M., Montero, M.L., Tsvetkov, C., Biscione, V., Puebla, G., Adolfi, F., Hummel, J.E., Heaton, R.F. and Evans, B.D., (2022). **Deep problems with neural network models of human vision. Behavioral and Brain Sciences.**

→ Bowers, J.S., Malhotra, G., Adolfi, F., Dujmović, M., Montero, M.L., Biscione, V., Puebla, G., Hummel, J.H. and Heaton, R.F., (2023). **On the importance of severely testing deep learning models of cognition. Cognitive Systems Research.**

→ Kazanina, N., & Poeppel, D. (2023). **The neural ingredients for a language of thought are available.** *Trends in Cognitive Sciences.*

One of the pleasures and dangers of doing interdisciplinary work is that it allows one to be risky in unanticipated ways – of course, at one's own peril. The cultural anthropologist Marshall Sahlins has an apt quote: "Interdisciplinary study is the process by which the unknowns of one's own subject matter are multiplied by the uncertainties of some other science." This challenge invites one to reflect periodically on the intellectual foundations of what the goals actually are, and what might reasonably be achieved. The brain and cognitive sciences can be relentlessly interdisciplinary, and as such this research motivates critical discussion of our presuppositions.

We regularly engage with questions concerning the foundations of the research. This includes examining which stimulus materials and task demands might yield the best experimental insights, what plausible linking hypotheses might be between neural measurements and cognitive models, or what the 'parts list' is the forms the basis for linguistic cognition. The most substantive reflection involves the big questions, methods, and concerns; and in that context, it has been a privilege to select and edit the chapters that describe the state of the art of our field(s) in 2020. While the experimental techniques we have used are of increasingly impressive spatial and temporal resolution, the research still lacks the necessary 'conceptual' – and it is this goal that our work emphasizes.

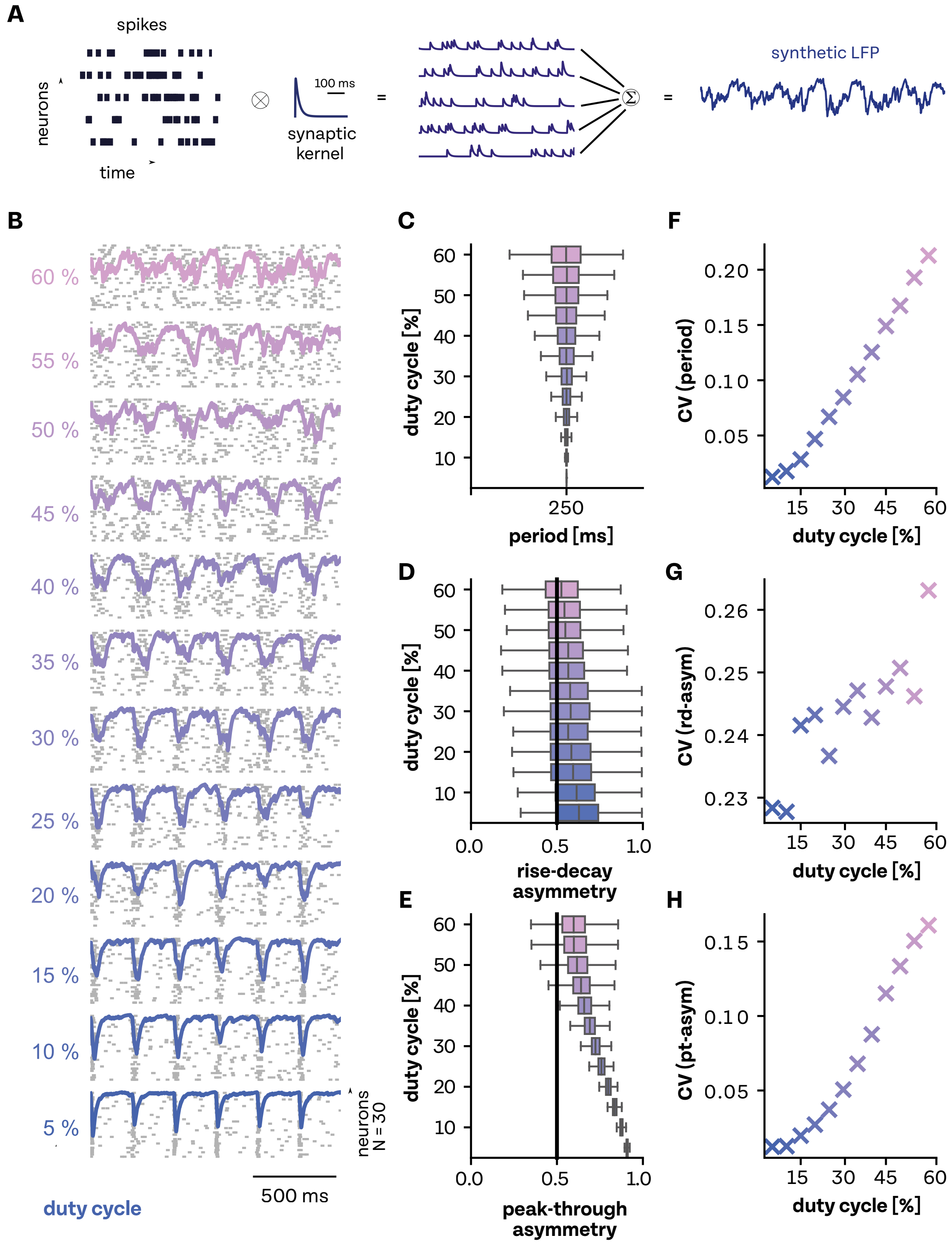


Figure 4: A linear model captures the differences in waveform shape between the frontal and auditory region. **(A)** Schematic illustrating how synthetic LFP signals were derived from spiking activity of a population of simulated neurons. **(B)** Representative spiking activity of a population of N=30 simulated neurons. The synchronicity across neurons varies with the duty cycle of a pulse train modulating firing rate (lower duty cycle, more synchronous). A synthetic LFP was calculated for each condition (overlaid traces; see panel A). The period **(C)**, rise-decay asymmetry **(D)**, and peak-trough asymmetry **(E)** values across all cycles detected by the bycycle algorithm for each duty cycle tested. The black line in panels D and E represents no asymmetry (i.e. a value of 0.5). CV values of features period **(F)**, rise-decay asymmetry **(G)**, and peak-trough asymmetry **(H)**. In panels C-H, values from each duty cycle simulation are color-coded according to panel B.

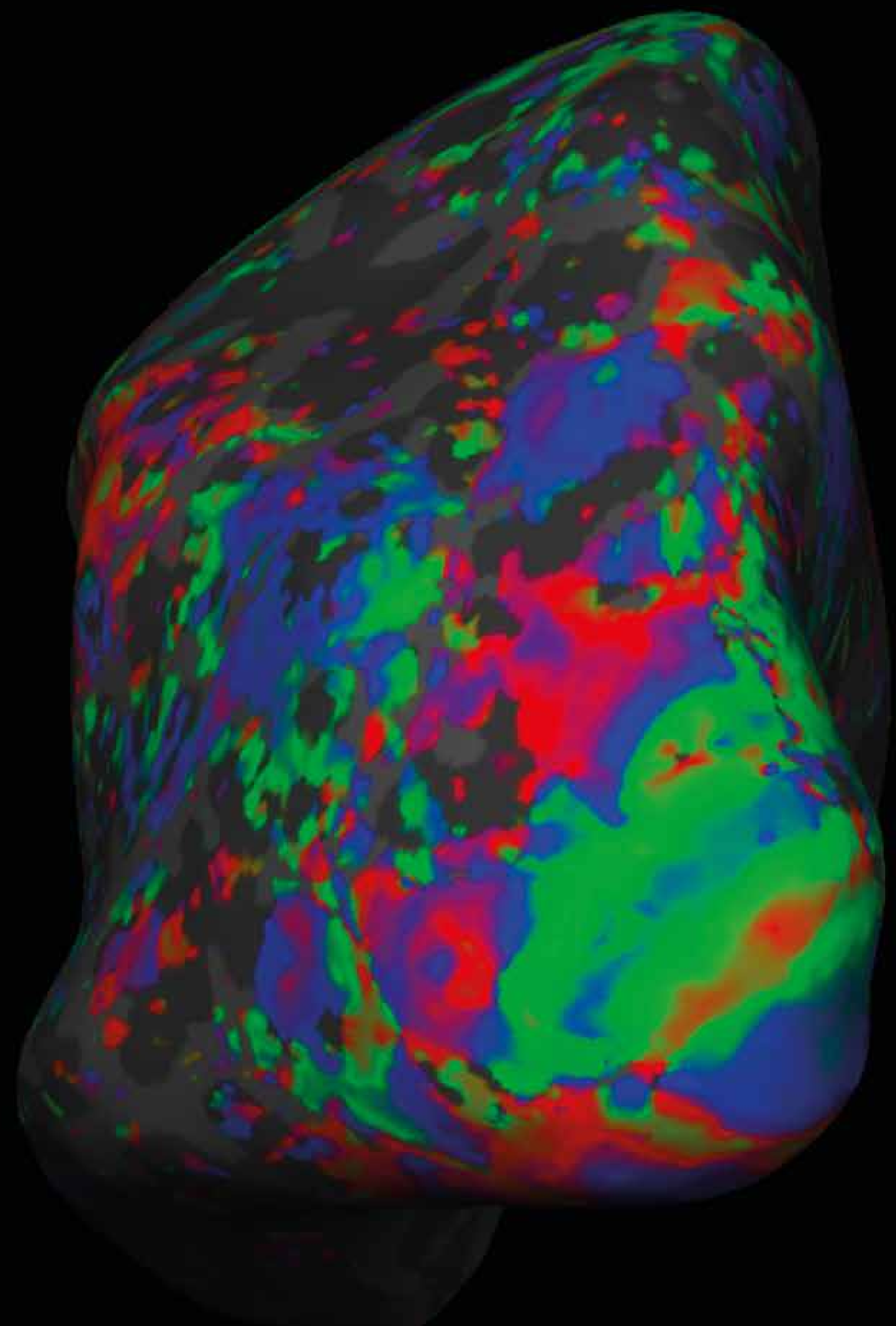
RADEMAKER LAB

THE VISUAL BRAIN AND HUMAN THOUGHT

Group leader Rosanne L. Rademaker / Postdoctoral fellow Michael J. Wolff Graduate students Giuliana Giorjiani, Maria Servetnik, Amit Rawal, Noa Krause, Nursima Ünver / Research assistant Lea Kerciku // CURRENT VISITORS // MD/PhD from Goethe Psychiatry on grant, co-supervised with Robert Bittner (1 year): Mishal Qubad / MD from Chulalongkorn University in Bangkok, Thailand (8 months): Kanathip Jongmekwamsuk // PAST VISITORS // Rotation students from the Max Planck School of Cognition: Meike Hettwer, Yulia Nurislamova / Visiting PhD student on EMBO scholarship, from the lab of Klaus Wimmer at the Centre de Recerca Matemàtica in Barcelona (2 months): Nicolás Pollán-Hauer / Visiting scholar and collaborator from Chulalongkorn University (2x one month): Chaipat Chunharas Students from the Interdisciplinary Neuroscience program at Goethe University doing a module (6 weeks) in our lab: 5 / Interns from other German schools (Würzburg, Marburg, Frankfurt, Darmstadt): 4 (as of December 2023)

“We study human perception and cognition using behavioral, computational, and neuroimaging approaches.”

The **RADEMAKER LAB** was established in July 2021. Our work is based on the premise that during everyday life, we constantly move our gaze and bodies around in a non-stationary environment, while simultaneously having a myriad of thoughts. To successfully navigate such a world, abound with concurrent sensory inputs and cognitive demands, we require a robust "central workspace" of the mind. After all, if we could not stably retain or manipulate relevant information inside our mind during ongoing sensory processing, many cognitive operations would break down. In our lab, we use quantitative and neuro-imaging techniques to formally link human behavioral and neural measures, looking primarily at the human visual cortex as a model system. In this way, we test theories of human cognition using working memory as a window into this central question about the nature of human thought – this "stream of consciousness" that unremittingly flows through our mind.



Maps of the visual field in the human brain (here: a left hemisphere, digitally rendered and inflated)

PhD student Maria getting one of our interns started with programming – a central skill for anyone passing through the lab.

A good lab atmosphere helps us learn faster, makes science more rigorous, *and ensures we show up for each other.*

Our lab launched amid the rocky circumstances of 2021, in a time still characterized by lockdowns and pandemic-related restrictions. But this moment harbored a hidden opportunity, giving pause to think deeply not only about the *research goals* and *questions* to delve into as a fledgling lab, but also about the *social context* in which we want to do that research – *together*.

From the first two graduate students who started that summer, to the complete research team of today, the idea of being stronger and smarter together has remained our guiding principle. Our lab's mission is to cultivate a collaborative environment where critical questions can always be asked, and where we do cutting-edge science that is also allowed to fail.

Over the lab's recent lifespan, and despite ample organizational challenges, we now have multiple setups running to conduct behavioral (psychophysics), functional magnetic resonance imaging (fMRI), and Magnetoencephalography (MEG) experiments. With local support, we recently pushed for a high-quality eye tracking system at the MRI scanner, and data collection is in full swing with new scans acquired every week. We can ramp up to our full potential by mid next year, after our current 3T scanner is relocated, and the decommissioned second 3T fMRI scanner is replaced. By next year we should also have a subject recruitment system available, making it easier to find what is perhaps our most valuable resource: the human participants who generously allow us to take a small peek into their minds (using only non-invasive methods, of course).

Two years into this eventful scientific journey, we are beginning to make some headway on our primary goal: to find ever more rigorous and principled ways to develop and test theories that relate human behavior to brain function, and to deepen the understanding of quantitative principles that govern brain functioning. Our approach is tailored to the questions we care about, ranging from mechanistic models to describe sensory system functioning, to considerations of everyday goals and how they shape human cognition. As a window into the human mind, our core focus is working memory – a central workspace for holding and manipulating moment-to-moment thoughts and mental images. Rather than the notion of a simple neural correlate (e.g., "where in the brain is working memory?") we are interested in a functional perspective (e.g., "how is working memory implemented to achieve goals?"). Such a functional system must be highly flexible, as goals may change rapidly in an exceedingly non-stationary environment in which we constantly move our gaze and bodies. Representations may need to be flexibly reformatted based

The whole lab at the Vision Sciences Society in Florida, presenting our very first projects.

RADEMAKER LAB

on such changes in the environment. In addition to flexibility, this same dynamic environment also demands robustness from the system. After all, if visual information could not be stably retained across a myriad of new retinal inputs, many cognitive operations would break down.

With a profoundly curious and determined research team, we're constantly deepening our understanding of these core capacities of human cognition. Thus far, with six independent conference presentations under our belt and one paper under review, the lab is well on its way to have a unique impact on the field of cognitive computational neuroscience. A subset of research lines and projects to highlight this contribution are described in more detail next.

A mechanistic understanding of human visual cortex during visual working memory

Striate cortex (V1) is the first cortical entry-point for visual input in the brain, but we also know that visual working memories can be decoded from this part of the brain. With eyes open, in a world teeming with visual inputs, how and why would the brain recruit V1 to also represent memories?

→ Rademaker, R.L., Chunharas, C., & Serences, J.T. (2019). **Coexisting representations of sensory and mnemonic information in human visual cortex.** *Nature Neuroscience*, 22:1336–44.

→ Iamshchinina, P., Christophel, T.B., Gayet, S., & Rademaker, R.L. (2021). **Essential considerations for exploring visual working memory storage in the human brain.** *Visual Cognition*, 29(7), 425–36.

In work done not long before the lab's inauguration, a surprising discovery was made: Neural population codes in V1 can support internally maintained visual representations alongside behaviorally irrelevant sensory inputs from the external environment. This discovery was made using mechanistic models of neural computation in combination with fMRI – a neuroimaging technique that can measure large swaths of cortex simultaneously. Because neural activity is noisy, large-scale measures of neural populations can be especially powerful to harness information from neurons with widely varying levels of activity. Through multivariate techniques (i.e., encoding and decoding models), representations in the brain can be tracked by measuring brain activity over many measurement "units" (3D voxels in fMRI; but this can be extended to any technique measuring multiple units). In this manner, remembered and perceived visual information were both decoded from activity patterns in visual cortex, highlighting the importance of an integrative methodological approach that relates computational models and neuroimaging techniques.

→ Rademaker, R.L & Serences, J.T. (2023). **Manipulating attentional priority creates a trade-off between memory and sensory representations in human visual cortex.** Conference talk, European Conference on Visual Perception.

This prior work provided an important starting point for showing how incoming sensory information and mnemonic information coexist in primary visual cortex. But what if sensory inputs cannot be ignored? For example, you might want to remember the face of someone you just met while engaging in a conversation with a close friend. We extended our previous findings with a new fMRI experiment looking at such multi-tasking in visual cortex. We found that the more attention is paid to sensory inputs, the better that sensory input is represented. On the flipside, concurrently remembered representations suffer when attention gets redirected to the external world. This suggests a limit on the computations carried out by sensory cortex, and implies a trade-off between competing top-down demands in this part of the brain.

It is perhaps not surprising that scientists who study the visual system enjoy visualising their thoughts on the white board.

On the one hand, it makes sense to recruit a cortical area, specialized to process visual inputs, to also maintain internally generated visual representations (an idea commonly known as "sensory recruitment theory"). On the other hand, co-opting cortical real-estate that is vital to basic perception presents a bit of a conundrum, because how do keep our perception of external reality apart from images that we hold in mind? Indeed, in order not to hallucinate, images should be represented differently depending on whether they are being perceived or held in memory – the former being driven by inputs from the environment, the latter being an internally maintained state. Given an abundance of evidence showing visual cortical involvement in healthy humans during visual working memory, what we need to understand first is how perception and working memory are different. It is possible that memories are simply noisier versions of perceptual input. Alternatively, memory representations may differ from perception in a fundamental way. For example, we have previously alluded to the possibility that working memory representations might be "abstracted away" from a purely sensory-driven format, with storage relying on more stable and lower dimensional representations.

→ Adam, K.C.S., Rademaker, R.L., & Serences, J.T. (2022). **Evidence for, and challenges to, sensory recruitment models of visual working memory.** *Routledge book on Visual Memory*, Chapter 1

RADEMAKER LAB

It's worth taking a moment to unpack the idea of abstraction. At its very core, the brain is an abstraction machine, constantly transforming physical quantities from the outer world into quantities for our inner world. More concretely, what we sense from our outer world are things like acoustic waves (sounds), photons (light), pressure (touch), etc. In the brain, various aspects of these quantities are represented in changes between neuronal connections, which in turn give rise to something highly abstract such as a concept or an experience. Through this abstraction, our very own reality is created. In the case of visual perception, the cortical arrangement in early sensory areas follows to a large extent the physical arrangement, representing the external world in a map-like fashion (called "retinotopy"). But the mind is capable of far more complex abstractions, and one can even argue that such abstractions are imperative for distilling those things that matter for our survival, from a myriad of different sensory inputs that matter less or not at all. By closely looking at the transformation that happens between images that are directly perceived and images that are temporarily moved into our mind's eye, we may capture the formation of mental abstractions – in human visual cortex.

In the very first study under review from our lab, we squarely address the question of how perception and memory differ in the visual brain by examining the "representational geometry" in visual cortex while people looked at, or remembered, different orientations (Fig. 1a). The geometry is obtained by correlating patterns of responses evoked by all possible orientations (a method known as "Representational Similarity Analysis", or RSA; Fig. 1b). Using the geometry gives us a lower-dimensional format of representation that is invariant to changes in underlying response patterns (unlike encoding or decoding models), getting directly at the heart of visual working memory abstraction.

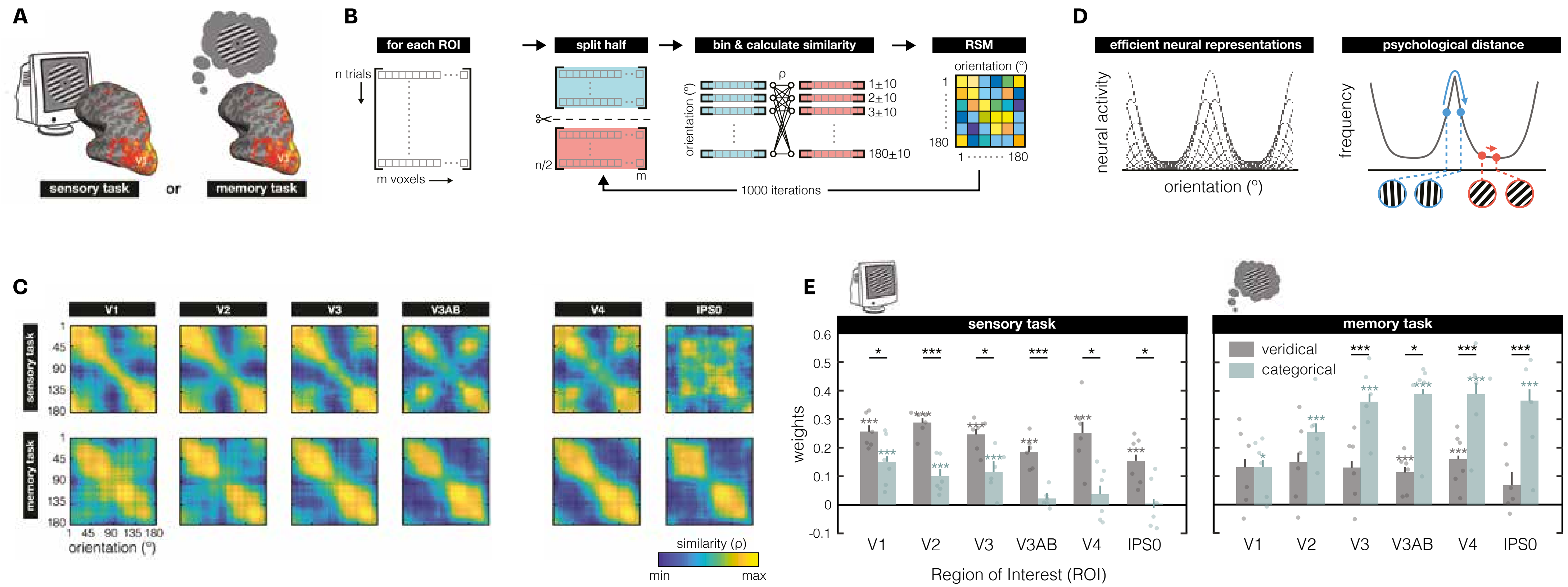
First, we provide clear evidence that the representational geometry is strikingly different between perception and working memory throughout retinotopic cortex (Figure 1c). This geometrical differentiation increases in more anterior visual regions (such as parietal cortex) known for their top-down signaling during working memory. Second, we provide evidence for a novel and unexpected form of information coding in visual cortex by showing that working memory representations are not merely abstracted, but they are categorized based on the input statistics (Fig. 1d,e) from the natural environment (i.e., inhomogeneities in the frequency with which different orientations are present in the natural world).

→ Chunharas, C., Hettwer, M.D., Wolff, M.J., & Rademaker, R.L. (under review). **A gradual transition from veridical to categorical representations along the visual hierarchy during working memory, but not perception.** *bioRxiv*.

→ Wolff, M.J. & Rademaker, R.L. (2023). **Neural representations of orientation reflect the oblique effect during perception, and repulsion bias during working memory.** *Journal of Vision abstract*, 23(9), 5849.

This work shows that visual cortex categorizes continuously varying visual inputs (such as orientation) into a stable and abstract format during working memory maintenance. Moreover, with the input statistics in hand, our model can predict both sensory and working memory geometry. This provides a potentially powerful approach for a wide range of stimuli beyond simple visual features and circumvents the reliance on a map-like organization. The models generated from the input statistics can be applied in an entirely agnostic manner to the whole brain using various measurement techniques, and in various species. Thus, these findings shed light on fundamental differences in the representational geometry between perception and working memory, and propose a candidate canonical mechanism for supporting abstraction based on the statistics of the environment.

Figure 1: (A) Human participants in the fMRI scanner either directly viewed images of oriented lines for 9 seconds at a time (left) or held the orientation in mind for 13 seconds (right), while we measured patterns of activity from their visual cortex, including area V1. **(B)** To examine orientation representations during perception and memory, we performed a Representational Similarity Analysis (RSA). In each Region of Interest (ROI), and for each participant, we employ a "split-half" procedure. This means we randomly split our trials in half, and for each half of trials we average the voxel patterns for each orientation shown or remembered (±10°). The pattern similarity (a correlation) is calculated between every orientation in one split of the data, and every other orientation in the other split, resulting in a 180×180 degree representational similarity matrix (RSM). This procedure is repeated 1000 times, and all RSMs are averaged to yield the final matrix, showing the representational geometry. **(C)** The representational geometry during perception (top row) looks more like a diagonal line, while the geometry during working memory (bottom row) looks more like two squares. There are also changes from earlier (V1) to later (IPS) visual areas. How do we quantify this? **(D)** The natural world has more horizontal and vertical ("cardinals") orientations in it than those in between ("obliques"). We start from this uneven probability distribution over orientation, and model what fMRI responses might look like when assuming that (on the left) the brain uses a veridical way to represent orientations (modeled by a bank of orientation filters), or assuming that (on the right) the brain categorizes orientations based on how different they appear in a more experiential sense (using a "psychological distance" measure). **(E)** During perception, the veridical model does a generally better job at explaining the data, but during working memory the representational geometry becomes increasingly more categorical along the visual hierarchy.



RADEMAKER LAB

Contextualizing the memory code

We tend to hold things in mind for good reasons. We may hold a number in mind to find our gate at the airport, or to punch it into our phone. Either way, we use memory contents in a goal-directed manner. Behavioral context can impose specific storage requirements. How do different contexts impact representation?

→ Henderson, M.M., Rademaker, R.L., & Serences, J.T. (2022). **Flexible utilization of spatial- and motor-based codes for the storage of visuo-spatial information.** *eLife*, 11, e75688.

Prior studies on working memory have typically focused on the mechanisms underlying passive storage during a delay phase and taught us that memory maintenance can be supported by sustained activity in frontal and parietal brain regions, and by involvement of early sensory cortices where response patterns reflect mnemonic contents. While such inquiries into mechanisms of passive storage have been fruitful, stored information is ultimately used to guide our *interactions* with the world and to generate adequate behavioral responses. We've already shown that representational formats in visual cortex can change between perception and memory, but there are numerous other contexts under which reformatting mental contents may be beneficial – behavioral goals being one such context. For example, from past work we know that how people ultimately have to report their memory can matter a great deal, suggesting that behavioral requirements may co-determine the format and locus of working memory representations.

If there's an image in mind (let's say, the image of my keys), there's generally also a goal in mind ("Where the heck are my keys, I cannot be late again, I must find my keys, I must frantically rummage through the mess on my desk"). Active and ongoing behavior can impact how a memory is represented. An intriguing and incidental finding showed an active manipulation of a recall probe yielding exceptionally high levels of memory decoding in early visual cortex. Higher decoding, in fact, than during passive perception of a full-contrast stimulus. Not only does this raise questions about what happens during closed-loop visuo-motor interactions when people report their memory, it also circles us back to the role of V1 during visual working memory. In a new fMRI study from our lab, we are now starting to disentangle the contributions of actively matching remembered contents to ongoing visual inputs (e.g., "Are those keys the keys I am looking for?"), making visual decisions (e.g., "I don't think those keys match"), and the influence of motor output during recall (e.g., "let me align these keys to make them match"). Of course, our participants do not look for their keys, but remember simplified orientation stimuli. We manipulate the extent to which motor engagement and active visual comparisons are required during recall and replicate the previous finding that closed-loop visuo-motor interactions during recall yield

The notion that *"I must frantically search for my keys and ransack my entire desk"* is a real daily inspiration.

PhD student Giuliana getting a participant ready for an fMRI experiment.

RADEMAKER LAB

By abstracting sensory information in our minds, *we shape our own unique reality.*

Noa during her MSc thesis work (before starting as a PhD student), getting our lab up and ready for MEG recordings.

very high levels of orientation decoding in early visual cortices. We furthermore show that this likely depends on visual matching, and not on motor engagement. However, we also show that a mental matching operation alone is not sufficient to boost representations in early visual cortex. So far, this provides us with new insight into how our memories are put to work during the (inter-)action with our external world, both via actions made of our own volition, or via actions that we keep track of, in our environment. It also hints at the role of V1, earmarking it as a possible site for active comparison between the external visual environment, and internally maintained images.

→ Chunharas, C., Rademaker, R.L., Brady, T.F., & Serences, J.T. (2022). **Adaptive distortions in visual working memory.** *Journal of Experimental Psychology*: General, 151(10): 2300-23.

We investigate this intimate link between behavioral context and mental representation via various other avenues as well. Importantly, what we mean by context here is *anything* in the environment that can provide a framework, or scaffolding, for an item held in mind. In a highly simplified case, if I ask you to remember two colored dots, each dot provides a "context" for the other. If the two colors are very similar, you may average them together, but if they are dissimilar, you may juxtapose them and exaggerate their difference. You probably take this "context" into account in your response because it helps stabilize your memory. An equally implicit but rather ubiquitous context is the spatial reference frames in which we represent the world around us. Visual objects are anchored to a real-world reference frame – a tall building remains upright even when you tilt your head. However, the projection of that building in terms of the retinal reference frame changes from a vertical to a diagonal orientation.

→ Servetnik, M.V., Hauer, N.P., Wolff, M.J., Chunharas, C., & Rademaker, R.L. (2023). **Visual representations shift from a retinal to a real-world reference frame during visual working memory.** *Journal of Vision abstract*, 23(9), 4809.

For a unified percept of your visual surroundings, integrating visual information over multiple reference frames is critical. We test how this happens by decoding visual orientation from electroencephalography (EEG) signals in both a head-centered and a world-centered reference frame. Presumably, early sensory cortex represents perceptual inputs in a retinal reference frame. But what happens when this visual information is now relayed to working memory? We can investigate which reference frame the brain uses to represent visual information by having people tilt their head, which dissociates retinal and real-world reference frames. Critically, we rely on multivariate decoding and cross-generalization: If remembered orientations are represented in a retinal reference frame, a decoder trained on data from when the head is upright would predict a 45° offset in decoded orientation when tested on head-tilted trials (after all, a vertical building becomes diagonal on the retina after head-tilt). Conversely, if mnemonic representations are anchored to the real world, no such offset should be observed. Via this handy trick, we revealed that perceptual representations exist in an approximately retinal coordinate frame, but approximate a real-world coordinate frame during working memory. These results suggest that visual representations can dynamically undergo a reference frame transformation that likely occurs during the transition from perception to working memory.

RADEMAKER LAB

Everyday life as a backdrop to study the mind

We perceive, think, and act in a dynamic world. That means that things around us move, we ourselves move, and our plans may go awry … In this explorative arm of the lab, we link our mechanistic understanding of mental representation to real-world scenarios in various new ways.

As the cliché goes, the world around us does not stand still. Yes, maybe things like buildings and mountains are rather stationary, but things like cars and frisbees often are not. Imagine catching a frisbee during a friendly game in the park. You need to estimate the frisbee's speed (and remember that speed in case the frisbee briefly moves behind a bush) and predict where the frisbee will be next in order for you to intercept it. This example is meant to show how in addition to mentally simulating the past (i.e., memory), we also need mental simulations for the future (i.e., prediction). Furthermore, extrapolation can happen over various time scales, because as your frisbee approaches it may be 10 seconds away, or just a few milliseconds.

→ Giorjiani , G.M. & Rademaker, R.L. (2023). **Speed estimation for spatiotemporally bound and unbound motion stimuli.** *Journal of Vision abstract*, 23(9), 5260.

→ Rawal, A. & Rademaker, R.L. (2023). **Naturalistic visual input during the working memory delay reduces microsaccades but increases recall error.** *Journal of Vision abstract*, 23(9), 5829.

In our lab, we've started investigating how various delays may impact people's estimate of speed, and replicated previous work showing that slower speeds are better remembered than faster speeds. Another interesting property about objects in motion is how they link space and time. We show how objects that are spatially bound (e.g., a frisbee or a ball) are better remembered that unbound objects (e.g., falling rain or moving dots), presumably because to estimate the speed of a bound object, the distance it traveled can be taken into account. How can storage of information about bound object dynamics be transformed into predictions about future positions across space and time? We're currently exploring this in a paradigm where items move in and out from occlusion. Psychophysical data show us that occlusions impact speed estimation, and we have preliminary fMRI evidence to suggest that spatiotemporal predictions involve early visual areas including area V1. Visual mental simulations, it seems, may draw upon a similar cortical architecture as perception and working memory, which we plan to investigate further using a deep oscillatory model.

The world may not stand still, but neither do we. We already highlighted how we generally depend on our working memory in the presence of ongoing visual input, and even attention toward visual input. But the problem gets even more dire when we take into account that in everyday life, visual input changes with every eye movement we make (Figure 2a). What is the impact of ongoing retinal input on internally maintained information, but also, how might the things we hold in mind impact our visual exploration? To gain better traction on these questions, the lab has been steadily expanding its scientific repertoire - adding new eye tracking techniques such as pupillometry, microsaccade analyses, and scanpath analyses using graph theory and deep neural networks. We are currently pioneering how visual input statistics, such as temporal and spatial regularities imposed by naturally occurring eye movements, affect recall performance. The idea being that, in order to robustly hold information in mind, our brains must have adapted to ignore visual inputs that conform to such everyday statistical regularities (but see Figure 2b). In turn, we discovered that recall performance, when split into the best and worst trials, is linked to small eye movements known as "microsaccades". Such microsaccades are believed to be involuntary and to happen outside of people's awareness, and seem to be suppressed when people are performing better (Figure 2c). Taking this one step further, we looked at how memory contents may impact explicit and voluntary eye movements. Preliminary data show higher recall errors for natural images (Figure 2d), that visual exploration is reduced with mental load, and that there may not be a gaze bias towards information that matches the contents of memory (Figure 2e). We're currently also looking at different saliency models to investigate the role played by image content.

With the vision of everyday life as an important backdrop for our work, we have started to explore contexts in which cognition may fail, and when neural processes go awry. Specifically, we have started to apply our computational approaches to psychiatric populations in collaboration with the the group of Robert Bittner at the Goethe University Psychiatry department. In one project, we look at how spatial working memory representations are affected in people with ADHD. Based on novel findings showing that visual acuity is associated with Schizophrenia resiliency, in another project we will measure how spatial receptive field properties in early visual cortex may play a role in this.

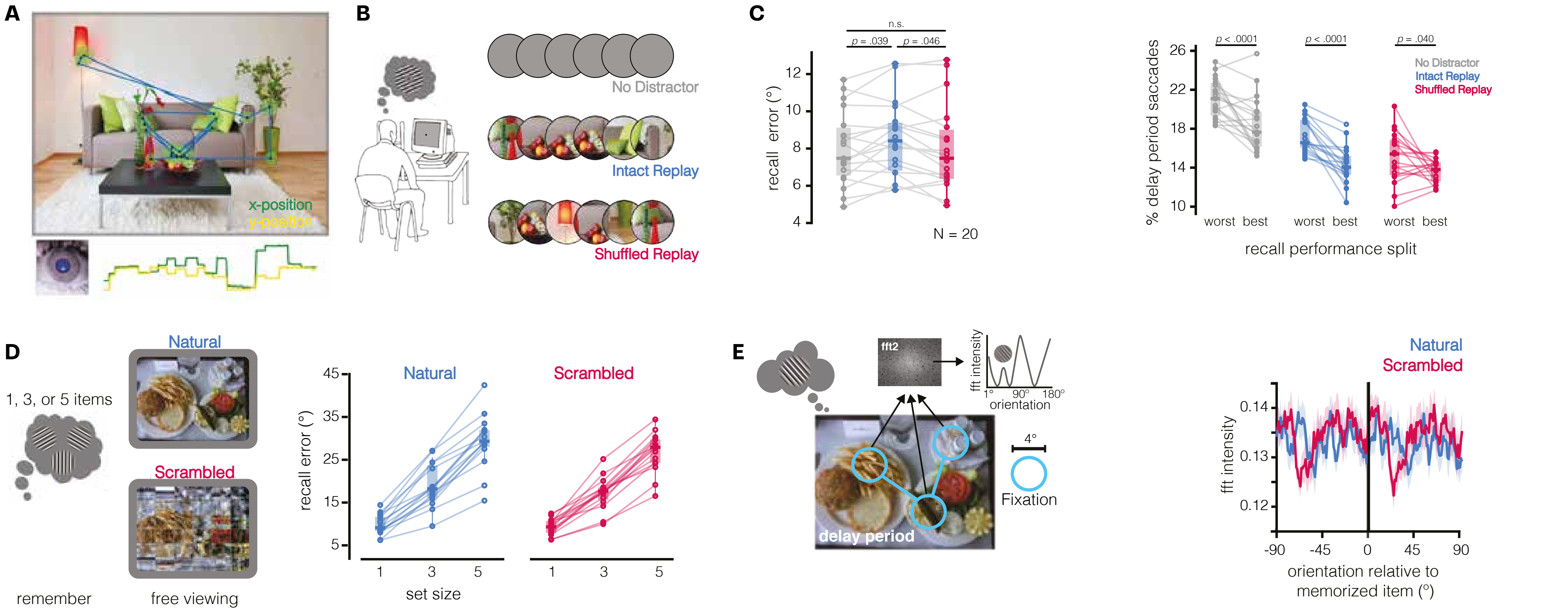


Figure 2: (A) By using an eye tracker while someone is looking at a picture shown on a computer screen (top), we can determine the x- and y-position of their eye (bottom), and reconstruct where they moved their gaze (overlaid on the picture in blue lines and green circles). **(B)** During everyday life, visual working memory happens while natural eye movements are ongoing. We play such natural visual input back to participants while they are otherwise engaged in a classical working memory task (i.e., remembering an orientation for subsequent recall while fixating throughout). **(C)** While we expected that intact replay of natural gaze behavior should be most easily ignored (as it matches the spatio-temporal structure of everyday inputs), this condition turned out to be most distracting, and negatively impacted recall performance (left). In turn, recall performance was also related to very small eye movements ("microsaccades") made by participants during the delay, with fewer of these involuntary microsaccades on trial where participants did better. **(D)** In another experiment from this series, participants were allowed to freely explore images while holding 1, 3, or 5 orientations in mind. Fourier phase-scrambled images were used to investigate how mnemonic contents impact visual exploration in scenes without semantics. In addition to a clear set size effect (higher recall error with more items in memory), we again observe that intact natural images are more distracting (higher recall error during exploration of natural compared to scrambled images). This may be due to the fact that visual exploration itself (either measured via scanpath length, or number of fixations) is more prevalent in natural images (not shown here). **(E)** Is the gaze of our participants biased towards low-level orientation information in the images that matches the orientation held in mind? We look at the fast-Fourier transform (fft) intensity across all possible orientations for those parts of the image where people fixated (within 4° diameter), to see if there may be more energy for the remembered orientation (left). However, in these preliminary data we do not yet observe a clear peak centered on the remembered orientation (right).

CONNECTOMICS OF NAVIGATION

Research Group Leader: Helene Schmidt, PhD / PhD students: Maria Corteze, Eleonora Grasso (as of September 2023)

This Otto Hahn Group was started in 11/2020 and is currently funded until 04/2024 with the possibility of an additional 2-year extension.

"Representation of space in the brain has been studied for decades. We want to fully resolve the underlying circuits."

SCHMIDT LAB The key goal of our lab is the acquisition and analysis of an unprecedented-scale neural circuit, which is at the core of our and other mammals' ability to navigate in the environment: the entorhinal - hippocampal circuitry. To achieve this we use state-of-the-art 3-dimensional Electron Microscopy and AI-based analysis technology. Since these techniques are strictly limited in imaging volume, we mainly focus on the brain of the Etruscan shrew, the smallest terrestrial mammal. For comparative study, we are also analyzing parts of this circuit step-by-step in mouse and rat, to ensure that our results will be interpretable in the evolutionary context. The start of the lab fell squarely into the COVID-19 pandemic, nevertheless the team was successful in setting up experiments, obtaining first proof-of-principle data and performing analyses. The main achievements are described below.

Glow discharging of a silicon wafer, in preparation of an EM experiment

Nerve cells (left screen) and the EM data (right screen) from which they were reconstructed

SCHMIDT LAB

Team discussion at the white board

Neuroscientists have been exploring the representation of space in the brain for decades, discovering a wide range of cell types representing different navigational features.

The two most prominent of these cell types were identified in the hippocampus and the medial entorhinal cortex: Place-modulated hippocampal neurons were found to be active only when an animal moves through a particular location in space (*"place cells"*). In the medial entorhinal cortex, cells were reported that respond in a periodic activity pattern as an animal moves through the environment (*"grid cells"*). Both brain regions were found to be highly interconnected, making it plausible to expect interactions between place and grid cells. Despite extensive anatomical and functional experiments, the *circuitry between grid and place cells*, and how they shape each other's activity, and the contribution of local and long-range inhibitory circuits, is *still unresolved* (Fig. 1).

With this, the goal of the Otto Hahn Group "Mapping of the entorhinal-hippocampal neuronal network" is to fully resolve the networks underlying spatial navigation tasks, in particular the interplay of neurons in the hippocampus and medial entorhinal cortex in mammals. The availability of cutting-edge methods for large-scale high-resolution imaging of neuronal circuits puts *the complete mapping of the entorhinal-hippocampal network* into reach. Increased throughput of these methods will also allow a comparative assessment of the navigational neuronal circuits across mammalian species - from mice to primates.

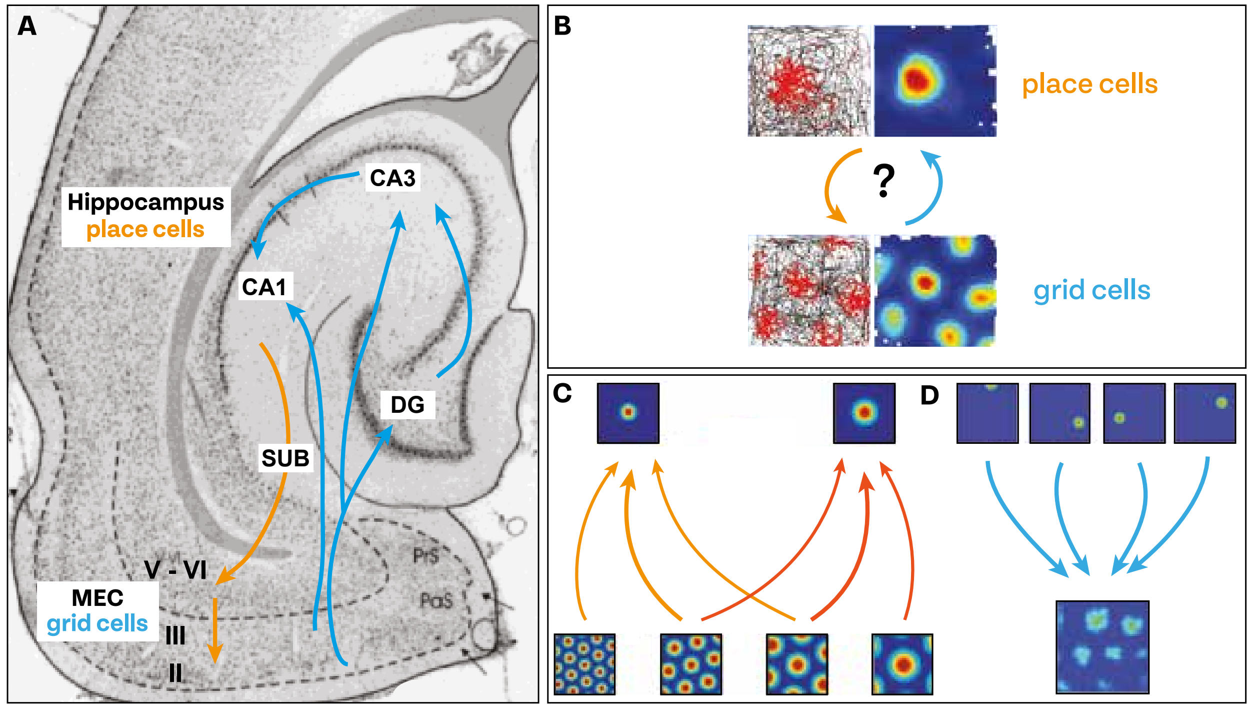


Figure 1: Do grid cells (medial entorhinal cortex) drive place cells (hippocampus CA1) or vice versa? (A) Horizontal section through the hippocampal formation and parahippocampal region of the rat brain illustrating the 'classical' view of the entorhinal-hippocampal loop: Direct (MEC layer III to CA1) and indirect (MEC layer II via trisynaptic projection) pathways to CA1 (blue) and feedback loop to MEC (orange). CA1-3, fields of Ammon's horn; DG, dentate gyrus, SUB, subiculum, MEC, medial entorhinal cortex. Adapted from (Witter et al. 2000). **(B)** Adapted from (Moser, Rowland, and Moser 2015). **(C)** Model showing how grid cells with different grid spacing and orientation but same spatial phase can be transformed to place cell firing. Adapted from (Solstad, Moser, and Einevoll 2006). **(D)** Model showing that grid cell firing fields could evolve from the convergence of multiple place cells with different spatial firing fields. Adapted from (Kropff and Treves 2008).

SCHMIDT LAB

Species choice for the first entorhinal-hippocampal 3D electron microscopy dataset

3D-electron microscopy (3D EM) based ultrastructural approaches have so far been limited to the study of local neuronal circuits, on a scale of a few 100 µm, and such technology allowed our first connectomic analysis of a piece of MEC in rat.

The recent enormous investment into methodological development, however, is enabling the acquisition of larger volumes. One key method for large-scale high-resolution mapping of neuronal circuits is a combination of an automated tape-collecting ultramicrotome (ATUM), with either TEM or a multibeam serial electron microscope (mSEM). With this approach, first petascale 3D EM datasets have been acquired. This means that datasets sized about 1-1.5mm on a side are beginning to be possible to acquire. But in the mouse or rat brain, not even a part of the hippocampus would fit into such a volume (Fig. 2).

When brain volume is of critical relevance, using particularly small species for investigation is a logical approach. In fact, the first full-brain connectome was obtained from the small worm C. elegans in the 1980s. To put the acquisition of the complete entorhinal/hippocampal circuit of a mammal in reach, we therefore decided to employ the possibilities of the Etruscan shrew (Suncus etruscus, the smallest terrestrial mammal). With a brain mass of about 60 mg, the Etruscan shrew possesses the smallest mammalian brain known. Its cortical thickness ranges from ~800 µm to as thin as 200 µm in cortices that were identified to correspond to the visual and entorhinal areas. Most importantly, the entire entorhinal-hippocampal circuit in fact fits into a bounding box of about 2 mm x 1.5 mm x 0.5 mm - while the same volume in rat or mouse would only provide a fraction of a part of the hippocampal circuit (Fig. 2).

→ Briggman, K. L., and D. D. Bock. 2012. **Volume electron microscopy for neuronal circuit reconstruction**, *Curr Opin Neurobiol*, 22: 154–61.

→ Schmidt, H., A. Gour, J. Straehle, K. M. Boergens, M. Brecht, and M. Helmstaedter. 2017. **Axonal synapse sorting in medial entorhinal cortex**, *Nature*, 549: 469–75.

→ Hayworth, K.J., N. Kasthuri, R. Schalek, and J.W. Lichtman. 2006. **Automating the Collection of Ultrathin Serial Sections for Large Volume TEM Reconstructions**, *Microsc Microanal*, 12 (Supp2): 86–87.

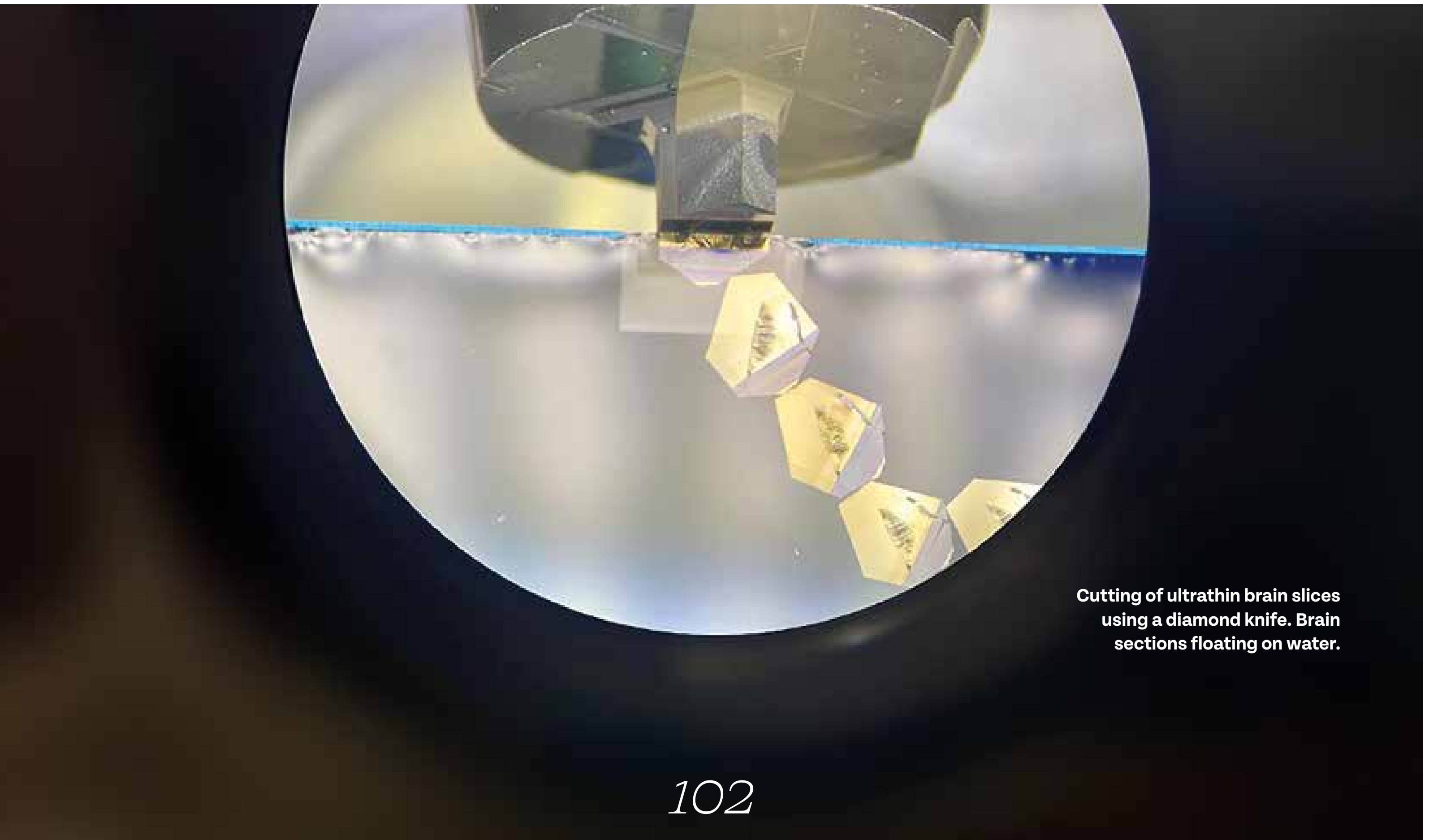
→ Kasthuri, N., K. J. Hayworth, D. R. Berger, R. L. Schalek, J. A. Conchello, S. Knowles-Barley, D. Lee, A. Vazquez-Reina, V. Kaynig, T. R. Jones, M. Roberts, J. L. Morgan, J. C. Tapia, H. S. Seung, W. G. Roncal, J. T. Vogelstein, R. Burns, D. L. Sussman, C. E. Priebe, H. Pfister, and J. W. Lichtman. 2015. **Saturated Reconstruction of a Volume of Neocortex**, *Cell*, 162: 648–61.

→ Eberle, A. L., and D. Zeidler. 2018. **Multi-Beam Scanning Electron Microscopy for High-Throughput Imaging in Connectomics Research**, *Front Neuroanat*, 12: 112.

→ Loomba, S., J. Straehle, V. Gangadharan, N. Heike, A. Khalifa, A. Motta, N. Ju, M. Sievers, J. Gempt, H. S. Meyer, and M. Helmstaedter. 2022. **Connectomic comparison of mouse and human cortex**, *Science*, 377: eabo0924.

→ Fons R, Stephan H, Baron G. 1984. **Brains of Soricidae I. Encephalization and macromorphology, with special refer-ence to Suncus etruscus**. *Z Zool Syst Evolutforsch* 22:145–158.

→ Naumann RK, Anjum F, Roth-Alpermann C, Brecht M. 2012. **Cytoarchitecture, areas, and neuron numbers of the Etruscan shrew cortex.** *J Comp Neurol*. 520(11): 2512-30.



Cutting of ultrathin brain slices using a diamond knife. Brain sections floating on water.

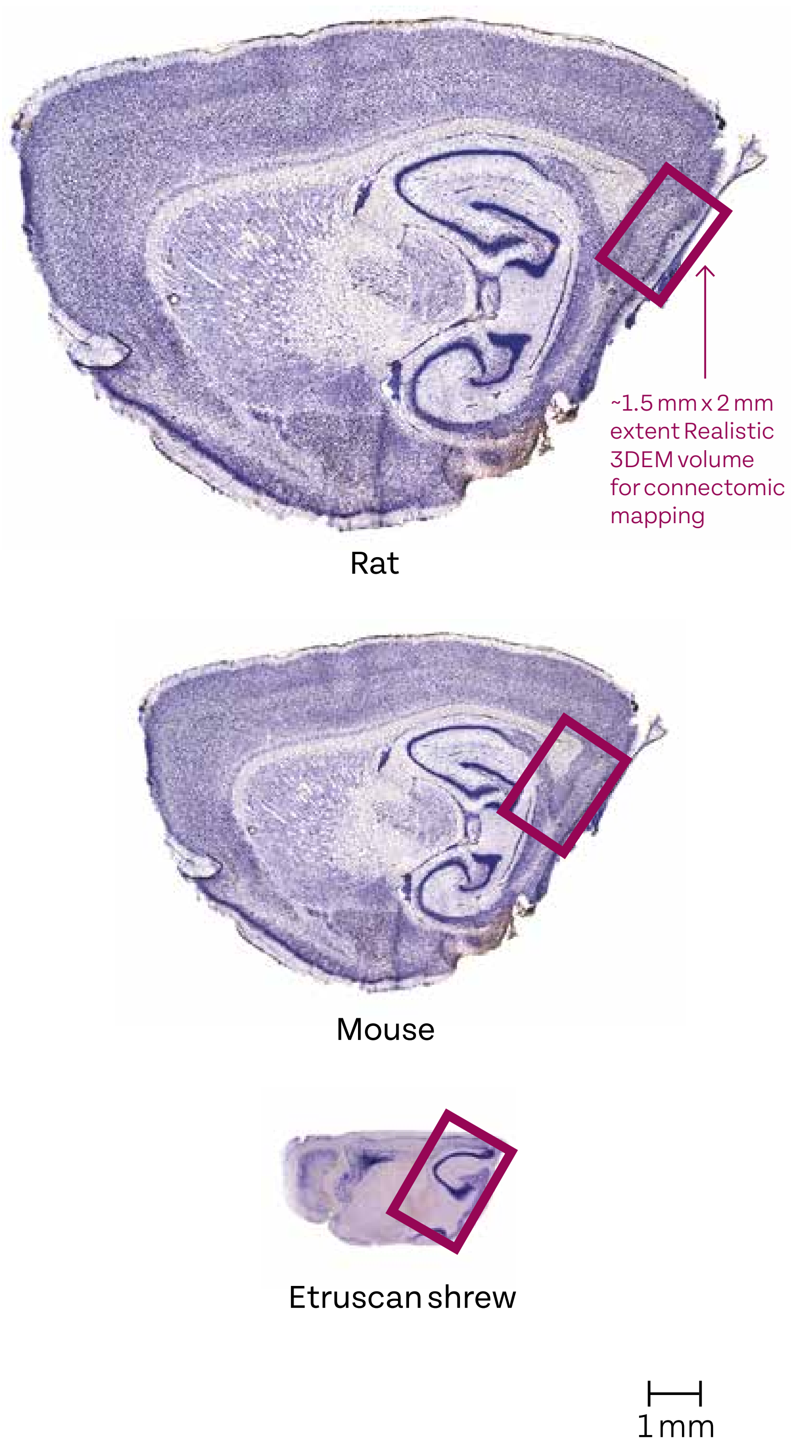


Figure 2: Comparison of the entorhinal-hippocampal circuit size across species. While the brain of rats and mice is too large to obtain a 3D EM dataset of the entire hippocampus and entorhinal area, in the Etruscan shrew (smallest terrestrial mammal) the whole circuit fits into a volume suitable for 3D EM data acquisition. An exemplary field of view for data acquisition of 1.5 mm x 2 mm shown in orange.

SCHMIDT LAB

Cutting device (ultramicrotome) allowing us to prepare brain slices as thin as 35 nm (more than a thousand times thinner than a human hair).

Parallel mapping of parts of the navigation circuit in mouse and shrew

While the key goal of our small laboratory is the complete navigational circuit mapping in the shrew, we are in the process of obtaining piecewise hippocampal and entorhinal circuits in larger mammals, as well, so we will be prepared to map possible evolutionary variation also onto the widely established mouse model system. Moreover, even these “pieces” of the circuit have still not been connectomically mapped. In fact, we have already acquired a full MEC dataset of mouse, which we are currently analyzing, and obtained the first connectomic analysis of CA3. So even these “steps” towards our main goal are major projects of their own, which we try to manage in parallel.

In the following the status of each subproject is described.

A – Connectomic analysis of the *mouse entorhinal cortex* (in collaboration with MPI for Brain Research)

As an intermediate step to our goal to understand the entorhinal-hippocampal network, we have acquired and aligned a millimetre-scale 3D EM dataset of the mouse medial entorhinal cortex, ready to map the circuitry at sufficient scale to unravel the entire L2, L3 and deep layer circuitry in MEC, as well as putative head direction input (from Parasubiculum) to MEC. Models about the network at the core of grid cell computations have been proposed for decades, but a final resolution of the implemented network model is still missing.

B – Connectomic analysis of mouse CA3

The hippocampus has been extensively studied for its role in learning and memory. Over decades, a large range of theoretical models of hippocampal function have been proposed. However, the validity of key model assumptions at synaptic level was not known. In particular, a recent study challenged the long-held assumption that the CA3 was a highly recurrent network with high synaptic connectivity, reporting only a very sparse connectivity rate of less than 1%.

→ Guzman, S. J., A. Schlogl, M. Frotscher, and P. Jonas. 2016. **Synaptic mechanisms of pattern completion in the hippocampal CA3 network**, *Science*, 353: 1117-23.

In a collaboration with the Schmitz lab (Charité, Berlin) and Kempter lab (Humboldt Universitaet zu Berlin), we therefore analyzed the recurrent connectivity of hippocampus area CA3 pyramidal cells in mouse. The hippocampus is a particularly challenging area for EM data acquisition, as it comprises very densely packed cell bodies that make en-bloc staining, ultrathin cutting and imaging much more difficult. Nevertheless, we were able to acquire a first high-resolution 3D EM dataset of the hippocampus (Fig. 3A) spanning the entire CA3 region, containing ~1000 pyramidal somata (Fig. 3B).

In our data, we found a much stronger connectivity between excitatory cells than previously reported, providing evidence for a highly interconnected CA3 network. The revised paper draft (accompanied by electrophysiological recordings from the Schmitz lab and computational modeling from the Kempter lab) is currently in press.

→ Sammons, R.P., M.Vezir, L. Moreno-Velasquez, G. Cano, M. Orlando, M. Sievers, E. Grasso, V. Metodieva, R. Kempter, H. Schmidt, and D. Schmidtz. **Structure and function of the hippocampal CA3 module**. In press.

SCHMIDT LAB

C – Connectomic analysis of mouse CA1

A further intermediate step to our goal to understand the navigational circuit in mammals, is the connectivity of hippocampal region CA1. We acquired an ATUM cut ultrathin series of 180 µm of the entire CA1 area (field of view: 0.8 mm x 1.3 mm) in mouse and are currently preparing the big data for analysis.

D – Local neuropil and circuit properties in *Etruscan shrew* cortex

When choosing a non-standard species, it is critical to observe possible fundamental differences in microscopic architecture that need to be taken into account for the future full-circuit analysis. For this, we have conducted proof-of-principle 3D EM experiments (small field of view serial block-face EM, SBEM) of shrew cortical tissue.

E – Connectomic analysis of the entire *shrew hippocampal-entorhinal system*

In order to reach our main goal of acquiring and analyzing data containing the whole hippocampal-entorhinal circuit, we have performed a number of proof-of-principle experiments (Fig. 4).

In iterations of shrew sample preparation, we determined the optimal way to orient our samples for ultrathin sectioning such that the z (cutting) dimension is minimized. We experimented with different shapes of the samples and studied their cuttability using ATUM. Further, we faced issues with obtaining good staining quality in shrew. While *en-bloc* staining protocols are available for whole mouse hemispheres, they are not transferable one-to-one to shrew. With the help of Dr. Kun Song, MPI for Brain Research, we were able to adjust the protocols and are currently running another round of shrew whole-brain staining. Each iteration takes about 3 months.

→ Song, K., Z. Feng, and M. Helmstaedter. 2023. **High-contrast en bloc staining of mouse whole-brain and human brain samples for EM-based connectomics,** *Nat Methods.*

"This is a major undertaking, which requires several methodological optimizations, and then long-term data acquisition and analysis. The Max-Planck Society and the Ernst Strüngmann Institute are ideal sites for such big-goal projects with a very ambitious outcome."

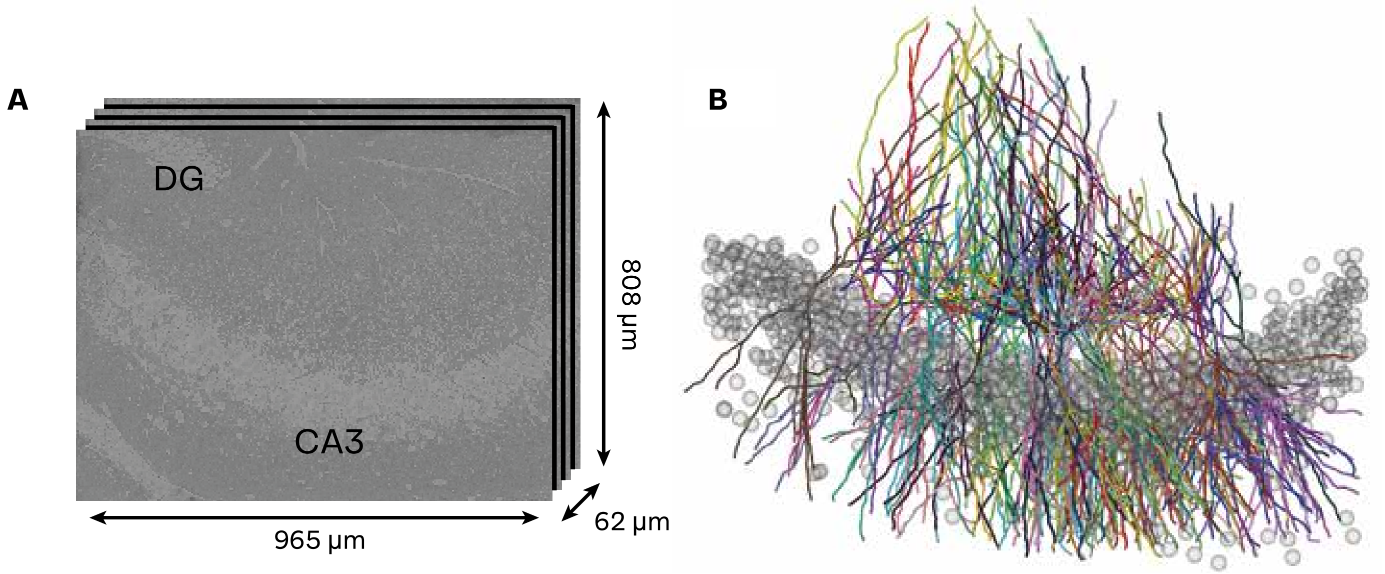


Figure 3: Structural connectivity analysis of CA3 pyramidal neurons using electron microscopy. (A) 3D EM dataset of area CA3 from a P31 mouse acquired using ATUM mSEM **(B)**, Dendritic reconstructions of 55 pyramidal cells out of 986 neurons (grey spheres).

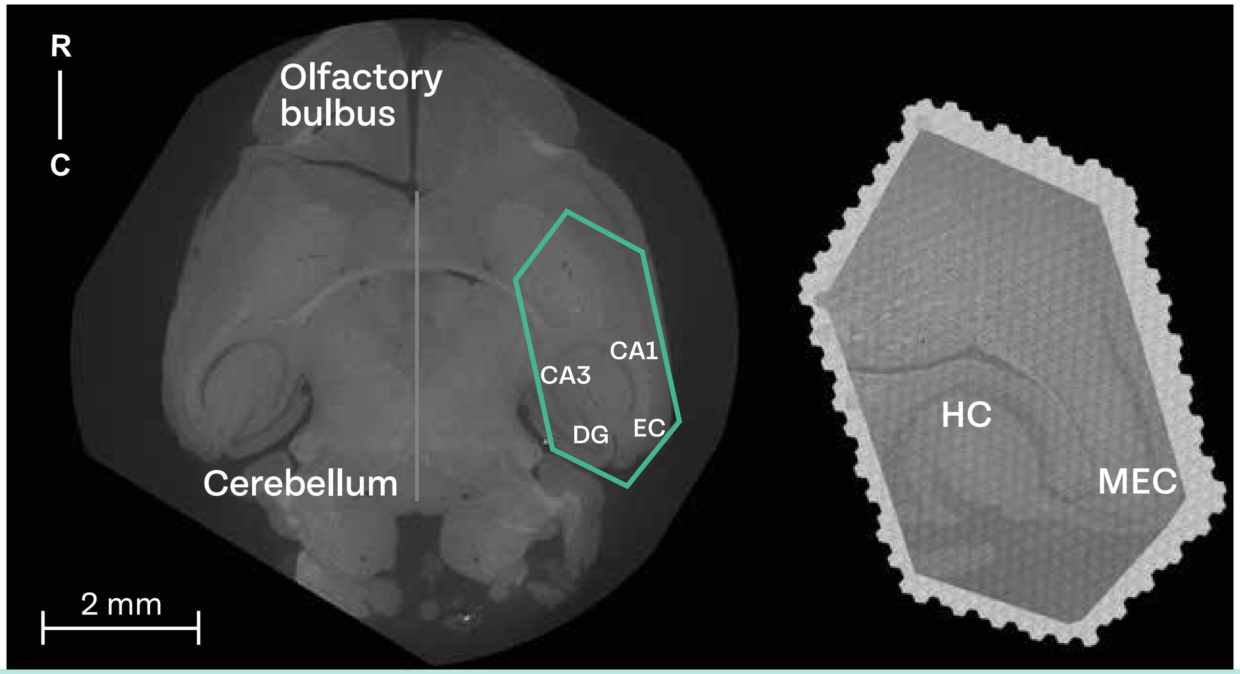


Figure 4: µCT of shrew brain (left), first electromicrograph of the hippocampus and entorhinal cortex in one section (right).

SINGER SENIOR RESEARCH GROUP

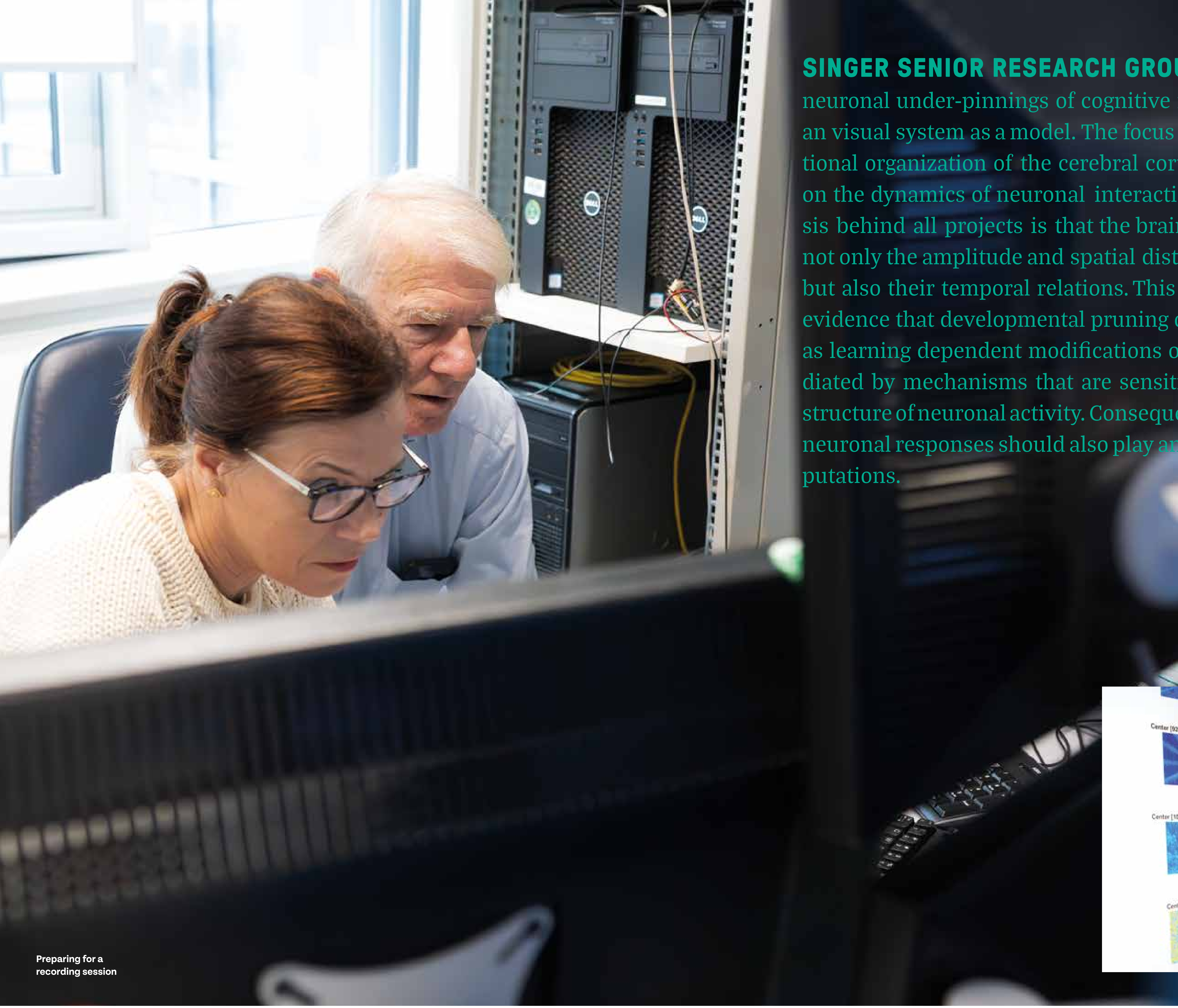
THE CEREBRAL CORTEX: A DYNAMIC SYSTEM

Principal Investigator Wolf Singer / Postdoc Felix Effenberger / PhD Students Pedro Carvalho, Igor Dubinin, Björn Mattes (Guest Student, part time) / Technical assistant Johanna Klon-Lipok / Past Postdoc Students, still collaborating Andreea Lazar (Zurich), Yiling Yang (Leuven), Nina Merkel (Frankfurt)

(as of December 31, 2023)

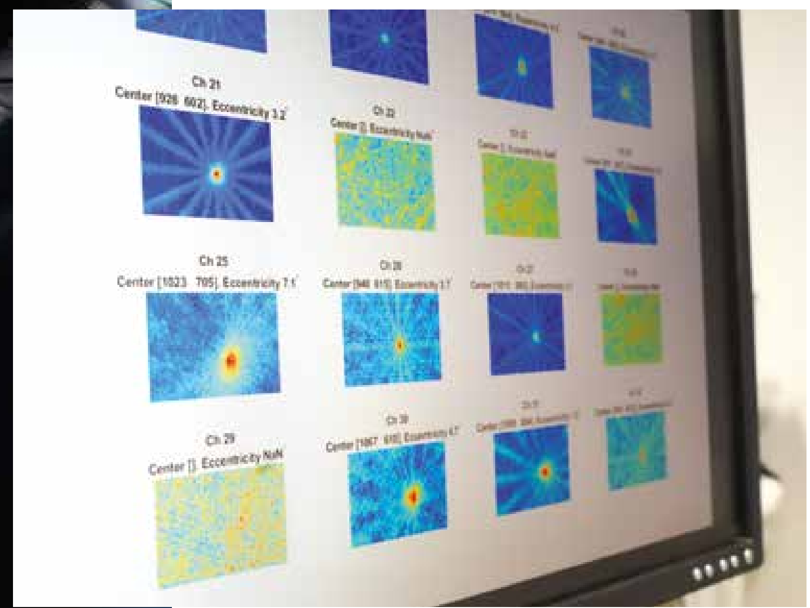
"The dynamics of recurrent networks resemble those of liquids."

SINGER SENIOR RESEARCH GROUP The Singer Lab explores the neuronal under-pinnings of cognitive functions, using the mammalian visual system as a model. The focus lies on the analysis of the functional organization of the cerebral cortex with a particular emphasis on the dynamics of neuronal interactions. The overarching hypothesis behind all projects is that the brain exploits for its computations not only the amplitude and spatial distribution of neuronal responses but also their temporal relations. This hypothesis is grounded on the evidence that developmental pruning of neuronal connections as well as learning dependent modifications of synaptic connections are mediated by mechanisms that are sensitive to the temporal correlation structure of neuronal activity. Consequently, temporal relations among neuronal responses should also play an important role in cortical computations.



Preparing for a recording session

Receptive fields of some of the simultaneously recorded neurons



SINGER SENIOR RESEARCH GROUP

In the visual cortex, neurons responding to features that often occur together, e.g. because they are characteristic for a particular object, become more strongly connected than neurons which get rarely activated at the same time. The reason is that the reciprocal connections between neurons are endowed with correlation sensitive synapses. Such correlation-based learning principles were postulated by D. Hebb and this principle is commonly referred to as "neurons that fire together, wire together". Temporal relations among neuronal responses are exploited to capture statistical regularities of the environment and to translate these correlations into the functional architecture of recurrent connections. In this way the brain builds an internal model of the world, reflected in so called priors.

→ Hebb, D.O., 1949. **The organization of behavior: A neuropsychological theory.**
→ Löwel, S. and Singer, W., 1992. **Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity.** *Science*, 255(5041)

The second indication for a functional role of temporal relations came from the serendipitous observation that neurons in the visual cortex tend to engage in highly synchronized oscillatory activity when activated by stimuli that match well with the priors stored in the architecture of the recurrent connections. These dynamical phenomena cannot easily be accounted for by serial feed forward processing but are a naturally emerging property of recurrent networks. Therefore, the lab concentrates on the analysis of the rich dynamics of recurrent networks to find out whether and if so, how the brain exploits the temporal dimension as a coding space for its computations.

→ Singer, W., 1999. **Neuronal synchrony: a versatile code for the definition of relations?** *Neuron*, 24(1)

→ Singer, W., 2021. **Recurrent dynamics in the cerebral cortex: Integration of sensory evidence with stored knowledge.** *Proceedings of the National Academy of Sciences*, 118(33)

In order to develop an intuition for the unique dynamics of recurrent networks and their potential to support complex computations, imagine a pond of water into which stones are thrown in a sequence at different locations (Fig. 1, left). Each impact will generate a wave that spreads over the water and whose origin, amplitude, and wave length reflects the site, the size, and the strength of the impact. After some time, the wave patterns will overlap and generate a complex, high-dimensional interference pattern that eventually fades. If one places several sensors into the pond that measure the amplitude, frequency and phase of the local oscillations, it is in most cases possible to reconstruct when and where the various impacts have occurred. The water "remembers" the impacts as long as the waves persist, and the interference pattern contains all the information required to reconstruct the series of events. Thus, the water performs several interesting computations. It transforms a stimulus into a stimulus specific oscillation, distributes information about the spatial and temporal properties of the stimulus over the whole medium, establishes relations between the spatial and temporal parameters of different events through interference, and transforms the low-dimensional sequence of stimuli into a high-dimensional dynamic pattern that is defined by the spatial distribution of the amplitude, the frequency and the phase of the oscillations. Due to fading memory and the high dimensionality of the dynamic landscape, the medium permits superposition and simultaneous representation of information about temporally segregated events. These are all very powerful computational operations that are exploited in numerous applications, and commonly referred to as "liquid" or "reservoir" computing. Note that these computations are analog, not digital, and that they are performed in the same medium that also serves as memory. Thus, there is no separation into memory and processing circuits as in conventional computers.

Storage, superposition and processing of information in high-dimensional dynamic state spaces

Interestingly, the dynamics of biological neuronal networks resemble in several aspects those of a pond of water (Fig. 1, right). Local activation of a node gives rise to spreading activity, so called travelling waves, that inform with some latency other nodes in the network and this reverberating activity keeps the trace of the stimulus alive for some time. However, in contrast to the waves in a pond, neuronal networks in the brain have an additional important property. In those networks, nodes are coupled through synaptic connections that can also mediate direct interactions between remote nodes and whose coupling strength is shaped by experience and found to be highly anisotropic (Fig. 2). As described above, the layout of these recurrent connections serves as a store for the internal model of the world. Hence, the stimulus-induced dynamics of natural networks do not only reflect the stimulus constellation but also the match between a particular stimulus constellation and stored priors, i.e. "knowledge". This allows recurrent networks to compare sensory signals with stored knowledge in a highly parallelized manner. Such a matching operation is essential for sensory processes because sensory signals tend to be sparse and ambiguous and require interpretation by a-priori knowledge, a process called predictive coding. In the lab, we pursue the hypothesis that this important step and a number of other fundamental operations, such as scene segmentation and pattern classification, are accomplished in the cerebral cortex by exploiting the unique dynamics of recurrent networks. Guided by this working hypothesis, a number of experimentally testable predictions can be formulated about relations between stimulus constellations, neuronal responses, and behaviour. In order to examine these relations, we examined neuronal responses in behaviourally trained monkeys while these performed specific cognitive tasks.

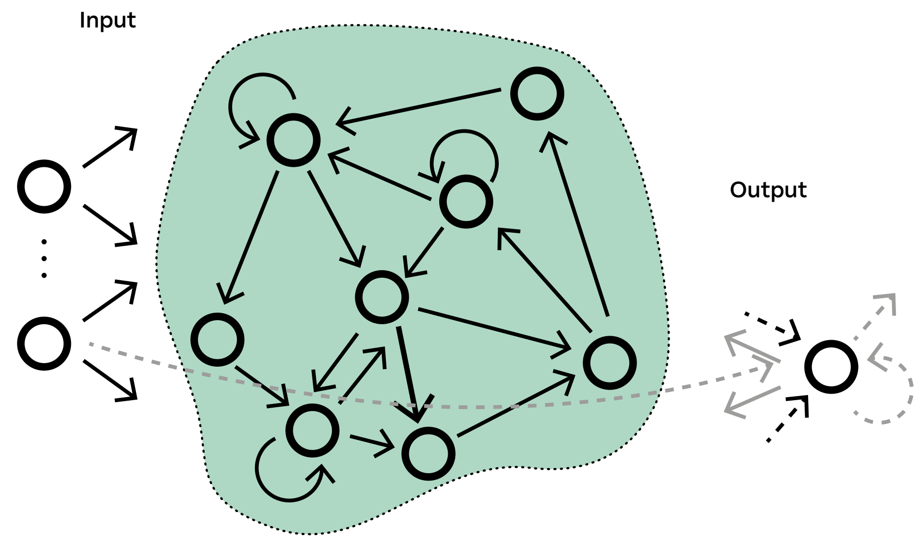
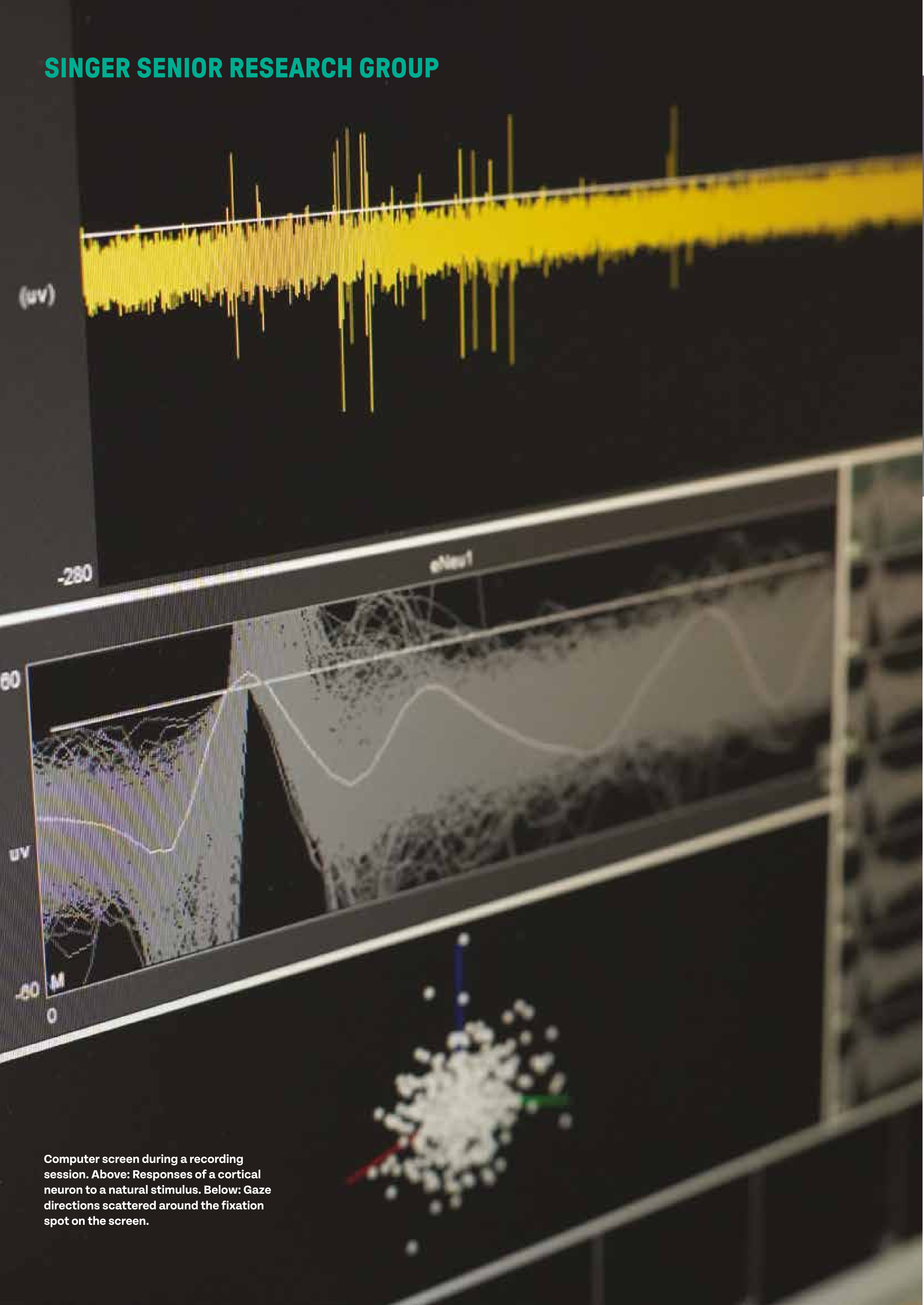
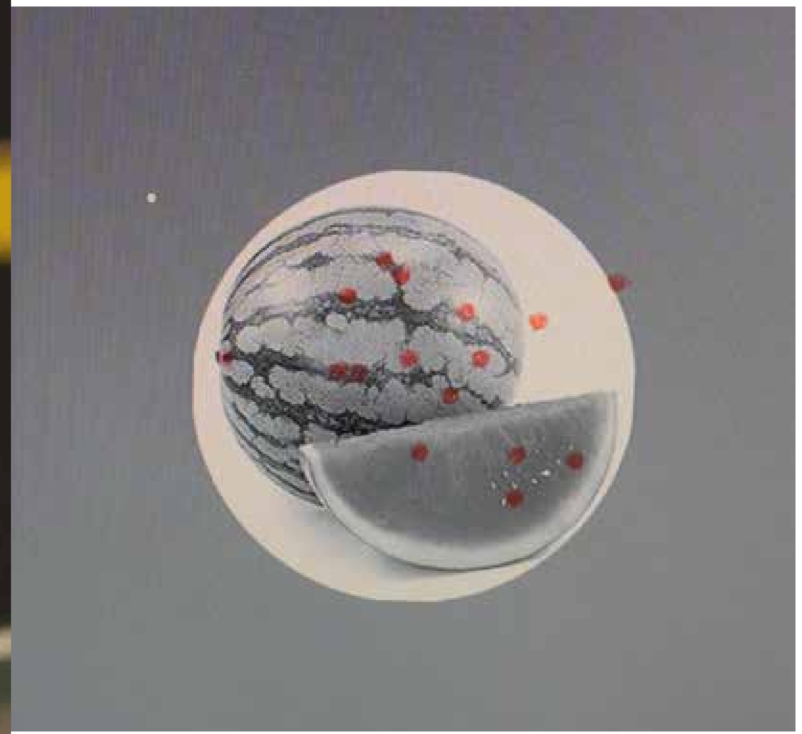


Figure 1, Left: Water drops eliciting oscillations and traveling waves on a water surface that lead to dynamically evolving interference patterns. **Right:** Schematic of a recurrent neuronal network in which sensory input and recurrent interactions lead to similar dynamics with spreading waves and interference patterns.

SINGER SENIOR RESEARCH GROUP



Computer screen during a recording session. Above: Responses of a cortical neuron to a natural stimulus. Below: Gaze directions scattered around the fixation spot on the screen.



Example of a stimulus shown on a computer screen over the receptive fields (red dots) of simultaneously recorded neurons

Macaque monkeys were implanted with recording devices that allow for simultaneous registration of neuronal responses from multiple sites of the cerebral cortex. Most of the tasks require discrimination of visual stimuli, retention of information in working memory, and manipulation of a mechanical lever to signal the outcome of the perceptual decision. The animals are rewarded for correct responses, and can terminate the measurement session whenever they wish. For the analysis of these data, mathematical methods are applied that capture not only the traditionally determined variables such as the latency and amplitude of responses, but also the temporal signatures of recurrent dynamics such as oscillations, synchrony, resonance, coherence, and phase shifts.

Predictions

If cortical networks exploit the dynamics of recurrent networks, several predictions can be formulated and tested experimentally:

1. There should be evidence for fading memory, i.e., network activity should retain information about the stimulus after it is switched off.
2. The spreading waves of activity should lead to sequential activation of network nodes, and the sequence order should contain information about the spatial and temporal properties of the stimulus.
3. Stimuli whose statistics match the priors stored in the network should lead to activity patterns that are less ambiguous and easier to classify than those evoked by stimuli that do not match priors.

To test these predictions, monkeys were trained to compare sequentially presented images. They were briefly shown on a video screen a sample picture and several seconds later a second image, the target stimulus. The sample and target stimuli were presented in variable combinations and the monkeys had to signal, whether the sample and the target were the same or different. While the monkey performed this task, neuronal responses were recorded from the primary visual cortex (V1) and an area downstream of V1 (V4). In both areas we obtained results that confirmed the predictions.

SINGER SENIOR RESEARCH GROUP

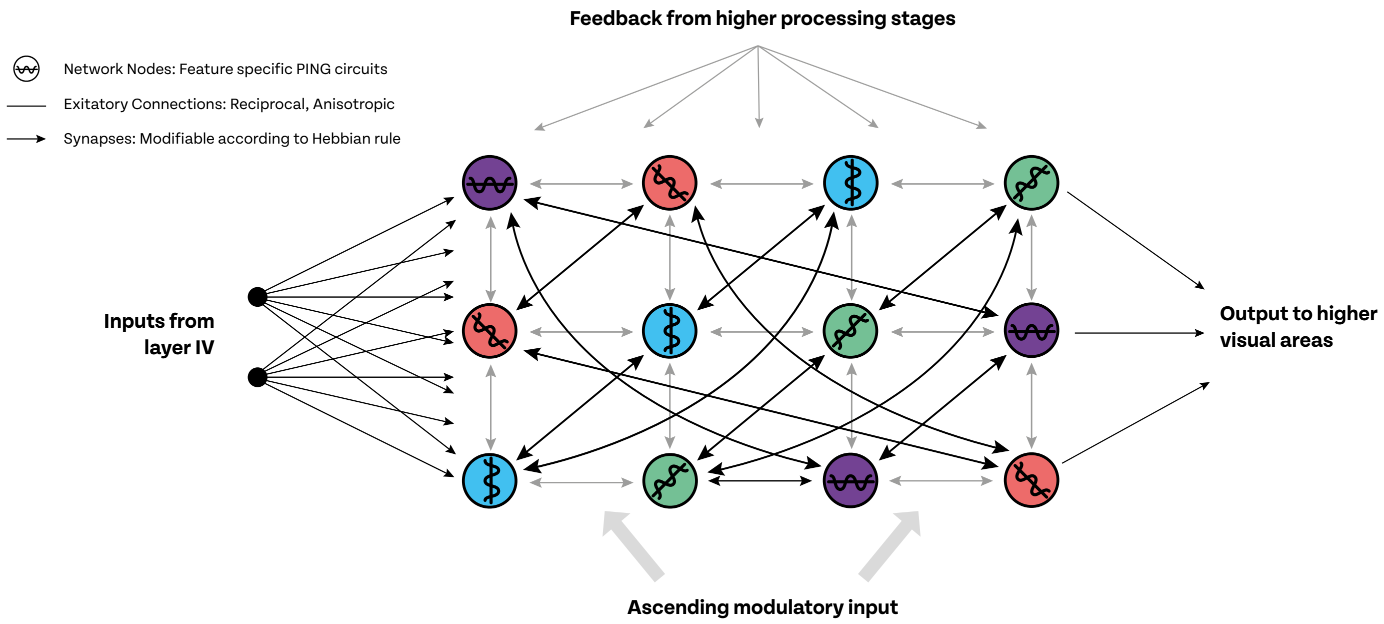


Figure 2: The cerebral cortex as an anisotropic, delay-coupled oscillator network. Colored network nodes indicate feature specific oscillatory PING circuits (features color-coded), arrows indicate excitatory anisotropic connections with Hebbian synapses (strength indicated by lightness). *Singer, 2021, PNAS.*

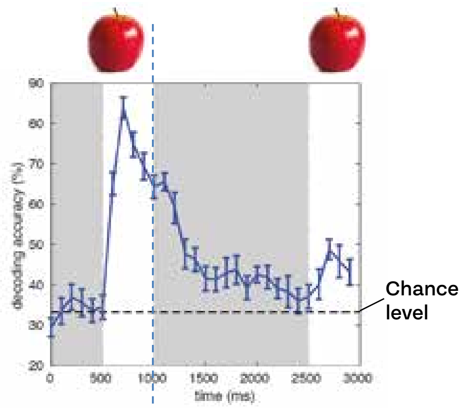


Figure 3: Superposition of information about successive stimuli in reverberating network dynamics, indicative of fading memory.

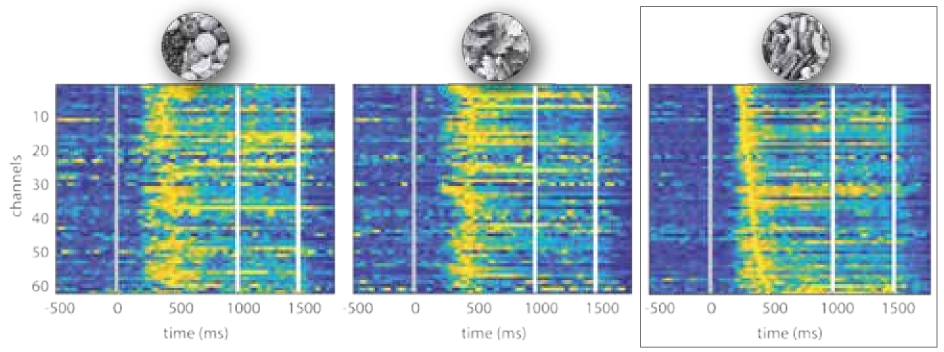


Figure 4: Natural stimuli evoke stimulus specific sequences of responses. Left panel (marked with square): Rank ordered response sequence of 60 neurons to the stimulus shown above the panel. Left and middle panel: Same neurons, ranked in the same way but activated with different stimuli show no sequence order of responses. *Yang et al., 2023, Nature Communications.*

After the sample stimulus had disappeared and activity slowly decayed back to the pre-stimulus level, the information on the identity of the sample stimulus was still preserved in the activity of the previously activated neurons (Fig. 3). Interestingly, this maintenance of stimulus specific information was also observed in trials in which monkeys were not required to memorize but to just detect a change of the fixation spot. This indicates that the maintenance of information (fading memory) was due to local network dynamics and not mediated by top-down projections.

Slowing the onset of the stimuli by slowly increasing their intensity revealed that the responses were not simultaneous but occurred in a sequence that was specific for the respective images (Fig. 4). Hence, the identity of the image could be decoded with high reliability from the sequence order of the neuronal responses. As predicted, these sequences were more robust and better decodable when evoked by natural stimuli that matched the priors stored in the network. Interestingly, the order of sequential activation was preserved when the sequences were expanded or compressed by varying stimulus contrast and kinetics. This provides strong evidence that the sequences were generated by recurrent interactions and not by mere differences in conduction delays or excitability. Because these sequences occur within the first phasic part of the responses and last only a few tens of milliseconds, they also allow for very fast decoding of stimulus identity. Deriving stimulus identity from the distribution of response amplitudes requires integration of discharges over sufficiently long temporal intervals to obtain a reliable measure of response amplitude. Given the low discharge rate of cortical neurons, this requires considerably more time than detecting the sequence order of responses. Humans scan visual scenes with saccadic eye movements about four times in a second. This leaves roughly 250 milliseconds for the processing of a new image. Considering this constraint, temporal codes would seem more compatible with such fast processing times than rate codes.

Analyses of responses to the test stimulus revealed yet another fascinating property of biological networks, namely their ability to represent simultaneously different contents in different subspaces of their high-dimensional dynamic state space. Following the appearance of the test stimulus, information about its identity was extractable from the responses to this stimulus by simple classifiers. However, with a delay of a few hundred milliseconds, it was also possible to decode from these very same responses, whether the monkey had decided that the test stimulus was the same as the sample or whether it differed. Thus, different categories of information can coexist in the responses of the same neuronal population This is possible because of the mixed selectivity of the neurons and the high dimension-ality of the dynamic space generated by the recurrent network.

Another strong prediction of the hypothesis is that familiarization of the networks in the visual cortex with particular stimuli by repeated exposure should lead to strengthening of connections between nodes that are jointly activated by the features of the stimulus. According to the Hebbian rule (see above), nodes that frequently engage in correlated firing will become coupled more strongly in this non-supervised learning process. This in turn should be reflected by changes in the correlation structure of the spontaneous activity of the network. The network should spontaneously generate activity patterns resembling those evoked by the familiar stimuli.

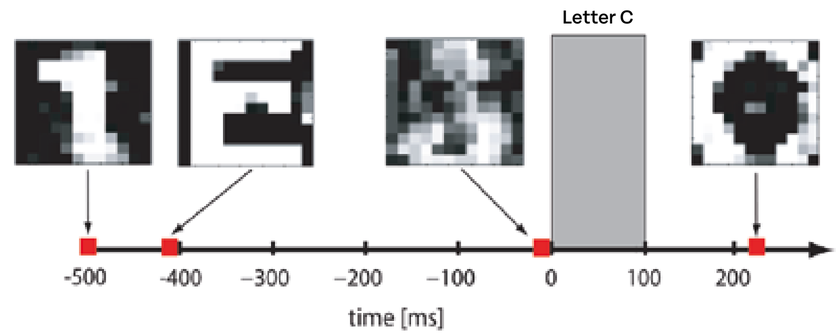


Figure 5: Replay of stimulus specific response vectors during spontaneous activity. A matrix of decoders was trained to detect the vectors corresponding to familiar stimuli and fed with stretches of spontaneous activity. Note that the decodability of the replayed vectors corresponding to "1" and "E" are of similar quality as the vector evoked by a real stimulus "C".

To test this prediction, we trained classifiers to detect the patterns of network activity evoked by the set of stimuli used for familiarization and then had these classifiers slide over long stretches of spontaneous activity. This revealed that the network reproduced at irregular intervals activity patterns that resembled those evoked by the stimuli used for familiarization. Thus, the network replayed activity patterns that it had "learnt" previously during repeated exposure (Fig. 5).

→ Lazar, A., Lewis, C., Fries, P., Singer, W. and Nikolic, D., 2021. **Visual exposure enhances stimulus encoding and persistence in primary cortex.** *Proceedings of the National Academy of Sciences*, 118(43)

SINGER SENIOR RESEARCH GROUP

Simulations: An attempt to assess the functional role of oscillatory activity.

It is notoriously difficult to establish causal relations between a particular experimentally identified feature and the putative function of this feature in physiological experiments. The classical approach to manipulate the respective feature and to investigate the functional consequences of this manipulation fails in complex, highly integrated systems such as recurrent neuronal networks. The reason is that manipulation of a single system variable inevitably affects numerous other variables. This makes it difficult to isolate the functional contribution of a particular feature and to determine whether a particular property is functionally relevant or just an epiphenomenon. The oscillatory patterning of neuronal responses, a ubiquitous feature of neuronal systems, is such a case. Accordingly, there is a longstanding debate in the field as to whether these oscillations have a function in information processing or whether they are an epiphenomenon of other mechanisms such as e.g. recurrent inhibition that serves gain control, competition and noise suppression but inevitably also causes oscillations.

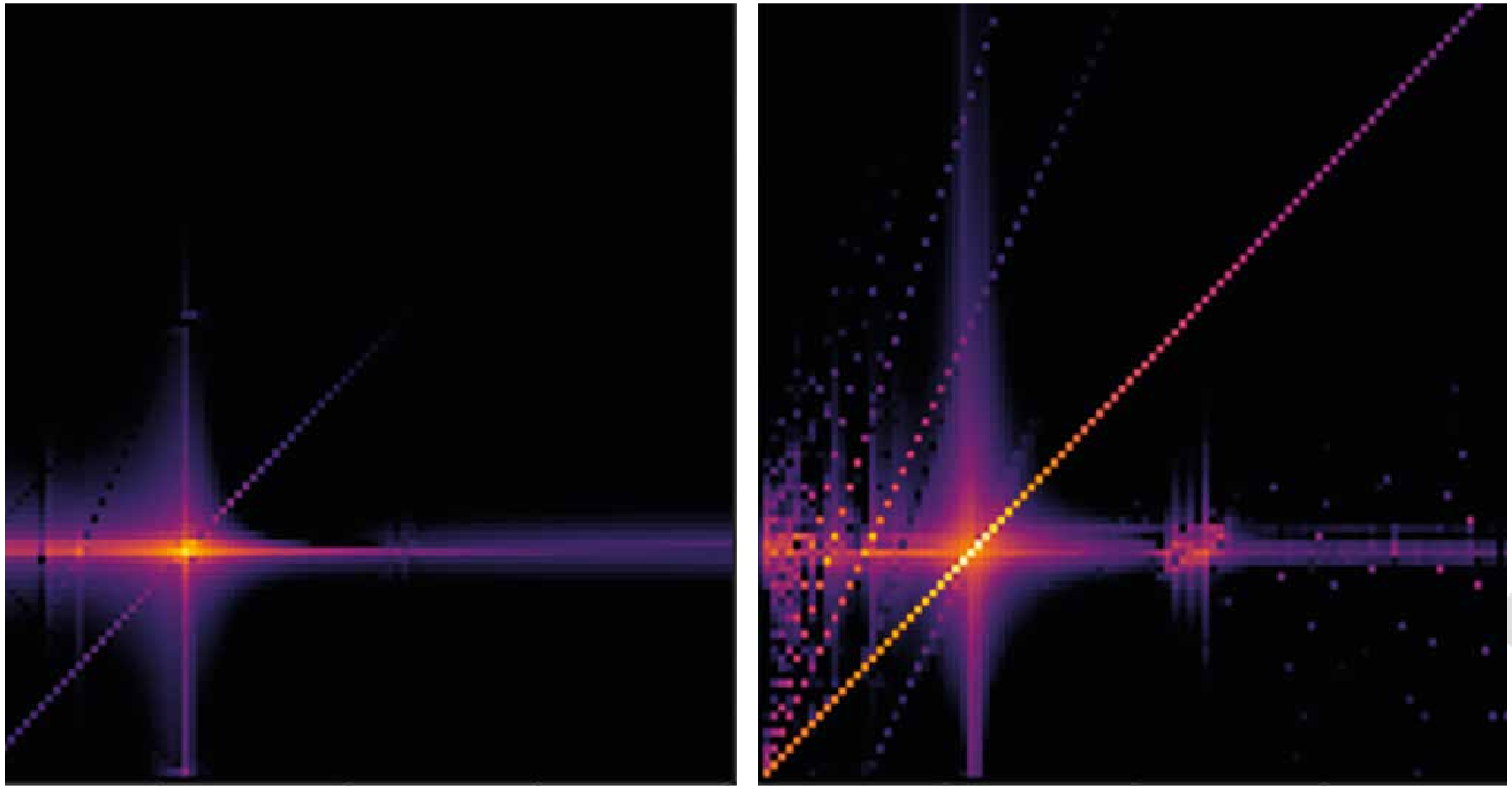
In order to alleviate this problem, we opted for a synthetic approach. We simulated recurrent neuronal networks on a digital computer and implemented step by step features that had been identified experimentally. Subsequently, we tested the functional consequences of these additions by testing the performance of the networks on standard benchmark tests for pattern classification.

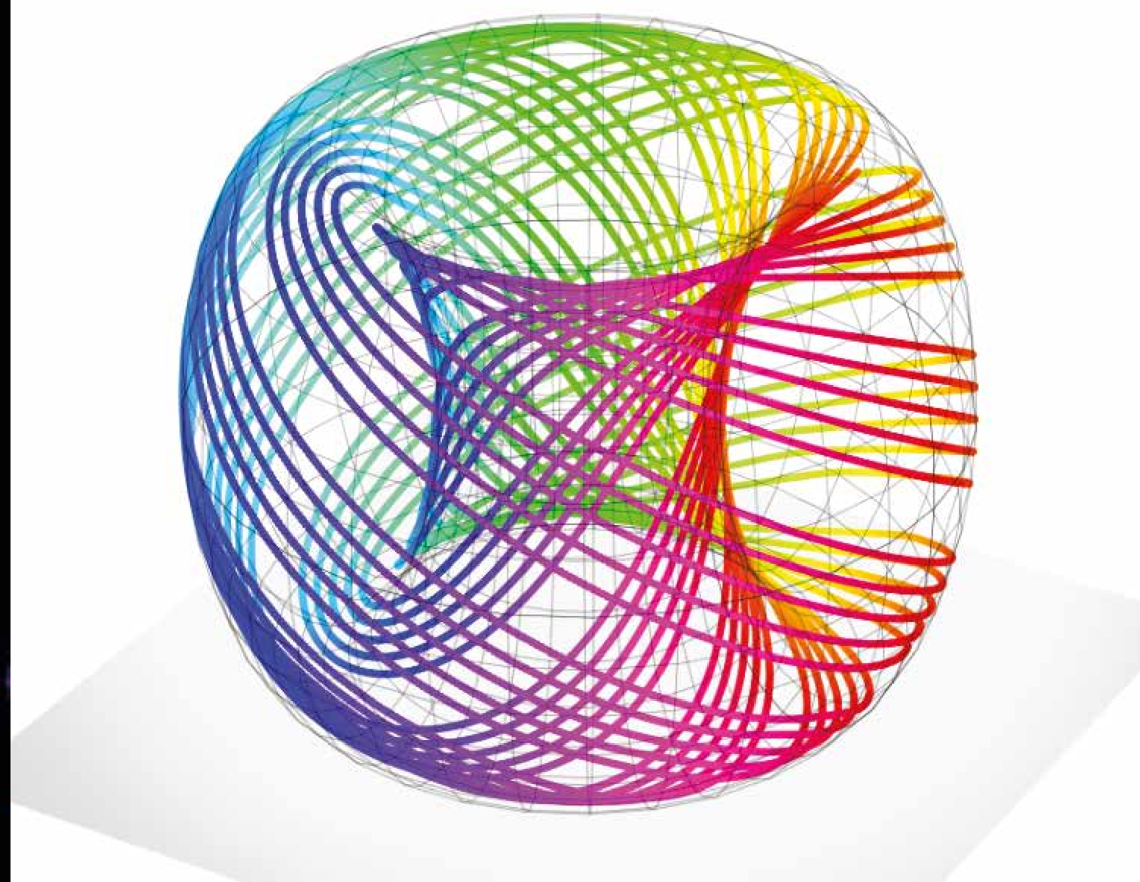
This revealed that configuring the nodes of the network as damped harmonic oscillators, which is a prominent feature of recurrent networks in the cerebral cortex, was a decisive step. We thus called our networks Harmonic Oscillator Recurrent Networks, or HORN for short.

→ Effenberger, F., Carvalho, P., Dubinin, I. and Singer, W., 2023. **A biology-inspired recurrent oscillator network for computations in high-dimensional state space.** *bioRxiv*

→ Spyropoulos, G., Saponati, M., Dowdall, J.R., Schölvinck, M.L., Bosman, C.A., Lima, B., Peter, A., Onorato, I., Klon-Lipok, J., Roese, R. and Neuenschwander, S., 2022. **Spontaneous variability in gamma dynamics described by a damped harmonic oscillator driven by noise.** *Nature communications*, 13(1)

Individual nodes in HORNs develop complex resonance behavior. The panels show the response to sinusoidal input stimulation before (right) and after training (left). The bright horizontal lines correspond to the natural frequencies of the nodes, vertical lines indicate resonance at input frequencies around the node's natural frequency, and bright diagonal lines indicate entrainment.



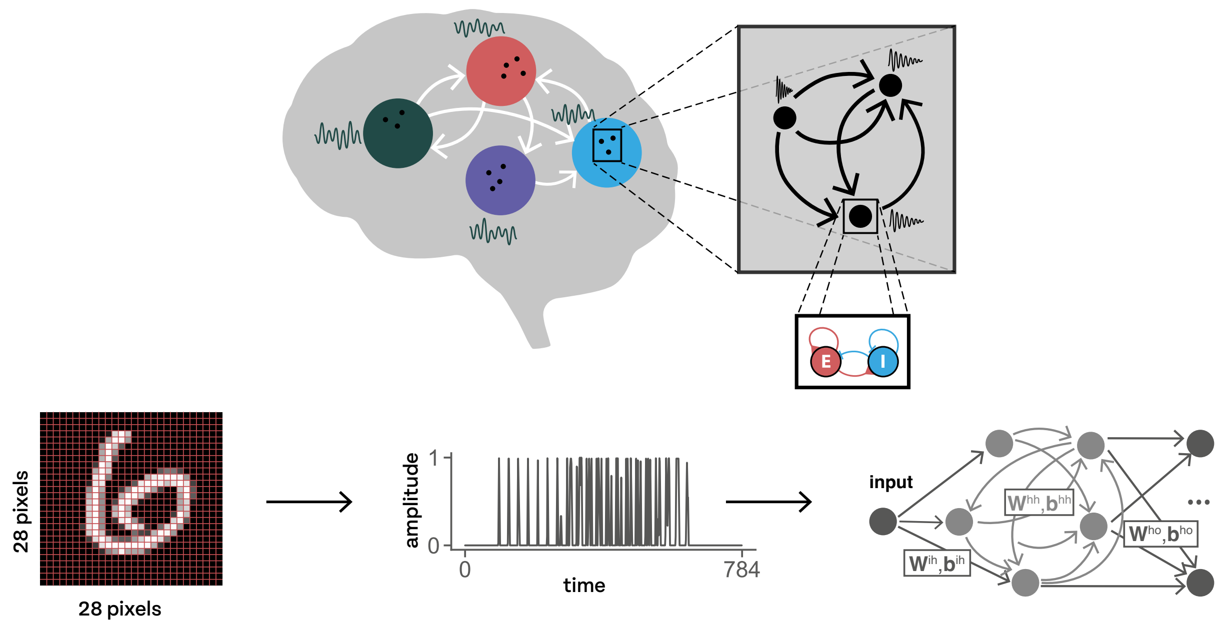


The trajectories of the dynamics of a driven oscillator lie inside a torus. The inner circles represent the phase space of the oscillator and the outer circles the input phase.

SINGER SENIOR RESEARCH GROUP

Other additions like introducing heterogeneous conduction delays, varying time constants and multilayer architectures further increased performance, but allowing the nodes to oscillate was crucial.
The oscillator network outperformed substantially the numerous, well established recurrent networks that lack this feature with respect to learning speed, noise tolerance and system size (Fig. 6). Analysis of the network dynamics revealed that the reasons for this remarkable gain of function were the unique properties of reciprocally coupled oscillators (Fig. 7, left). The nodes of HORNs convert all stimuli in oscillatory responses and this allows the nodes to engage in highly dynamic interactions that are characterized by synchronisation, resonance, entrainment, frequency and phase shifts and dynamic gain modulation. Consequently, the networks can fully exploit both the spatial and the temporal dimension for computations. The transformation of all stimulus parameters into the continuous variables of oscillations permit analogue computations. The travelling waves, the substrate of fading memory, and the resulting interference between the responses of the interconnected nodes permit a virtually simultaneous evaluation of both spatial and temporal relations between multiple, spatially and temporally segregated stimuli. And because the functional architecture of the recurrent coupling connections represents an internal model of the world, this computation within memory allows for a highly parallelized match of sensory evidence with stored priors. All these operations are crucial prerequisites for perceptual processes such as scene segmentation and ultimately the representation of complex perceptual objects. It is noteworthy that in this framework the representations of perceptual objects do not consist of pattern specific read-out units but are non-local, non-stationary and wholistic. They consist of dynamic landscapes that exhibit a complex and fine-grained correlation structure (Fig. 7, right). As all nodes, not only those stimulated directly, contribute to these representations, stimulus specific information can be extracted from all nodes, like in a hologram. In the cerebral cortex this read out does not require convergence of the nodes' activity onto classifier units because the distributed activity patterns serve in turn as input to downstream recurrent neuronal networks whose nodes are reciprocally connected to nodes of the respective upstream areas.

In conclusion, both the experimental and the simulation studies performed during the last few years provide strong support for the notion that the cerebral cortex exploits for its computations the unique properties of recurrently coupled oscillator networks in which the functional architecture of the coupling connections contains information about the statistical regularities of the world; the topology and strength of these coupling connections is partly determined by a genetically specified blueprint that harbours information about the world acquired by evolutionary selection, but it is in addition shaped by experience that adapts this internal model of the world to the actual environment of the respective organism.



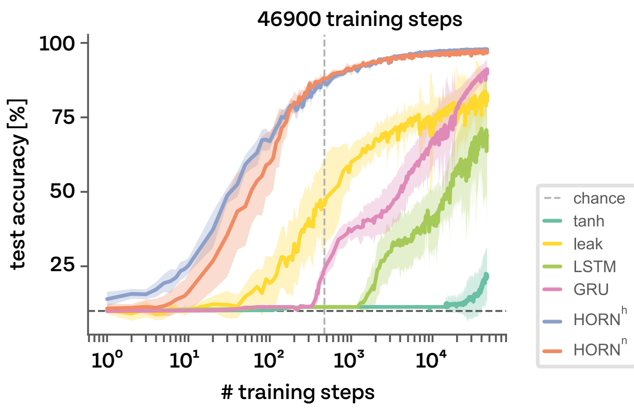


Figure 6, left: Simulation of a harmonic oscillator recurrant network and presentation of MNIST stimuli as time series. **Right:** Learning dynamics of HORN oscillator networks on the sMNIST digit classification task, in comparison to non-oscillating architectures. Note the log scale in the number of training steps. *Effenberger et al., 2023.*

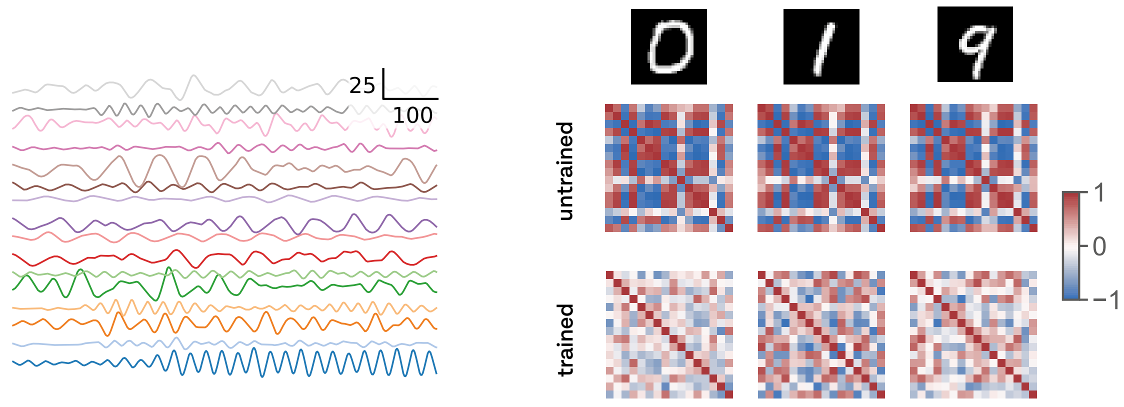


Figure 7: Learning-induced emergence of stimulus-specific spatio-temporal interference patterns in HORN networks trained on sMNIST digit classification. **Left:** Dynamics of a 16 node HORN resulting from stimulation with an sMNIST digit (horizontal axis: time, vertical axis: amplitude). **Right:** Pairwise Pearson correlation coefficients of node dynamics show the emergence of learning-induced, fine-scale, stimulus-specific correlation.

Outlook

The simulation studies suggest that essential operations in the cerebral cortex can be reproduced by assuming purely analog computations. At the same time, the data obtained from the monkey experiments indicate that the timing relations between action potential emitted from spatially distributed neurons matter. This notion is further supported by the fact that neurons are exquisitely sensitive coincidence detectors and that virtually all mechanisms of activity dependent synaptic plasticity are sensitive to the temporal relations between discharges of their pre- and postsynaptic neurons.

Future studies will therefore be devoted to the question of how these different signals, the continuously varying variables exploited by analogue computing strategies, expressed in fluctuations of the neurons' membrane potentials, and the discrete, frequency modulated discharges of neurons can be accommodated in a unified model. Our prediction is that introducing discrete thresholds for spikes in the nodes and using frequency modulated spike trains for the coupling of nodes will further enhance the performance of model networks, in particular when these become multilayered. The thresholds will contribute to noise reduction and the discretisation of the transmitted signals will allow the system to exploit with much finer temporal resolution the temporal relations between the responses of the nodes.

In parallel we plan to investigat whether the unique dynamics of HORNs can be exploited for the encoding of complex, time varying sequences. We plan to concentrate on natural language as example of complex temporal patterns and examine, to which extent the networks can generate representations that are invariant to the temporal compression or dilatation of the input sequences, a necessary prerequisite for language comprehension in humans.

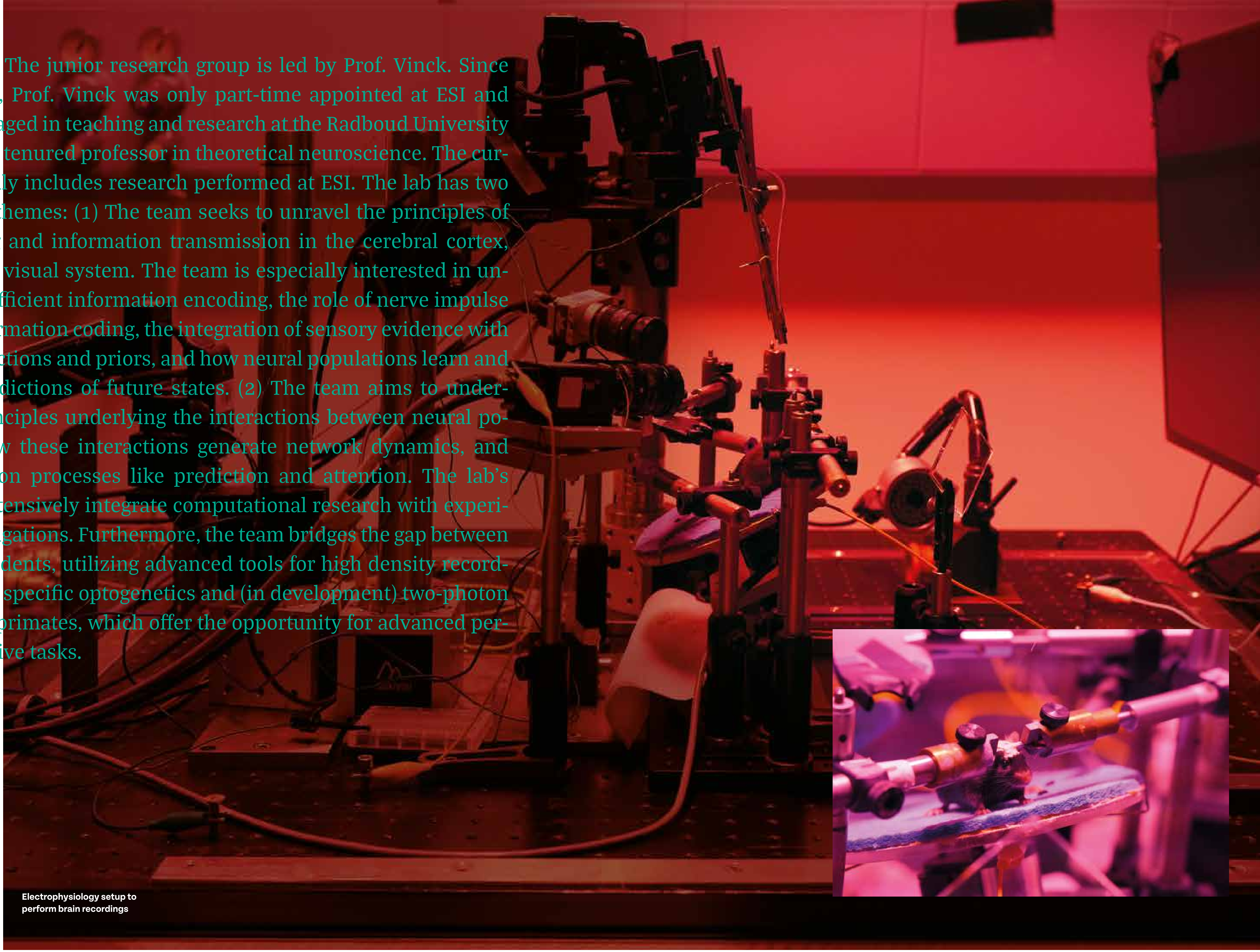
VINCK LAB

PRINCIPLES OF NEURAL CODING AND INTER-AREAL INTERACTIONS

Group Leader Martin Vinck / Postdoc Giorgos Spyropoulos, Ana Broggini, Brian Rummell / PhD Students Cem Uran, Nisa Cuevas, Jahand Esfandiari, Marius Schneider, Jinke Liu, Boris Sotomayor-Gomez, Amr Farahat, Matteo Saponati, Irene Onorato / Lab Manager Athanasia Tzanou (as of December 31, 2021)

"Our lab uses an integrative approach to neuroscience combining computational modelling, neural invasive recordings, and causal manipulations via optogenetics, and where students from different backgrounds work together."

VINCK LAB The junior research group is led by Prof. Vinck. Since January 2021, Prof. Vinck was only part-time appointed at ESI and part-time engaged in teaching and research at the Radboud University Nijmegen as a tenured professor in theoretical neuroscience. The current report only includes research performed at ESI. The lab has two key research themes: (1) The team seeks to unravel the principles of neural coding and information transmission in the cerebral cortex, especially the visual system. The team is especially interested in understanding efficient information encoding, the role of nerve impulse timing in information coding, the integration of sensory evidence with sensory predictions and priors, and how neural populations learn and represent predictions of future states. (2) The team aims to understand the principles underlying the interactions between neural populations, how these interactions generate network dynamics, and their impact on processes like prediction and attention. The lab's vision is to intensively integrate computational research with experimental investigations. Furthermore, the team bridges the gap between research in rodents, utilizing advanced tools for high density recordings, cell-type specific optogenetics and (in development) two-photon imaging, and primates, which offer the opportunity for advanced perceptuo-cognitive tasks.



Electrophysiology setup to perform brain recordings

Electrophysiology setup to perform brain recordings

A. Principles of information coding in cortex

Sensory stimuli can impact observers in markedly different ways depending on the context in which they are presented. Likewise, neural responses to the same stimuli are strongly context-dependent, which represents a fundamental feature of cortical circuits: In each circuit, feedforward inputs are integrated with both top-down feedback and horizontal feedback from neural populations in the same area.

A promising theoretical framework to understand the context-dependence of sensory processing is predictive coding. Predictive coding posits that neural responses are amplified when bottom-up sensory inputs are surprising, i.e. do not match with top-down contextual predictions, leading to the efficient encoding of information. In this ERC project, we tested this theory in the visual cortex of awake monkeys. This required us to solve a major computational problem, namely develop a measure of predictability for natural stimuli. We solve this by training deep neural networks on a large number of images to predict subsets of images using the rest of the image. We then quantify predictability by using human perceptual similarity metrics to quantify the similarity of the predicted and the actual image. The measure of predictability can be readily applied to each recorded V1 neuron, by determining its receptive field. Utilizing this novel approach, we achieved two significant conceptual advancements.

First, our team discovered that predictability is a primary factor explaining the synchronization of neuronal activity in the primary visual cortex. Thus, neurons exhibit synchronized activity when they encounter inputs that are well predicted by the remainder of the image. Synchronization-through-predictability points directly to possible functions of this synchronized activity, namely to efficiently encode information, but also to strengthen synaptic connections based on predictive relations in the image. These findings provide evidence for our theory (Vinck & Bosman, 2016) of what governs the emergence of synchronized activity in visual cortex.

→ Uran C. PhD Thesis. **Contextual modulation of neural signals in the primary visual cortex of awake macaque monkeys.**

→ Uran C, Peter A, Lazar A, Barnes W, Klon-Lipok J, Shapcott KA, Roese R, Fries P, Singer W, Vinck M. **Predictive coding of natural images by V1 firing ratesand rhythmic synchronization.** *Neuron.* 2022 Sep 7; 110(17):2886-2887. doi:10.1016/j.euron.2022.07.021

Using the same approach, we provide further insight into the nature of prediction error signals. We find V1 neurons fire more spikes when information is not predicted by the context. Thus, the number of spikes and their synchronization have opposite relations to predictability. However, spike counts and synchrony provide unique information: Synchronization primarily reflects the predictability of simple visual features, likely reflecting local recurrent interactions within V1. Spike counts reflect the predictability of more complex, high-level visual features, suggesting a critical dependence on feedback from higher visual areas to V1. Our findings thus reveal distinct roles of synchronization and spike counts in the predictive coding of natural images, providing the basis for new theories of contextual modulation (Vinck et al., 2023). Furthermore, we provide computational methods to predict synchronization and contextual modulation of spike counts for any visual image.

→ Vessel EA, Pasqualette L, Uran C, Koldehoff S, Bignardi G, Vinck M. **Self-Relevance Predicts the Aesthetic Appeal of Real and Synthetic Artworks Generated via Neural Style Transfer.** *Psychol. Sci.* 2023 Sep; 34(9):1007-1023.doi: 10.1177/09567976231188107.

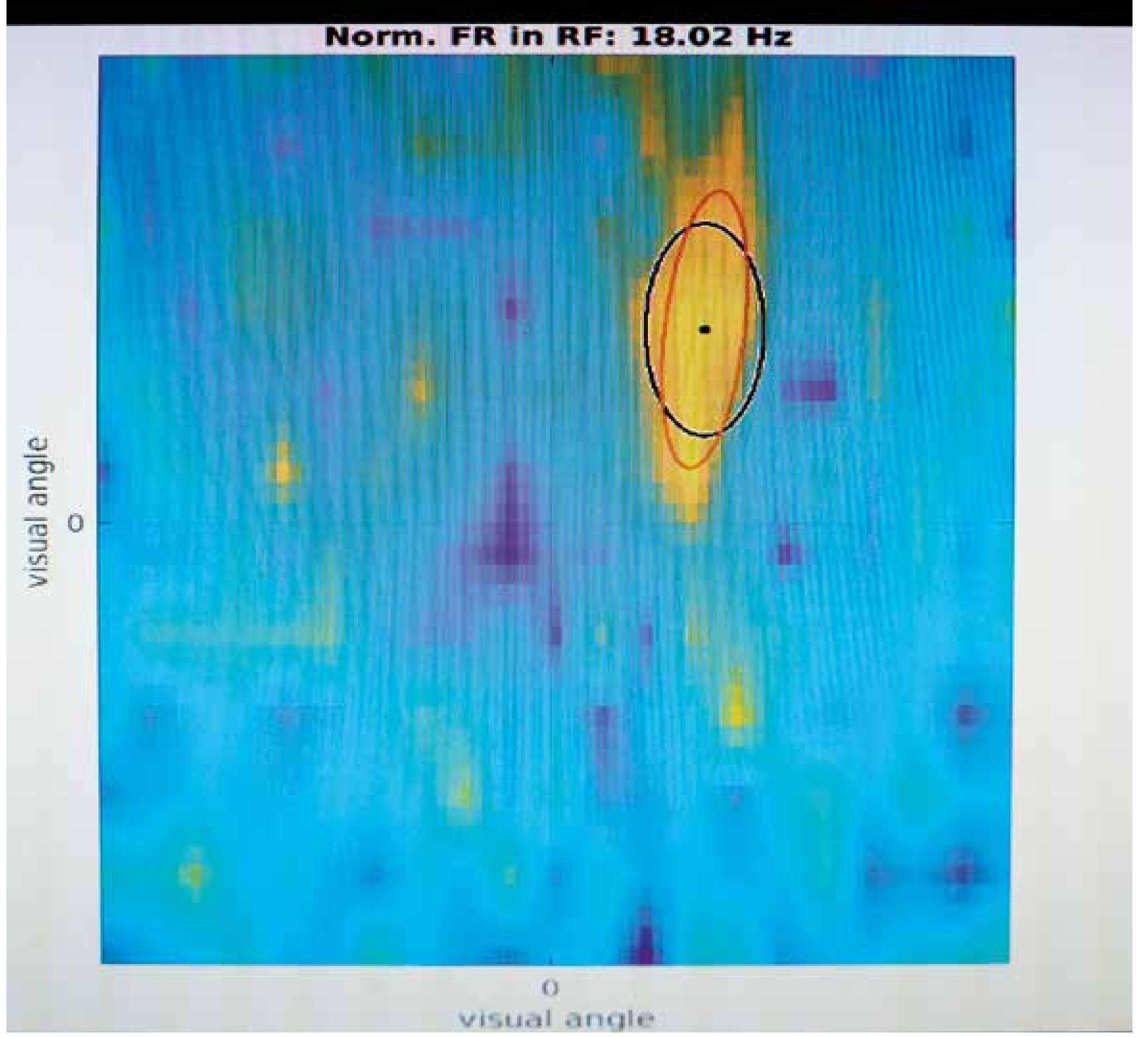
We continue to study these processes using marmoset electrophysiology and human MEG recordings. To study how the priors of natural statistics influence visual responses, we manipulate the statistics of images by applying different artistic styles to images with machine learning methods. We then present these synthetic artworks to observers while recording brain activity. For each style, we generate predictions about neural responses using predictive models, and test these with empirical data. These are related also to human behavior, e.g. visual memory of images. Furthermore, in a cooperation

Understanding the way in which biological neural networks compute and encode information, with incredible energy efficiency and robustness compared to human-designed systems, *is one of the greatest remaining scientific challenges.*

with the Max Planck Institute for Empirical Aesthetics (MPIEA), we have also used synthetic artworks to determine a strong influence of the artwork's content and its relevance to the observer on aesthetic appeal.

Predictive processing through recurrent connections is one mechanism via which neuronal groups can learn spatial relationships across space. However, it is commonly assumed that feedforward neural networks, like the ubiquitous convolutional (deep) neural networks (CNNs), also have the capacity to learn spatial relations and exploit the arrangement of features for object recognition. Alternatively, CNNs may primarily rely on surface regularities of objects. In this case, object recognition would result from an accumulation of local evidence without exploiting the spatial relations among features. Our team investigated this question by training CNNs in which information from small receptive fields (RFs) is accumulated in a spatially unspecific manner. The network is therefore necessarily blind (i.e. has no access) to the spatial configuration of local features. We then assess the additional information that CNNs can extract by exploiting spatial relations by: 1) training a follow-up network that integrates local features, and (2) disturbing this integration by scrambling the spatial locations of the features.
We find CNNs use distinct strategies for different datasets, rather than one unified strategy. Classification strategies varied even between classes within the same dataset. A continuous spectrum of CNN strategies ranges from exclusive reliance on local features to a strong reliance on spatial relations. For texture-rich datasets (e.g. animals), CNNs do not use spatial relations between features. For shape-dominated datasets (e.g. sketches), CNNs do rely on long-range spatial relationships. Nevertheless, we show that CNNs only integrate spatial relations up to intermediate spatial ranges, and do not use the global shape information of objects. These findings have numerous implications for understanding the algorithmic basis of object recognition. They predict that the brain can rapidly classify most objects by (1) extracting diagnostic features in early visual areas, and (2) average these in a spatially unspecific way, while a multi-stage processing strategy is required for shapes.

→ Farahat A, Effenberger F, Vinck M. **A novel feature-scrambling approach reveals the capacity of convolutional neural networks to learn spatial relations.** *Neural Networks* 2023 Aug 18; 167:400-414.doi:10.1016/j.neunet.2023.08.021.



Neuronal receptive field, mapped in real time

These studies focused on predictive relationships through space, rather than time. Anticipating and signaling events ahead of time is a pivotal ability for organisms. Theories of predictive processing are typically formulated at a network level. We hypothesized that self-supervised predictive processing may also be implemented at the level of individual neurons. We propose a possible computational mechanism, in which predictability is a key determinant of synaptic plasticity: Synaptic inputs carrying much information about the future are strengthened, while synaptic inputs that are redundant and predicted by other inputs are weakened. We implemented this predictive learning rule in a single-neuron model. Neurons with this plasticity rule learn sequences over long timescales, develop sequence anticipation, and encode their inputs in an energy-efficient manner. The learning rule reproduces the experimentally observed phenomenon of sequence recall, whereby a network of neurons recalls longer sequences given the initial inputs. Strikingly, the learning rule can explain experimental observed principles of how synaptic connections change based on the timing of the inputs (STDP), including e.g. the dependence of STDP on the initial synaptic strength; its frequency dependence; and its behavior for complex input patterns.

→ Saponati M, Vinck M. **Sequence anticipation and spike-timing-dependent plasticity emerge from a predictive learning rule.** *Nature Communications* 2023 Aug 21;14(1):4985.doi:10.1038/s41467-023-40651-w

---

A major question that arises is whether the predictive learning rule allows neurons to discriminate and anticipate multiple temporal sequences. Indeed, we find the presence of many input sequences prevents the development of sequence anticipation. Introducing an optimal level of inhibitory feedback between neurons can solve this

→ Saponati M, Vinck M. **Inhibitory feedback enables predictive learning of multiple sequences in neural networks.** *Biorxiv.* 2023

→ Saponati, M. PhD thesis. **A study of synaptic plasticity and predictive processes in biological and artificial networks.**

problem, and leads to sparse firing in the network, with neurons selectively firing at the beginning of specific sequences. Consequently, different neurons provide independent information with a high degree of information per spike. The resulting network activity allowed for rapid and energy-efficient classification of sequences, compared to standard supervised neural network algorithms. These findings have important implications for the understanding of plasticity mechanisms in cortical circuits and the design of energy-efficient neuromorphic hardware. Our team has been conducting further mice experiments to test predictions, testing if neurons anticipate future visual motion (funded by Netherlands Science Organization).

→ Sotomayor-Gómez B, Battaglia FP, Vinck M. **SpikeShip: A method for fast, unsupervised discovery of high-dimensional neural spiking patterns.** *PLoS Comput Biol.* 2023 Jul 31; 19(7):e1011335. doi:10.1371/journal.pcbi.1011335.

The capacity of neurons to learn temporal sequencies leads to the question what the role of sequences is in information coding. While traditional studies of coding are based on the number of nerve impulses, a richer coding space may be provided by the relative timing relationships between neurons. Yet sequences can be carried by very large ensembles of neurons, posing a major computational challenge to capture the information in the temporal structure of neural activity. In this BMF-funded project, the team introduced SpikeShip, a measure based on the mathematical framework of optimal transport. SpikeShip determines how similar any two patterns are by computing the minimum energy to transform one pattern into another pattern. SpikeShip captures the information contained in all of the relative timing relationships among neurons, rather than just pairwise interactions, and has many advantages compared to other measures: very fast computational speed; independent of spike count; no binning required; and high detection performance. SpikeShip detected high-dimensional spiking sequences that reliably distinguished between natural images or behavioral states, and carried complementary information to conventional spike-count codes. SpikeShip opens new avenues for studying neural coding by rapid and unsupervised detection of temporal spiking patterns.

→ Sotomayor-Gómez B, Battaglia FP, Vinck M. **Differential population coding of natural movies through spike counts and temporal sequences.** *Biorxiv.* 2023

We used SpikeShip to study the encoding of natural movies in ensembles of thousands of neurons. SpikeShip detect temporal sequences that carry unique information about natural movies, exceeding the information in spike counts. These temporal sequences are highly stable, and do not drift across presentations. By contrast, spike counts show substantial representational drift and slowly decaying temporal correlations unrelated to stimulus content. These find-ings show that V1 populations robustly encodes visual information via precise spike timing relations. Our work on SpikeShip continues with the recently funded (>20 mil. €) Dutch Brain Interface Initiative, of which Martin Vinck is one of the PIs, to provide fast readout of neural information for brain-computer interfaces, with the aim to develop novel therapeutic and prosthetic interventions.

→ Liu J, Vinck M. **Improved visualization of high-dimensional data using the distance-of-distance transformation.** *PLoS Comput Biol.* 2022 Dec 20; 18(12):e1010764. doi:10.1371/journal.pcbi.1010764.

Combined with techniques like t-SNE, SpikeShip allows to visualize high-dimensional neural patterns into different clusters. We have recently shown that visualization techniques like t-SNE, a widely used data-science tool, can be strongly improved by a mathematical transformation of distances between data points.

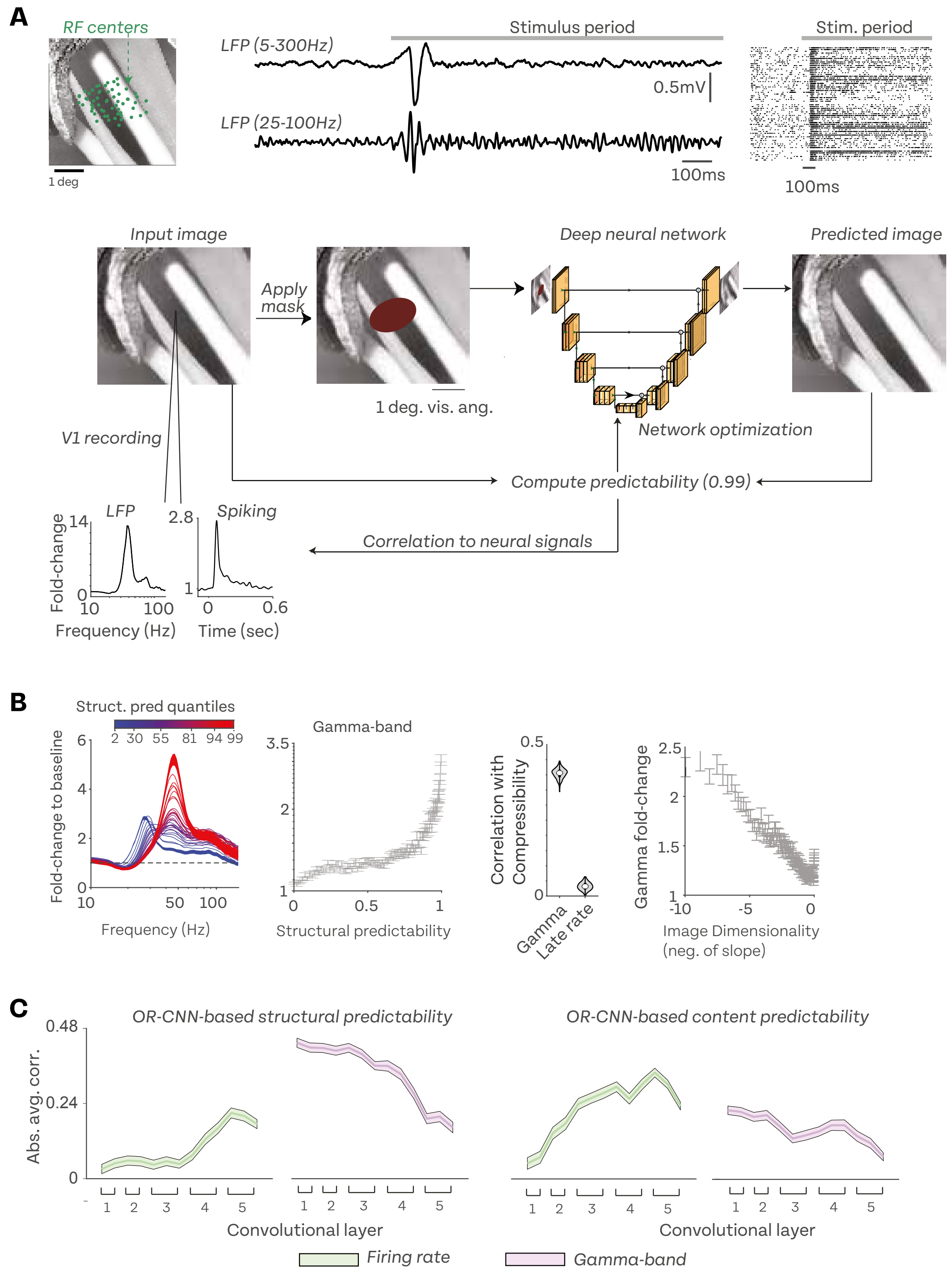


Figure 1: (A) Natural images (11 x 11 degrees) were presented for 1.2 s, while recordings were made from macaque V1. Green dots indicate locations of RF centers of the recording array. Median example trace of the LFP for the image shown with a filtered trace. On the right, an example spiking raster plot. Bottom: Illustration of a deep neural network (DNN) trained to predict visual inputs into the RFs (receptive field). A mask of approximately the same size as the recording site's RF is applied to an image. The image with the mask is then entered as an input to a DNN with a U-net architecture. This DNN generates (predicts) the full image, i.e., the image content behind the mask is filled in. Stimulus predictability is computed by comparing the ground-truth input image and the predicted image and then used for network optimization during the training stage. After network training, a novel set of images is presented to both the DNN and the monkeys. The predictability score is then correlated with LFP and spiking responses across images. **(B)** Gamma increases with spatial stimulus predictability, and increases with image compressibility. Gamma is strongest for low-dimensional images. **(C)** We distinguished between the predictability of low and high-level features. Gamma primarily increases for low-level spatial predictability, while firing rates are increased with high-level features have low predictability. *See Cem Uran, Alina Peter et al. (2022, Neuron).*

B. Circuit and computational mechanisms underlying local and large-scale neural integration.

The cortex is a high-dimensional, non-linear dynamical system whose key feature is recurrent activity within and between areas. Our team seeks to unveil the principles guiding these neural interactions, and determine how interactions between various cell types and cortical layers contribute to processes such as prediction and attention.

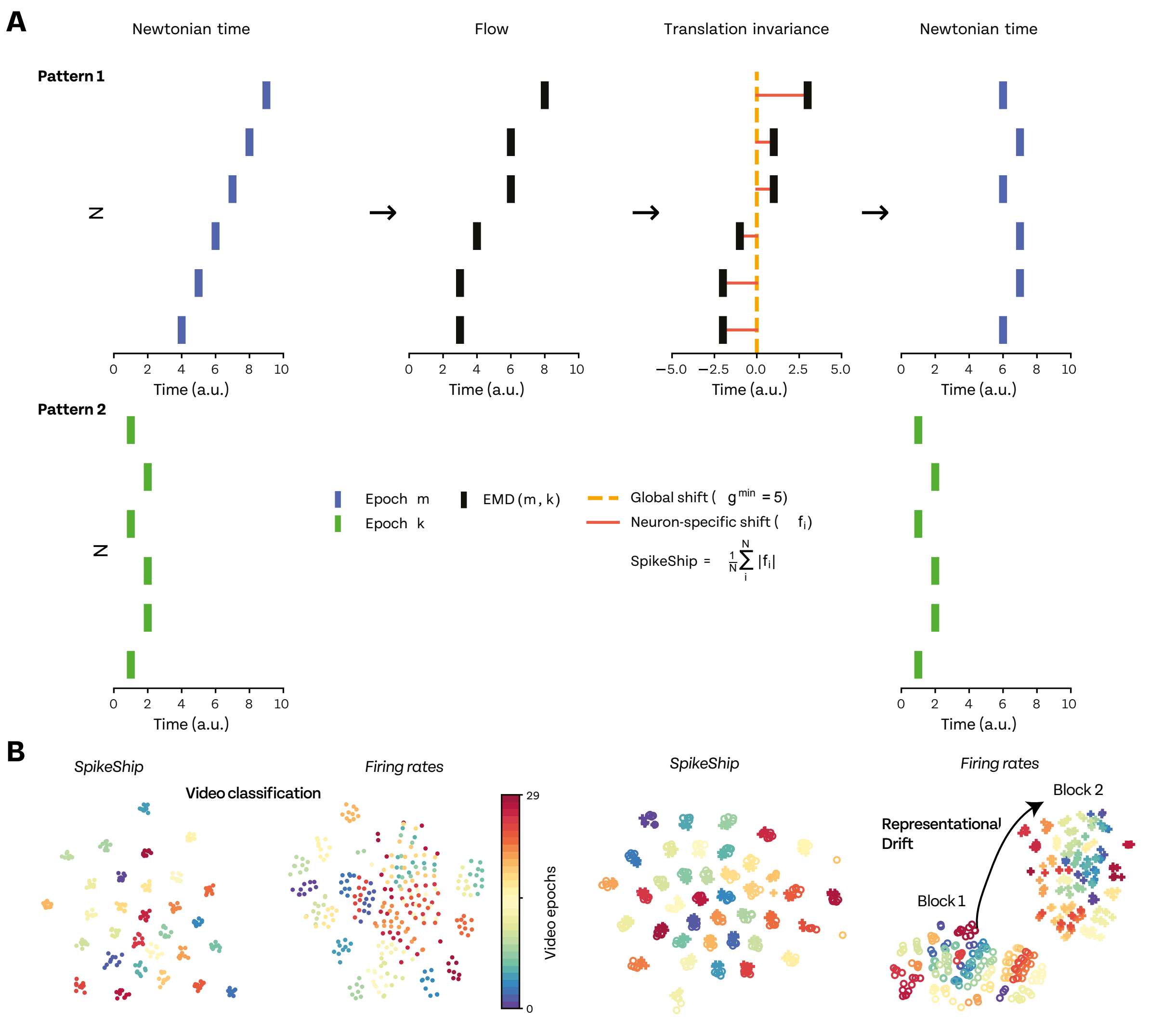


Figure 2: (A) SpikeShip, a measure that captures spiking information in all the relative spike timing relationships in a population of neurons. Example of SpikeShip computation of multi-neuron activity between two epochs *m* and *k*. In the first step, the difference between spike times is computed. SpikeShip correspond to the total neuro-specific flows (i.e., f_i) relative to a global translation term (i.e., g^{min}) based on minimum transport cost of spikes across neurons. SpikeShip extracts temporal information of neural sequences based on the cost to align spikes between two epochs of multi-neuronal spike trains.
(B) Because SpikeShip has a very efficient computational cost, we could apply it to neural ensembles consisting of thousands of neurons, analyzing how natural videos are encoded through spiking patterns. Temporal sequences highly precisely encoded natural videos, whereas firing rate population vectors did not allow for precise encoding. Furthermore, SpikeShip showed stable encoding within a session, whereas firing rates showed substantial representational drift between stimulus blocks. *See Boris Sotomayor et al. (2023, PLoS Computational Biology, 2023, Biorxiv)*

Through the interactions between neurons, the cerebral cortex creates dynamic activity patterns with typical statistical regularities observable across many levels, from scalp to intracellular voltage potentials. A prime example is rhythmic network activity (30-80Hz) in visual cortex, which is associated with numerous functions. In this work we illuminated how these rhythms stem from interactions between inhibitory and excitatory neurons. Cortical gamma rhythms are conventionally modeled as self-sustained oscillators that can be entrained by external forces, akin to the heart or circadian rhythm. Yet, gamma rhythms show notable variability in cycle amplitude and duration. We developed new mathematical methods to track these moment-to-moment fluctuations. By analyzing macaque V1 data, we uncovered a number of statistical regularities, showing e.g. that instantaneous amplitudes are highly predictable over time, whereas instantaneous frequencies are essentially random and very weakly correlated with amplitude. The statistical regularities are explained by an elegant model that results from excitatory-inhibitory interactions: A damped harmonic oscillator driven by stochastic noise, where quasi-oscillatory behavior emerges because of resonance to noise. The model has several computational implications. For example, it predicts that interactions within V1 and with other areas are governed by resonance rather than entrainment. Recent work from Singer lab also suggests that inserting damped harmonic oscillator units into recurrent neural networks enhances task performance.

→ Spyropoulos G, Saponati M, Dowdall JR, Schölvinck ML, Bosman CA, Lima B, Peter A, Onorato I, Klon-Lipok J, Roese R, Neuenschwander S, Fries P, Vinck M. **Spontaneous variability in gamma dynamics described by a damped harmonic oscillator driven by noise.** *Nature Commun.* 2022 Apr 19;13(1):2019. doi:10.1038/s41467-022-29674-x.

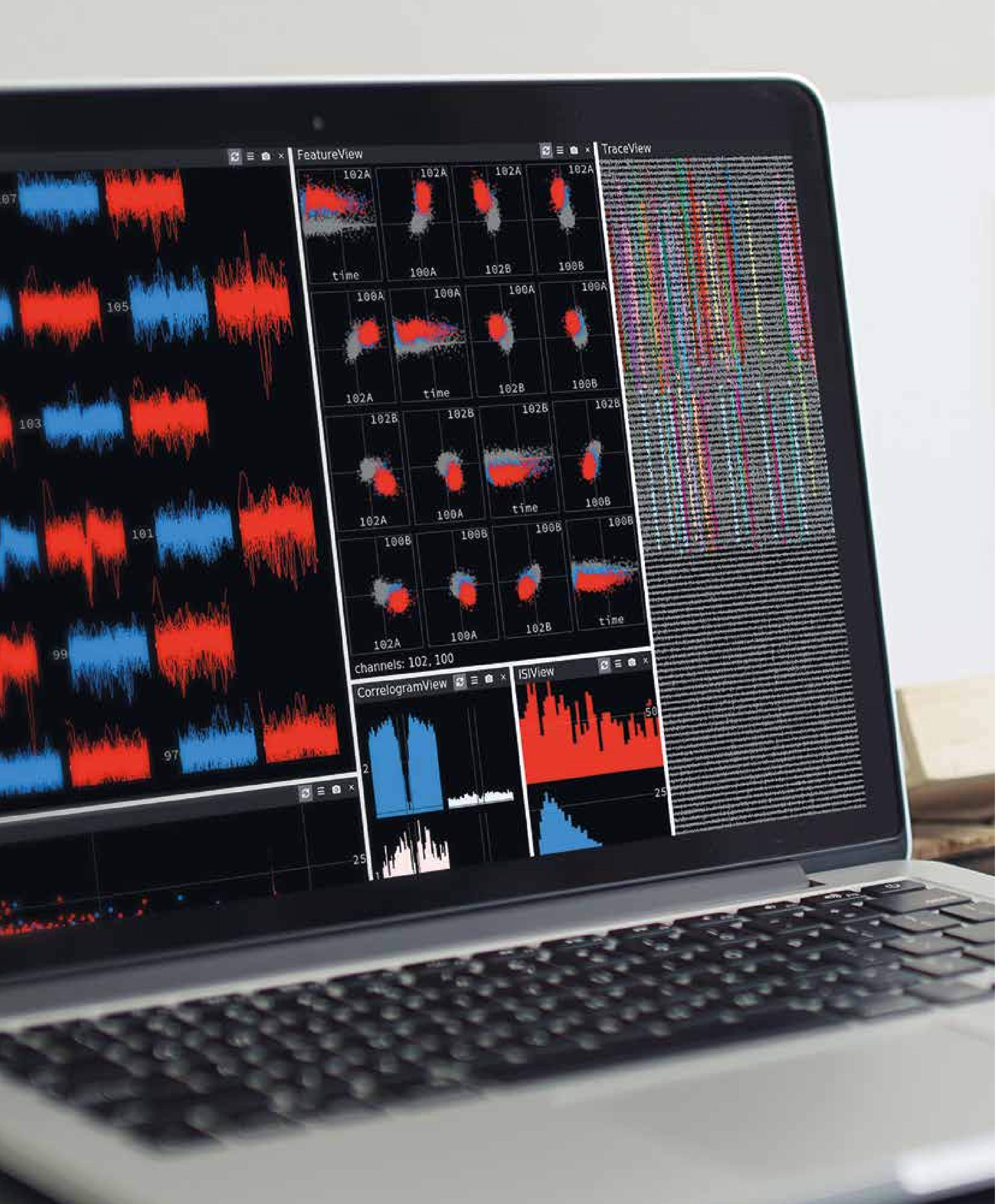
Models of gamma-rhythmic activity typically describe interactions between two neural populations: excitatory (E) and inhibitory (I) neurons. However I and E populations are subdivided in many subclasses. A main aim of the lab is to understand the interactions between and functions of these distinct subclasses. We have established in macaque (Onorato et al., 2020, Neuron), and recently in mice, the importance of bursting E cells for rhythmic activity. We recently investigated whether two main subclasses of I cells, Parvalbumin (PV) and Somatostatin-expressing (Sst) interneurons, play distinct roles. These neurons allow differential control of the activity of E cells: PV cells control the spiking output of E cells in the soma, and Sst neurons target the E cells' dendrites and thus directly interact with excitatory synaptic inputs arriving there. The exact mechanism by which network activity arises from the timed interactions between I and E subtypes remains unclear. To determine these mechanisms, it is necessary to measure their activity in vivo. This cannot be achieved with electrophysiology alone. The lab therefore develops techniques to record from different cell types. We use viral approaches to make PV and Sst interneurons excitable by light (optogenetics), and then record their activity using high-density silicon probes. The data reveals major differences between Sst and PV interneurons in mouse visual cortex. PV interneurons were substantially

→ Onorato I, PhD thesis. **Interaction between excitatory and inhibitory neuronal types in controlling cortical dynamics: An investigation in the early visual cortex of monkeys and mice.**

→ Onorato I, Tzanou A, Uran C, Broggini A, Vinck M. *Biorxiv*. 2023 (in revision for Cell Reports).

Preparation glass pipettes for virus injections

VINCK LAB



Spike sorting to identify individual neurons from electric signals

(several fold) more phase locked to network oscillations than E cells and Sst interneurons, suggesting a key role in driving synchronized, rhythmic network activity. Moreover, we observed that PV and Sst interneurons fired at distinct temporal phases. Each gamma cycle starts with a burst of excitation that is rapidly followed by PV interneuron activation, while Sst interneurons fire with a substantial delay at the end of the cycle. These findings suggest that PV and Sst interneurons control the excitability of, respectively, somatic and dendritic neural compartments of E cells with precise time delays coordinated by gamma oscillations. These findings suggest a new, richer model of gamma-rhythmic activity and contribute to our understanding of distinct functions of inhibitory cell classes.

→ Schneider M, Broggini AC, Dann B, Tzanou A, Uran C, Sheshadri S, Scherberger H, Vinck M. **A mechanism for inter-areal coherence through communication based on connectivity and oscillatory power.** *Neuron*. 2021 Dec15; 109(24): 4050-4067.e12. doi:10.1016/j.neuron.2021.09.037 Behavior

Another core interest of the lab is to understand the principles of inter-areal interactions. In a series of studies we delved into the mechanisms underlying the emergence of coherent activity across areas. Brain signals often exhibit coherence across areas, with systematic dependencies on many cognitive processes. Influential theories posit inter-areal coherence facilitates flexible communication and information transmission across brain areas. Alternatively, coherence may merely result as a product of inter-areal communication, without playing a functional role. Through mathematical modelling, our team uncovered a well-described mechanism through which inter-areal coherence is produced: Cortical neurons form synaptic contacts both within their own area and with cells in other target areas. Consequently, spiking activity in a sending area causes synaptic potentials in the same area and highly correlated synaptic potentials in another receiving area (at a delay). The developed mathematical model (Synaptic Source Mixing, SSM) explains why a sending and receiving area will naturally exhibit coherent activity. The resulting coherent activity is a consequence and not a cause of communication. The model predicts coherence precisely based on connectivity strength and oscillation power, and accounts for prominent changes in fronto-parietal and LGN-V1 coherence in macaque and mouse brain across behavioral conditions. We confirmed key predictions of the model with optogenetics perturbation experiments.

→ Vezoli J, Vinck M, Bosman CA, Bastos AM, Lewis CM, Kennedy H, Fries P. **Brain rhythms define distinct interaction networks with differential dependence on anatomy.** *Neuron*. 2021 Dec 1;109(23):3862-3878.e5. doi:10.1016/j.neuron.2021.09.052.

The model suggests a new interpretation of the functional role of neuronal coherence. This issue is especially crucial for understanding electrophysiological signals like EEG, MEG, and ECoG, widely used in human brain activity analysis. The model can be used to predict functional from structural connectivity data, and vice versa. The lab is exploring the link between structural and functional connectivity in various datasets. Consistent with the SSM model, large scale ECoG recordings reveal a close relation between structural and functional connectivity, with oscillatory power being another major predictor.

→ Dowdall JR, Schneider M, Vinck M. **Attentional modulation of inter-areal coherence explained by frequency shifts.** *Neuroimage*. 2023 Aug 15; 277:120256. doi:10.1016/j.neuroimage.2023.120256. Epub 2023 Jun 29. PMID: 37392809.

The SSM model can account for another notable empirical finding: Attention increases inter-areal V1-V4 coherence at gamma frequencies (~30-80Hz) while also increasing the sender's (V1) oscillation frequency (Bosman et al., 2012). The SSM model predicts this observation and indicates that coherence increases as a byproduct of a change in oscillation frequency, without enhanced information transfer. Our analyses also allowed us to determine whether the receiver (V4)

VINCK LAB

exhibits resonance to input from the sender (V1). We show that the data is compatible with linear mixing, but not with resonance. An important implication is that coherence is generally not diagnostic with regard to the inter-areal transfer function. This motivated us to develop a new measure of inter-areal interactions, Explained Power, which can determine the receiver's transfer function.

→ Dowdall JR, Vinck M. **Coherence fails to reliably capture inter-areal interactions in bidirectional neural systems with transmission delays.** *Neuroimage.* 2023 May 1;271:119998. doi: 10.1016/j.neuroimage.2023.119998.

The team extended the SSM model to bidirectional communication, revealing a crucial role of inter-areal transmission delays. We find differences in coherence values (and Granger-causality) can occur because of transmission delays between two bidirectionally connected areas. This dependence is not a property of the inter-areal communication itself, and does not reflect a true modulation of the strength of the inter-areal communication. Rather, it is a consequence of how coherence is computed. To solve this problem, we developed two methods that recover the directed coherence independent of transmission delays. Hence, previously reported differences in coherence are not unequivocal evidence of differences in inter-areal communication, and transmission delays need to be factored into quantitative analyses of inter-areal interactions.

→ Schneider M, Tzanou A, Uran C, Vinck M. **Cell-type-specific propagation of visual flicker.** *Cell Reports* 2023 May 30;42(5):112492. doi:10.1016/j.celrep.2023.112492. Epub 2023 May 16. PMID: 37195864.

In another series of studies we investigated how different input frequencies are integrated by a receiving neural circuit. We probe this integration via rhythmic stimulation, which is also of interest for neurological and psychiatric diseases. For example, recent work shows 40 Hz (i.e. gamma) visual flicker stimulation reduces beta-amyloid plaques in Alzheimer's mice models. A possible mechanism is brain-wide rhythmic entrainment including hippocampus and prefrontal cortex. Yet it remains poorly understood how rhythmic synchronization propagates across cortical levels, and how different frequencies influence distinct cell types in local circuits. Our team developed an approach to simultaneously record from the LGN (lateral geniculate nucleus), different layers of the primary visual cortex (V1) and CA1 hippocampus with Neuropixels. Inhibitory subtypes were identified using optogenetics. Mice viewed visual flicker stimuli of different frequencies. Our work presents two significant advantages:

First, signal propagation was highly frequency-dependent: At higher frequencies (gamma: 40Hz and higher), phase locking of neurons to the rhythmic flicker decreased at each processing stage by about a factor 10. Thus, phase-locking is strongly attenuated from LGN to L4 to L2/3 in V1, and non-detectable in hippocampal CA1 units. The data suggest that high-frequency visual inputs do not cause brain-wide entrainment, and that gamma-frequency rhythms are not conducive to feedforward communication, counter to influential theories. Second, the effects of rhythmic stimulation are highly cell-type specific. At higher frequencies (gamma and above), flicker mainly entrains fast-spiking inhibitory interneurons (primarily PV, and a subtype of Sst cells), with substantially weaker effects on excitatory neurons. A neuromorphic model explains the differences between neurons based on dendritic filtering. Thus, low-frequency synchronization propagates effectively across cortical areas and recruits excitatory and inhibitory neurons to a similar extent, whereas high-frequency synchronization stays local and primarily recruits fast-spiking inhibitory interneurons in downstream target populations.

We made similar observations by direct optogenetic stimulation of cortex (Broggini et al., in prep). The work is followed up by a DFG Schwerpunkt grant.

→ Spyropoulos, G., Schneider, M., van Kempen, J., Gieselmann, M. A., Thiele, A., & Vinck, M. **Distinct feedforward and feedback pathways for cell-type specific attention effects.** 2022. *Biorxiv* (in revision for Neuron)

We made similar observations in macaque visual cortex. Here, rhythmic activity in the lower area V1 only drives fast-spiking inhibitory neurons in the input layer of the higher visual area, V4. Surprisingly, excitatory neurons do not participate. We show that attention leads to enhanced phase locking of the inhibitory neurons, but not excitatory neurons in V4. This finding strongly argues against the theory that the gamma-frequency coherence between V1 and V4 is a mechanism to boost communication, and that an increase in this coherence mediates selective attention. Analyses of local circuit dynamics in V4 also reveal various changes in neural activity that cannot be explained by enhanced V1-to-V4 coherence: V4 firing rates increase for both excitatory neurons and inhibitory interneurons with attention. This increase is most prominent in superficial layers and precedes the modulations in V1 in time, consistent with a feedback modulation. The rate changes also track attention much more reliably than the interareal coherence, and these processes are not correlated from trial to trial. Together these findings reveal two distinct feedforward and feedback pathways for attentional modulation with

Brain recordings from mouse, control room of experimentator desk

VINCK LAB

cell-type and layer-specific physiological effects. They strongly speak against the theory that gamma-coherence mediates the selective transmission of information with attention from V1 to V4, and rather argue that attentional effects depend on feedback entering superficial layers. These findings fit with the anatomical organization of feedback and the predictions that we have made about the top-down feedback pathways mediating attention.

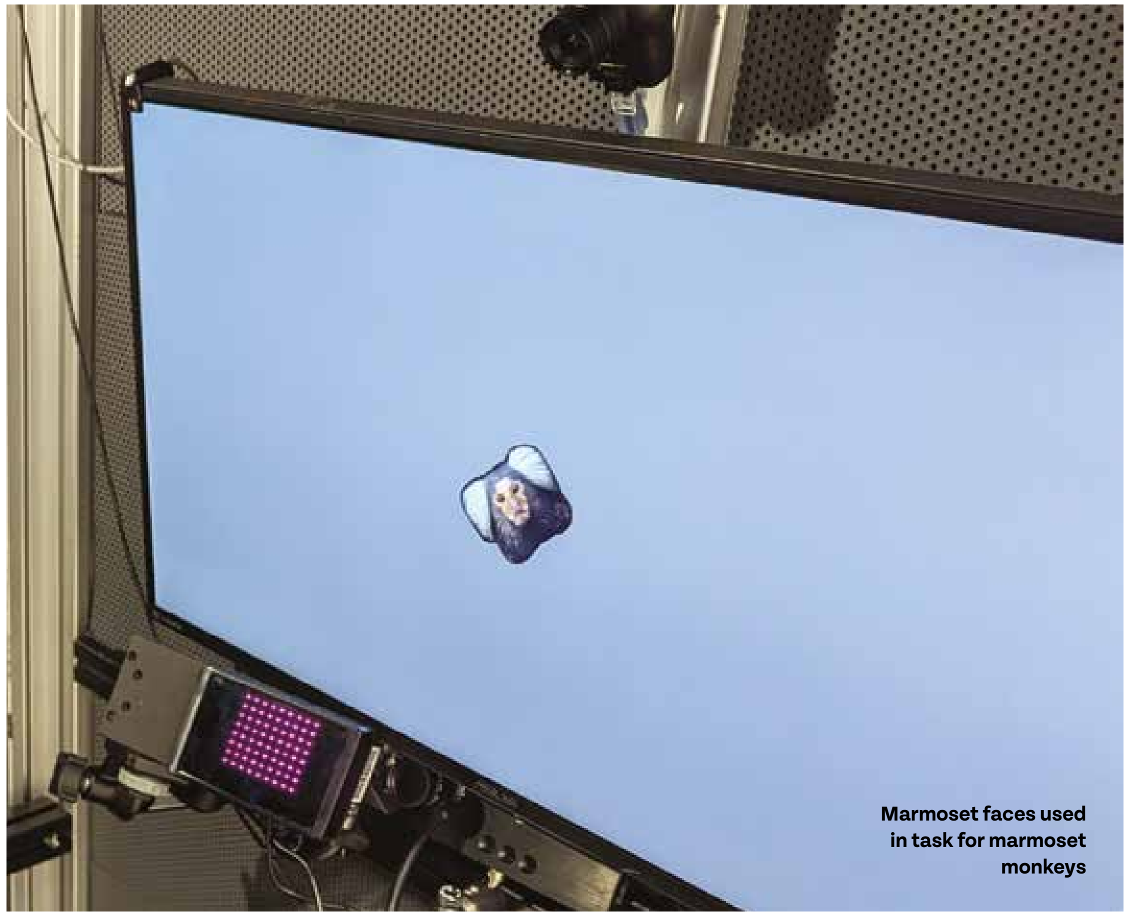
→ Vinck M, Uran C, Spyropoulos G, Onorato I, Broggini AC, Schneider M, Canales-Johnson A. **Principles of large-scale neural interactions.** *Neuron.* 2023 Apr 5;111(7):987-1002.doi:10.1016/j.neuron.2023.03.015.

Based on these data we propose a new theory of how selective attention is solved through recurrent neural dynamics biased by top-down inputs (Vinck et al., 2023). With a spiking neural network implementation (Bernstein meeting, 2023) we have shown that attention can be resolves through top-down biasing of non-linear recurrent dynamics in a circuit receiving competing inputs. This model reproduces various aspects of the empirical data.

→ Yusuf PA, Lamuri A, Hubka P, Tillein J, Vinck M, Kral A. **Deficient Recurrent Cortical Processing in Congenital Deafness.** *Front Syst Neurosci.* 2022 Feb 25;16:806142. doi:10.3389/fnsys.2022.806142. PMID: 35283734; PMCID: PMC8913535.

→ Yusuf PA, Hubka P, Tillein J, Vinck M, Kral A. **Deafness Weakens Interareal Couplings in the Auditory Cortex.** *Front Neurosci.* 2021 Jan 21;14:625721. doi:10.3389 fnins.2020.625721. PMID: 33551733; PMCID: PMC7858676.

In a cooperation with the VIANNA institute for audio neurotechnology, we applied several of the mathematical techniques developed by the lab to study brain dynamics during cochlear implant stimulation. We show genetically deaf subjects have reduced functional influences from higher to lower cortical areas, and reduced correlations between neurons indicative of a deficit in recurrent processing. These deficits occur in the absence of changes in bottom-up activa-



Marmoset faces used in task for marmoset monkeys

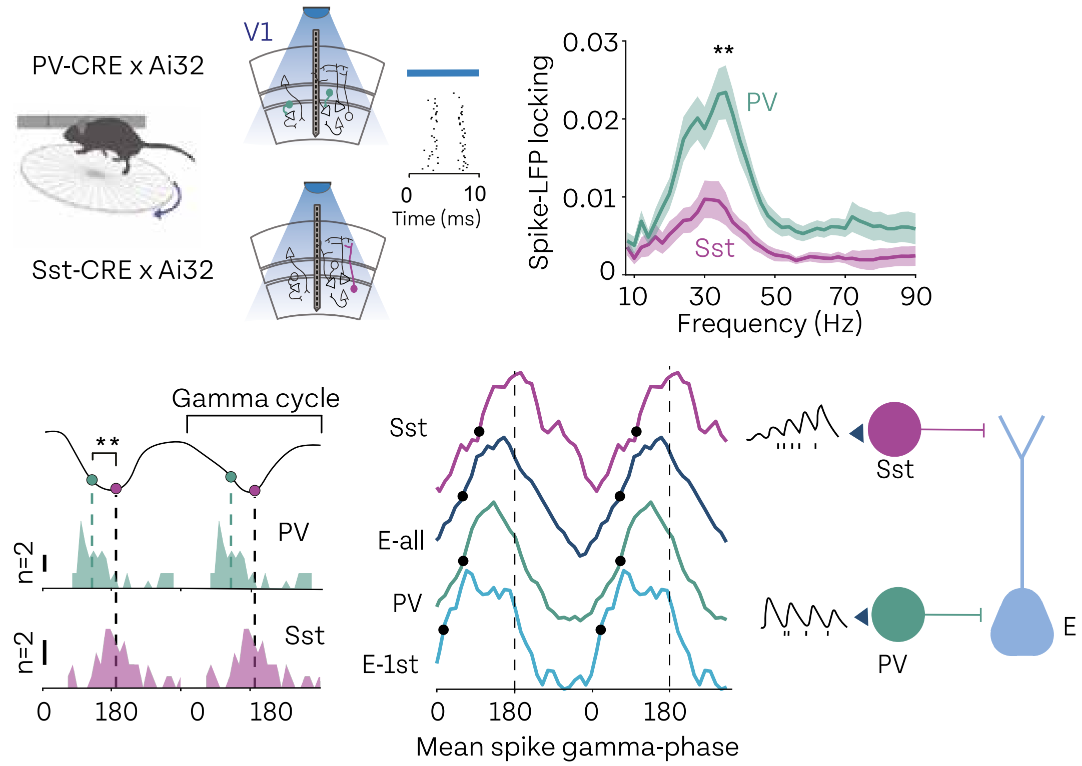


Figure 3: We used optogenetics and high-density electrophysiology to record from identified GABAergic populations in area V1 of mice, in particular PV+ and SSt+ interneurons, two of the main subpopulations of GABAergic interneurons that control the excitability of pyramidal neurons at the somatic and dendritic compartments, respectively. We found substantial stronger phase locking to network oscillations in PV+ interneurons than SSt+ interneurons. Within each gamma cycle, PV+ interneurons fired very shortly after the initial increase in excitatory firing, whereas SSt+ interneurons fired with a substantial delay. These findings indicate network synchronization of excitatory neurons is primarily controlled by PV+ interneurons, while PV+ and SSt+ control the excitability of somatic and dendritic neural compartments at different times. *See Irene Onorato et al. (2023).*

tion strength via cochlear stimulation. These findings provide new insights into the way in which deafness affects cortical integration and the way in which the brain processes cochlear implant stimuli.

The lab's work on this theme was featured in an invited Perspective paper for Neuron's special issue on neural dynamics. We discuss new insights into the mechanisms underlying flexible inter-areal communication in the cortex. We discuss major challenges for communication-through-coherence based on layer- and cell-type-specific analyses of spike phase-locking, heterogeneity of dynamics across networks and states, and computational models for selective communication. As an alternative, we propose that coherence arises as a consequence of communication, with a lawful dependence on structural connectivity and signal power. We further argue that resonance and non-linear integration are viable alternative mechanisms that facilitate computation and selective communication in recurrent networks. Finally, we propose dual roles for transient and rhythmic modes in cortex: We propose that feedforward propagation of prediction errors relies on the non-linear amplification of aperiodic transients, whereas gamma and beta rhythms represent rhythmic equilibrium states that facilitate sustained and efficient information encoding and amplification of short-range feedback via resonance.

SERVICE
SUPPORT
GROUPS

SCIENTIFIC CORE FACILITY

THE POWER OF SHARED RESOURCES

Head of Scientific Core Facility Thomas Wunderle

The Scientific Core Facility at ESI serves to support all scientists in their research with hightech equipment, trainings and maintenance.

The concept is simple: Instead of a decentralized structure where, let's say, each research group buys its own microscope, the core facility provides a microscope that every researcher can use. This has several advantages including cost reduction, optimal use and maintenance, and perhaps most importantly, it ensures that the knowledge of how best to use and operate the microscope remains within the institute. The following paragraphs describe the services available at ESI's Scientific Core Facility.

The Histology Lab

ESI has a central histology laboratory that provides scientists with the basic equipment needed to perform histological examinations of brain tissue, such as equipment for perfusion, cryosectioning, or immunohistochemistry. It also provides equipment and chemicals for the preparation of various chemical buffers and solutions. Scientists and technical staff are also trained in histological procedures and the safe handling of chemicals.

The Microscopy Facility

The core facility provides a microscope for wide field imaging of histological sections, covering most applications. For more specialized needs, we have access to a confocal laser scanning microscope (CLSM) located at the Physiological Institute II of the Goethe University. For calcium live cell imaging in awake behaving animals, the core facility also operates a two-photon microscope. This system is flexible and can be adapted to the requirements of the experimenters. The Core Facility also provides training in microscopy and microscopy data analysis, as well as software tools and protocols for image processing.

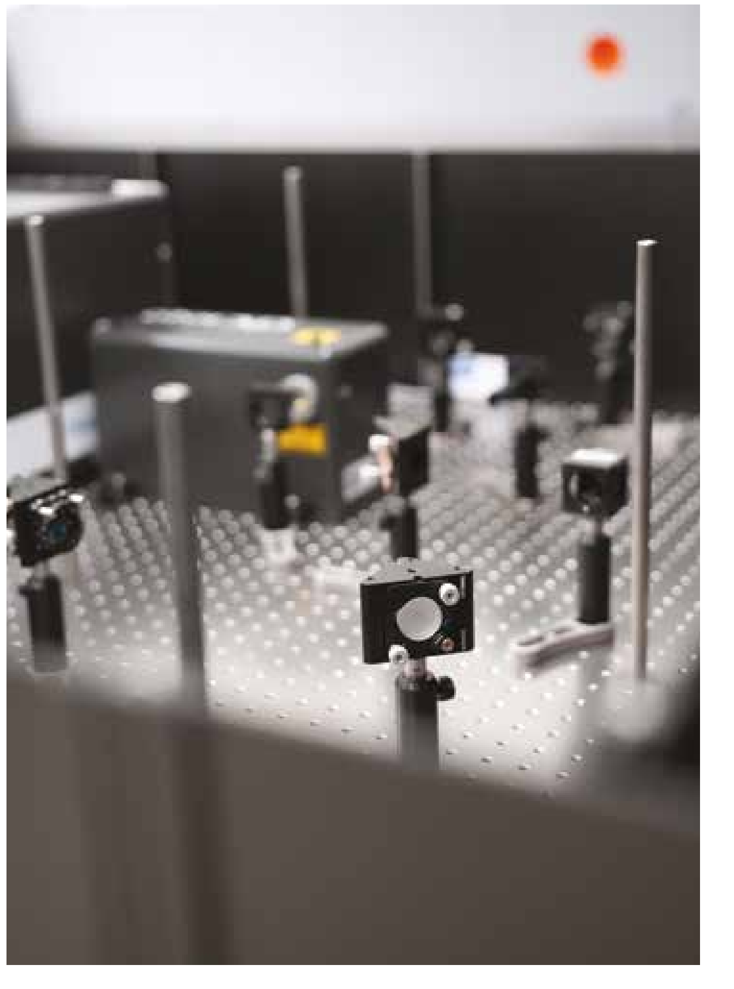
The Surgery Facility

The core facility includes operating rooms for large and small animals equipped with the necessary tools and facilities to perform sterile surgery. These include surgical instruments, microscopes, and machines for various sterilization methods such as autoclaving or low-temperature H_2O_2 sterilization. Additionally, in the surgical facility 3D radiographs can be taken using ESI's x-ray machine, essential for proper planning of the animal's implants.

A surgical microscope which, in addition to the classic optics, also contains a camera with which the whole team can follow the surgery

The Cooperative Brain Imaging Center

ESI is part of the Cooperative Brain Imaging Center (CoBIC) in collaboration with the Goethe University Frankfurt and the Max Planck Institute for Empirical Aesthetics. The CoBIC will soon move into its new building next to ESI and will be equipped with two 3T and one 7T scanner for use in both human and animal research. In addition, the CoBIC operates a 275-channel MEG system, which is also used by ESI researchers. The core facility serves as a link between ESI and the CoBIC.



Optical pathway of the laser light used for in vivo two-photon calcium imaging

TECHNICAL GROUP

FROM RAMs TO 3D

The Technical Group (TG) provides support for ESI scientists and staff members with three teams working closely together under the guidance of Kai Rönnburg.

IT-TEAM

Kai Rönnburg IBM Power, Linux, HPC, Network, Security, File Services, Backup & Archive
Michael Schwickart MacOS, Storage Systems, user support
Alexander Göllner Windows Active Directory, Provisioning, Network, ESXi, Print Services, PBX
Michael Stephan Lab support & Software development, Windows, Network
Stefan Fürtinger Lab support & Software development, Linux, HPC, Archive
Florian Bayer (student trainee) Security, Linux, HPC, File Services, Linux trainings

ESI data archive: the tape library is the digital custodian that holds the collected history of every experiment, recording, and analysis performed at the institute safeguarded on magnetic tapes.

Besides the "regular" IT services, ESI IT operates a relatively large HPC cluster with:

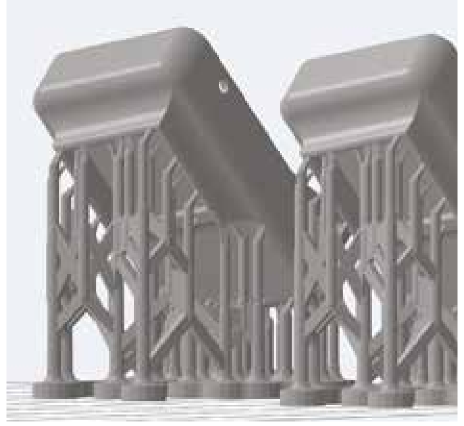
- +156 users (within ESI and worldwide collaborations),
- 51 Intel Xeon Nodes (816 Threads) with 6.5 TB of Ram,
- 6 Intel/AMD/Power GPU Nodes (23 GPUs) with 1.6 TB Ram,
- 5 IBM Power E880 Nodes, 320 x IBM power8 cores (5120 Threads) with 28 TB Ram.

They are connected via 200 GB/s Infiniband infrastructure to an IBM ESS file server with 1.244 TB capacity (80/60 GB/s read/write). A high performance network with transmissions speeds up to 120 GB/s connects lab-spaces with ESI IT. The Cluster will grow up to 96 TB with about 9.216 Threads by March 2024.
Besides services for the staff members e. g. printing, WLAN, SAP, intranet and file services, an ESI-wide in-house backup and archive service is provided with two IBM TS4500 tape libraries with a total capacity of about 3.100 tapes, currently holding about 3.9 PB in backup and about 560 TB of scientific archive data at two different locations within ESI.

ELECTRONICS WORKSHOP

Georg Haas Lab support, customized electronics, 3D surface reconstruction, and rapid prototyping

Besides electronic projects, the electronic workshop supports scientists with the 3D design of custom implants and chambers used in various experimental setups. Additionally, the electronics workshop supports the installation of lab space and equipment, MEG and CT devices hosted at the University campus and ESI, and the processing of 3D images taken with them.



Preparation for a 3D printjob on a stereolithography (SLA) 3D printer. A slicing software uses automatic algorithms to set up the layout of a 3D print – in this case some lids to cover chambers.

MECHANICAL WORKSHOP

David Konietzny Technical design and production
Sven Haja Production & assembly
Joshua Leibrock Production & assembly

Mechanical workshop projects range from the design and construction of a new recording booth or animal holding facilities to the manufacturing of small implants for primates, cats, and rodents. Based on 3D models generated from MEG/CT scans the workshop plans together with the scientists the required pieces for setups and implants. In order to accomplish all these challenging tasks, the mechanical workshop utilizes 3D workstations for CAD/CAM and several automated machines.

- Hermle C22 / Fully automated 5-axis milling machine used for manufacturing of implants and small pieces up to 450 mm in size
- Alzmetall CS600 / Fully automated 3-axis milling machine with optional upgrade to 4- and 5-axis used for parts up to 60 cm in size
- Kunzmann WF4 / Half-automated 3-axis milling machine for bigger parts
- Weiler E30 / Automated turning machine for production of pieces from 3 mm up to 160 mm

Even though manual tools, e.g. saws and drilling machines, belong to the equipment of the workshop, the majority of parts is produced on automated machines, to ensure high quality and reproducibility.

5-axis simultaneous milling of a chamber made of titanium grade 5 Eli; designed and programmed using CAD/CAM

ANIMAL FACILITY

WITH CARE FOR ANIMAL WELFARE

Veterinary Specialists Christa Tandi, Alf Theisen / Animal Care Takers Luisa Ehret, Franziska Kaiser, Stefanie Kranz, Marie Kunz, Nadine Schieche

The Animal Facilitiy of the Ernst Strüngmann Institute keeps the animal species required for the respective research projects in a manner appropriate to animal welfare.

Within the facilities of the MPG, ESI Animal Facilitiy offers the unique possibility of keeping non-human primates (NHPs) as well.
There are currently three animal husbandry areas:

- a barrier facility for rodents to keep mice and rats according to SPF status,
- a facility for marmoset monkeys,
- and a facility for macaques.

The macaques even have outdoor enclosures at their disposal. In total, about 400 mice, 22 marmoset monkeys, and 21 macaques are currently kept.

Female macaque "Bienchen" curiously observes the photography session. She is one of 21 macaques who live at the ESI.

FACILITY MANAGEMENT

WELL-ROUNDED FOLDER OF MULTIPLE DISCIPLINES

Team-Leader Michael Schmitt / Facility Maintenance Mathias Blum, Bachar Dady, Daud Pajvastun, Anto Starcevic, Matej Suzanj / Gardener Jürgen Lange

The FM (Facility Management) team is made up of several key members, each with a specific role and responsibilities within the team to ensure that the facilities and working environment are managed efficiently. This includes the manager, who is also ESI's Occupational Safety and Fire Protection Officer. In addition, there are two electricians, a gardener, and two all-rounders. This composition suggests a well-rounded FM team capable of managing various aspects of facility maintenance, safety, and aesthetics. The manager's dual role as the Occupational Safety and Fire Protection Officer under-scores the importance of safety within the organization.

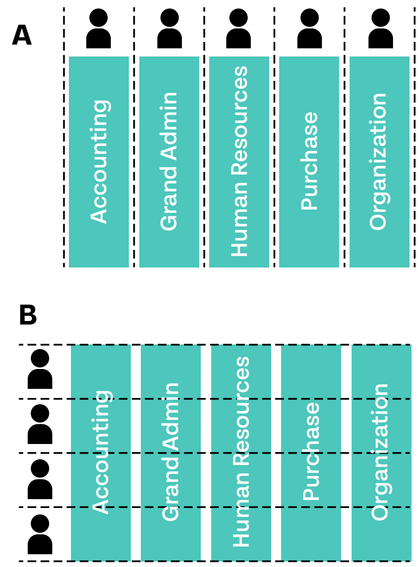
ADMINISTRATION

FLEXIBLE AND EFFICIENT

Head of Administration Matthias Baumgarten / Team-Leader Michal Mastalirz / Team Marcus Euler, Fabian Messer, Thomas Tenzler, Julia Trommershäuser

The administration of Max Planck Institutes is subdivided in specialized domains (A). The remarkable aspect is that the Ernst Strüngmann Institute (ESI) was able to implement an alternative, horizontal way of organizing the administration due to its independent status (B).

This innovative approach enables the administration to keep pace with the growth of the institute without interface problems between the traditional administrative departments of Human Resources, Accounting, Purchasing and Organization. This in turn helps to optimize and facilitate service delivery. So far, this novel form of organization has proven to be highly effective and is instrumental in ensuring the efficiency and smooth functioning of ESI. The flexible adaptability of the administration to the needs of the Institute enables ESI to achieve its research and development goals in a harmonious and coordinated environment. This model could also serve as an inspiring example for other research institutions on how administration can be optimally structured to successfully support an institution's mission and goals.



PUBLIC RELATIONS & INFORMATION MANAGEMENT (PRIM)

TALKING SCIENCE

Communications Officer Katharina Hempel / Information Manager Simone Plewik / Graphic Design Claudia Kernberger

The Public Relations and Information Management Department maintains information flow within and beyond the Ernst Strüngmann Institute (ESI) for Neuroscience, handling internal and external communications as well as library services.

The annual ESI Systems Neuroscience Conference (ESI SyNC) is the scientific highlight of every year and is accompanied and promoted by the press department using a range of media, from press releases to the institute's social media channels.

External Communication

The PRIM department keeps the institute's website, social media channels, and press distribution services up-to-date. It creates news relevant to the public in an appropriate format and disseminates it through the relevant channels. The department translates research findings into blog posts, tweets, or press releases and is always happy to hear about and report on ongoing or completed experiments from ESI scientists! To achieve optimal targeting the department utilizes text, images, videos and infographics. Additionally, the communications department handles press inquiries and supports journalists in finding suitable interviewees or experts for background discussions.

Another form of external communication involves organizing or supporting various outreach events, such as Girls' & Boys' Day, lecture evenings, or scientific conferences, and symposia. ESI is committed not only to conducting cutting-edge research, but also to effectively communicate it to the outside world!

Internal Communication

The aim of internal communications is to inform and inspire employees while fostering their sense of identification with the institute. Our summer and winter parties contribute to this objective. A monthly internal email newsletter updates employees on new colleagues, events, celebrations, and important or interesting information related to everyday life at the institute. PRIM sends short-term, important information via separate emails to a general or more specific internal distribution list. Alternatively, it is displayed as a poster in the elevator, a more traditional but equally effective method.

Information Management

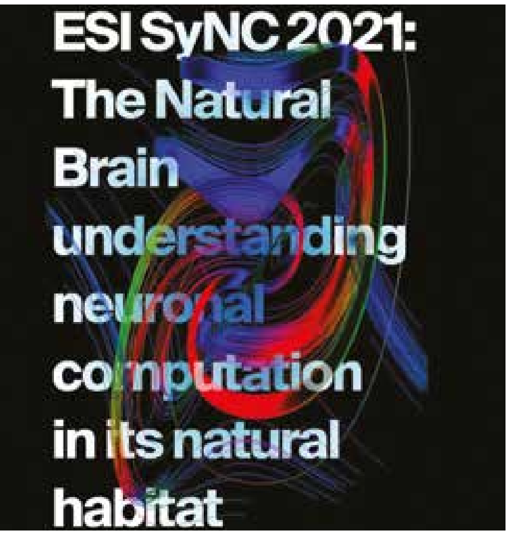
The library takes care of digital and analog access to scientific literature and manages the publications of ESI researchers in a publication database.

Information Management supports the global effort towards open science, encouraging researchers to publish in open-access journals and to make data available to other researchers through repositories. To support the underlying transformation process towards publication-based subscriptions, ESI has joined the MPDL-coordinated "Project DEAL" with the publishers Wiley and Springer Nature, and as of 2024, with the publisher Elsevier.

Publications are organized and administered using the Max Planck Society's PuRe database and, when legally feasible, are made publicly available as publisher's versions or postprints along with the dataset. The database is connected to ESI website so that the latest lists of publications of the entire institute as well as individual research groups are readily available.
To address the growing importance of preprints, the library also maintains its own channel on the preprint server BioRxiv, which collects all ESI-linked preprints published there.

One highlight event of 2023 was the premiere of the new "ESImeets..." series with Frankfurt-based renowned music formation Ensemble Modern. The series aims to inspire a broad audience for neuroscience in an entertaining way.

OUTREACH & EVENTS



ESI SyNC. The annual systems neuroscience conference brings about a dozen lecturers to ESI for two days of intensive lectures and discussions. The conference is conceived, planned, organized, and executed by ESI students and postdocs.

On **Girls' Day** at ESI, 24 female high school students came for the day to learn about neuroscience and visit different labs. Thanks to PI Dr. Rosanne Rademaker, this outreach and education event was a tremendous success that ESI aims to repeat.

Cutting Gardens. This innovative conference on how to analyze electrophysiological data combined local workshops and lectures with global lectures and discussions. A number of internationally distributed 'gardens' served as local sites, hosting workshops, poster sessions, and lectures. At specified times, all local sites across the world gathered at the same time to listen to globally broadcast lectures. Thanks to ESI local organizer Dr. Natalie Schaworonkow, the event was a huge academic and social success.

ESImeets... aims to expose the community to what the institute's research is about – while also providing entertaining and fun events. At our first event, ESImeets...Music, the world-renowned Ensemble Modern played a series of pieces, in alternation with David Poeppel providing glimpses of research into auditory perception.
Next in 2024: ESImeets...Magic.

PUBLICATIONS

Neuron

Article

A mechanism for inter-areal coherence through communication based on connectivity and oscillatory power

Highlights

- Synaptic projections from a sending to a receiving area explain long-range coherence
- Inter-areal coherence can be predicted by power and

Authors

Marius Schneider, Ana Clara Broggini, Benjamin Dann, ..., Swathi Sheshadri, Hansjörg Scherberger, Martin Vinck

nature communications

Article

https://doi.org/10.1038/s41467-023-38587-2

Robust encoding of natural stimuli by neuronal response sequences in monkey visual cortex

Received: 1 June 2022

Accepted: 8 May 2023

Published online: 25 May 2023

Yang Yiling[1,2,3], Katharine Shapcott[1,4], Alina Peter[1,2,3], Johanna Klon-Lipok[5], Huang Xuhui[6,7], Andreea Lazar[1] & Wolf Singer[1,4,5]

eLife

RESEARCH ARTICLE

Flexible utilization of spatial- and motor-based codes for the storage of visuo-spatial information

Margaret M Henderson[1,2,3]*, Rosanne L Rademaker[4,5], John T Serences[1,4,6]

[1]Neurosciences Graduate Program, University of California, San Diego, San Diego, United States; [2]Department of Machine Learning, Carnegie Mellon University, Pittsburgh, United States; [3]Neuroscience Institute, Carnegie Mellon University, Pittsburgh, United States; [4]Department of Psychology, University of California, San Diego, San Diego, United States; [5]Ernst Strüngmann Institute (ESI) for Neuroscience in Cooperation with Max Planck Society, Frankfurt, Germany; [6]Kavli Foundation for the Brain and Mind, University of California, San Diego, San Diego, United States

PNAS

RESEARCH ARTICLE | PSYCHOLOGICAL AND COGNITIVE SCIENCES

Syllables and their beginnings have a special role in the mental lexicon

Yue Sun[a,1] and David Poeppel[a,b,c]

Edited by Patricia Kuhl, University of Washington, Seattle, WA; received September 14, 2022; accepted June 13, 2023

The beginnings of words are, in some informal sense, special. This intuition is widely shared, for example, when playing word games. Less apparent is whether the intuition is substantiated empirically and what the underlying organizational principle(s) might be. Here, we answer this seemingly simple question in a quantitatively clear way. Based on

Significance

How spoken words are stored in the mind/brain is a fascinating

Neuron

Article

Predictive coding of natural images by V1 firing rates and rhythmic synchronization

Highlights

- Predictability in natural images quantified with self-supervised neural networks
- V1 firing rates decrease with predictability of high- not low-level image features
- γ-synchronization increases with predictability of low-level

Authors

Cem Uran, Alina Peter, Andreea Lazar, ..., Pascal Fries, Wolf Singer, Martin Vinck

Correspondence

cem.uran@esi-frankfurt.de (C.U.), martin.vinck@esi-frankfurt.de (M.V.)

PLOS COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

Dendritic normalisation improves learning in sparsely connected artificial neural networks

Alex D. Bird[1,2,3]*, Peter Jedlicka[2,3], Hermann Cuntz[1,2]

1 Ernst Strüngmann Institute for Neuroscience (ESI) in co-operation with Max Planck Society, Frankfurt, Germany, **2** Frankfurt Institute for Advanced Studies (FIAS), Frankfurt, Germany, **3** ICAR3R-Interdisciplinary Centre for 3Rs in Animal Research, Faculty of Medicine, Justus Liebig University Giessen, Giessen, Germany

* bird@fias.uni-frankfurt.de

2021

Barnes-Scheufler C, Passow C, Rösler L, Mayer J, Oertel V, Kittel-Schneider S, Matura S, Reif A, Bittner R (2021). **Transdiagnostic comparison of visual working memory capacity in bipolar disorder and schizophrenia.** *International Journal of Bipolar Disorders,* 9(1), 12. https://doi.org/10.1186/s40345-020-00217-x

Bird AD, Jedlicka P, Cuntz H (2021). **Dendritic normalisation improves learning in sparsely connected artificial neural networks.** *PLoS Computational Biology,* 17(8), e1009202. https://doi.org/10.1371/journal.pcbi.1009202

Bird AD, Deters LH, Cuntz H (2021). **Excess neuronal branching allows for local innervation of specific dendritic compartments in mature cortex.** *Cerebral Cortex,* 31(2), 1008-1031. https://doi.org/10.1093/cercor/bhaa271

Corrigan AE, Taylor R, Rallis KS (2021). **Next-generation sequencing of cancer genomes: lessons learned.** *Future Oncology,* 17(31), 4041-4044. https://doi.org/10.2217/fon-2021-0764

Cuntz H, Bird AD, Mittag M, Beining M, Schneider M, Mediavilla L, Hoffmann FZ, Deller T, Jedlicka P (2021). **A general principle of dendritic constancy: A neuron's size- and shape-invariant excitability.** *Neuron,* 109(22), 3647-3662.e7. https://doi.org/10.1016/j.neuron.2021.08.028

Engel TA, Schölvinck M, Lewis CM (2021). **The diversity and specificity of functional connectivity across spatial and temporal scales.** *NeuroImage,* 245, 118692. https://doi.org/10.1016/j.neuroimage.2021.118692

Fries P (2021). **Hemispheres in harmony.** *Neuron,* 109(6), 916-917. https://doi.org/10.1016/j.neuron.2021.02.026

Gupta DS, Bahmer A (2021). **Editorial: Understanding the importance of temporal coupling of neural activities in information processing underlying action and perception.** *Frontiers in Computational Neuroscience,* 15, 729296. https://doi.org/10.3389/fncom. 2021.729296

Jendritza P, Klein FJ, Rohenkohl G, Fries P (2021). **Visual neuroscience methods for marmosets: efficient receptive field mapping and head-free eye tracking.** *eNeuro,* 8(3), 1-16. https://doi.org/10.1523/eneuro.0489-20.2021

Kienitz R, Schmid MC, Dugué L (2022). **Rhythmic sampling revisited: Experimental paradigms and neural mechanisms.** *European Journal of Neuroscience,* 55(11-12), 3010-3024. https://doi.org/10.1111/ejn.15489

Kienitz R, Cox MA, Dougherty K, Saunders RC, Schmiedt JT, Leopold DA, Maier A, Schmid M (2021). **Theta, but not gamma oscillations in area V4 depend on input from primary visual cortex.** *Current Biology,* 31(3), 635-642.e3. https://doi.org/10.1016/j.cub.2020.10.091

Lazar A, Lewis C, Fries P, Singer W, Nikolic D (2021). **Visual exposure enhances stimulus encoding and persistence in primary cortex.** *Proceedings of the National Academy of Sciences of the United States of America,* 118(43), e2105276118. https://doi.org/10.1073/pnas.2105276118

Lewis CM, Ni J, Wunderle T, Jendritza P, Lazar A, Diester I, Fries P (2021). **Cortical gamma-band resonance preferentially transmits coherent input.** *Cell Reports,* 35(5), 109083. https://doi.org/10.1016/j.celrep.2021.109083

Mao D, Avila E, Caziot B, Laurens J, Dickman JD, Angelaki DE (2021). **Spatial modulation of hippocampal activity in freely moving macaques.** *Neuron,* 109(21), 3521-3534.e6. https://doi.org/10.1016/j.neuron.2021.09.032

Michels A, Frank AM, Günther DM, Mataei M, Börner K, Grimm D, Hartmann J, Buchholz CJ (2021). **Lentiviral and adeno-associated vectors efficiently transduce mouse T lymphocytes when targeted to murine CD8.** *Mol Ther Methods Clin Dev,* 23, 334-347. https://doi.org/10.1016/j.omtm.2021.09.014

Peter A, Stauch BJ, Shapcott K, Kouroupaki K, Schmiedt JT, Klein L, Klon-Lipok J, Dowdall JR, ... Fries P (2021). **Stimulus-specific plasticity of macaque V1 spike rates and gamma.** *Cell Reports,* 37(10), 110086. https://doi.org/10.1016/j.celrep.2021.110086

Rimmele JM, Sun Y, Michalareas G, Ghitza O, Poeppel D (2023). **Dynamics of functional networks for syllable and word-level processing.** *Neurobiology of Language,* 4(1), 120-144. https://doi.org/10.1162/nol_a_00089

Schaum M, Pinzuti E, Sebastian A, Lieb K, Fries P, Mobascher A, Jung P, Wibral M, Tüscher O (2021). **Right inferior frontal gyrus implements motor inhibitory control via beta-band oscillations in humans.** *eLife,* 10, e61679. https://doi.org/10.7554/eLife.61679

Schneider M, Broggini AC, Dann B, Tzanou A, Uran C, Sheshadri S, Scherberger H, Vinck M (2021). **A mechanism for inter-areal coherence through communication based on connectivity and oscillatory power.** *Neuron,* 109(24), 4050-4067.e12. https://doi.org/10.1016/j.neuron.2021.09.037

Singer W (2021a). **Neuroscience history interview with Professor Wolf Singer, emeritus director at the Department of Neurophysiology, Max Planck Institute for Brain Research in Frankfurt am Main.** *Journal of the History of the Neurosciences.* London: Smith-Gordon. https://doi.org/10.1080/0964704X.2021.1904714

Singer W (2021c). **The cerebral cortex: A delay-coupled recurrent oscillator network?.** In: Nakajima K, Fischer I (Eds.): Reservoir computing. Theory, physical implementations, and applications (pp. 3-28). Singapore: *Springer Nature Singapore.* https://doi.org/10.1007/978-981-13-1687-6_1

Singer W (2021b). **Recurrent dynamics in the cerebral cortex: Integration of sensory evidence with stored knowledge.** *Proceedings of the National Academy of Sciences of the United States of America,* 118(33), e2101043118. https://doi.org/10.1073/pnas.2101043118

Stauch BJ, Peter A, Schuler H, Fries P (2021). **Stimulus-specific plasticity in human visual gamma-band activity and functional connectivity.** *eLife,* 10, e68240. https://doi.org/10.7554/eLife.68240

Sun Y, Michalareas G, Poeppel D (2021). **The impact of phase entrainment on auditory detection is highly variable: Revisiting a key finding.** *European Journal of Neuroscience,* 55(11-12), 3373-3390. https://doi.org/10.1111/ejn.15367

Tang-Wright K, Smith JET, Bridge H, Miller KL, Dyrby TB, Ahmed B, Reislev NL, Sallet J, ... Krug K (2022). **Intra-areal visual topography in primate brains mapped with probabilistic tractography of diffusion-weighted imaging.** *Cerebral Cortex,* 32(12), 2555-2574. https://doi.org/10.1093/cercor/bhab364

van der Plas M, Braun V, Stauch BJ, Hanslmayr S (2021). **Stimulation of the left dorsolateral prefrontal cortex with slow rTMS enhances verbal memory formation.** *PLoS Biology,* 19(9), e3001363. https://doi.org/10.1371/journal.pbio.3001363

van Heukelum S, Geers FE, Tulva K, van Dulm S, Beckmann SF, Buitelaar JK, Glennon JC, Vogt BA, ... França ASC (2021). **Structural degradation in midcingulate cortex is associated with pathological aggression in mice.** *Brain Sciences,* 11(7), 868. https://doi.org/10.3390/brainsci11070868

van Heukelum S, Tulva K, Geers FE, van Dulm S, Ruisch IH, Mill J, Viana JF, Beckmann CF, ... França ASC (2021). **A central role for anterior cingulate cortex in the control of pathological aggression.** *Current Biology,* 31(11), 2321-2333.e5. https://doi.org/10.1016/j.cub.2021.03.062

van Leeuwen TM, Sauer A, Jurjut A-M, Wibral M, Uhlhaas PJ, Singer W, Melloni L (2021). **Perceptual gains and losses in synesthesia and schizophrenia.** *SCHIZOPHRENIA BULLETIN,* 47(3), 722-730. https://doi.org/10.1093/schbul/sbaa162

Vezoli J, Vinck M, Bosman CA, Bastos AM, Lewis CM, Kennedy H, Fries P (2021). **Brain rhythms define distinct interaction networks with differential dependence on anatomy.** *Neuron,* 109(23), 3862-3878.e5. https://doi.org/10.1016/j.neuron.2021.09.052

Vezoli J, Magrou L, Goebel R, Wang X-J, Knoblauch K, Vinck M, Kennedy H (2021). **Cortical hierarchy, dual counterstream architecture and the importance of top-down generative networks.** *NeuroImage,* 225, 117479. https://doi.org/10.1016/j.neuroimage.2020.117479

Yusuf PA, Hubka P, Tillein J, Vinck M, Kral A (2021). **Deafness weakens interareal couplings in the auditory cortex.** *Frontiers in Neuroscience,* 14, 625721. https://doi.org/10.3389/fnins.2020.625721

Zaidel A, Laurens J, DeAngelis GC, Angelaki DE (2021). **Supervised multisensory calibration signals are evident in VIP but not MSTd.** *The Journal of Neuroscience,* 41(49), 10108-10119. https://doi.org/10.1523/jneurosci.0135-21.2021

2022

Adam KCS, Rademaker R, Serences JT (2023). **Dynamics are the only constant in working memory.** *Journal of Cognitive Neuroscience,* 351, 24-26. https://doi.org/10.1162/jocn_a_01941

Adolfi F, Wareham T, van Rooij I (2023). **A computational complexity perspective on segmentation as a cognitive subcomputation.** *Topics in Cognitive Science,* 15(2), 255-273. https://doi.org/10.1111/tops.12629

Bowers JS, Malhotra G, Dujmović M, Montero ML, Tsvetkov C, Biscione V, Puebla G, Adolfi F, ... Blything R (2022). **Deep problems with neural network models of human vision.** *Behavioral and Brain Sciences,* 1-74. https://doi.org/10.1017/S0140525X 22002813

Donhauser PW, Klein D (2022). **Audio-Tokens: A toolbox for rating, sorting and comparing audio samples in the browser.** *Behavior Research Methods.* https://doi.org/10.3758/s13428-022-01803-w

Edwards LJ, McColgan P, Helbling S, Zarkali A, Vaculčiaková L, Pine KJ, Dick F, Weiskopf N (2022). **Quantitative MRI maps of human neocortex explored using cell type-specific gene expression analysis.** *Cerebral Cortex,* bhac453. https://doi.org/10.1093/cercor/bhac453

Edwards LJ, McColgan P, Helbling S, Zarkali A, Vaculčiaková L, Pine KJ, Dick F, Weiskopf N (2023). **Quantitative MRI maps of human neocortex explored using cell type-specific gene expression analysis.** *Cerebral Cortex,* 33(9), 5704-5716. https://doi.org/10.1093/cercor/bhac453

Freudenberg F, Althen H, Falk K, Bittner RA, Reif A, Plichta MM (2022). **Test-retest reliability of prepulse inhibition (PPI) and PPI correlation with working memory.** *Acta Neuropsychiatrica,* 34(6), 344-353. https://doi.org/10.1017/neu.2022.19

Fries P, Maris E (2022). **What to do if N is two?** *Journal of Cognitive Neuroscience,* 34(7). https://doi.org/10.1162/jocn_a_01857

García-Rosales F, López-Jury L, González-Palomares E, Wetekam J, Cabral-Calderín Y, Kiai A, Kössl M, Hechavarría JC (2022). **Echolocation-related reversal of information flow in a cortical vocalization network.** *Nature Communications,* 13, 3642. https://doi.org/10.1038/s41467-022-31230-6

Gwilliams L, King J-R, Marantz A, Poeppel D (2022). **Neural dynamics of phoneme sequences reveal position-invariant code for content and order.** *Nature Communications,* 13, 6606. https://doi.org/10.1038/s41467-022-34326-1

Henderson MM, Rademaker R, Serences JT (2022). **Flexible utilization of spatial- and motor-based codes for the storage of visuo-spatial information.** *eLife,* 11, e75688. https://doi.org/10.7554/eLife.75688

Hettwer MD, Lancaster TM, Raspor E, Hahn PK, Mota NR, Singer W, Reif A, Linden DEJ, Bittner RA (2022). **Evidence from imaging resilience genetics for a protective mechanism against schizophrenia in the ventral visual pathway.** *SCHIZOPHRENIA BULLETIN,* 48(3), 551-562. https://doi.org/10.1093/schbul/sbab151

Jedlicka P, Bird AD, Cuntz H (2022). **Pareto optimality, economy-effectiveness trade-offs and ion channel degeneracy: improving population modelling for single neurons.** *Open Biology,* 12(7), 220073. https://doi.org/10.1098/rsob.220073

Kienitz R, Kouroupaki K, Schmid MC (2022). **Microstimulation of visual area V4 improves visual stimulus detection.** *Cell Reports,* 40(12), 111392. https://doi.org/10.1016/j.celrep.2022.111392

Kienitz R, Schmid MC, Dugué L (2022). **Rhythmic sampling revisited: Experimental paradigms and neural mechanisms.** *European Journal of Neuroscience,* 55(11-12), 3010-3024. https://doi.org/10.1111/ejn.15489

Laurens J (2022). **The otolith vermis: A systems neuroscience theory of the Nodulus and Uvula.** *Frontiers in Systems Neuroscience,* 16, 886284. https://doi.org/10.3389/fnsys. 2022.886284

Liu J, Vinck M (2022). **Improved visualization of high-dimensional data using the distance-of-distance transformation.** *PLoS Computational Biology,* 18(2), e1010764. https://doi.org/10.1371/journal.pcbi.1010764

Lu Y, Rodriguez-Larios J (2022). **Nonlinear EEG signatures of mind wandering during breath focus meditation.** *Current Research in Neurobiology,* 3, 100056. https://doi.org/10.1016/j.crneur.2022.100056

McNeill RV, Kehrwald C, Brum M, Knopf K, Brunkhorst-Kanaan N, Etyemez S, Koreny C, Bittner RA, ... Kittel-Schneider S (2022). **Uncovering associations between mental illness diagnosis, nitric oxide synthase gene variation, and peripheral nitric oxide concentration.** *Brain, Behavior, and Immunity,* 101, 275-283. https://doi.org/10.1016/j.bbi.2022.01.006

Niso G, Krol LR, Combrisson E, Dubarry AS, Elliott MA, François C, Héjja-Brichard Y, Herbst SK, ... Chaumon M (2022). **Good scientific practice in EEG and MEG research: Progress and perspectives.** *NeuroImage,* 257, 119056. https://doi.org/10.1016/j.neuroimage.2022.119056

Poeppel D, Idsardi W (2022). **We don't know how the brain stores anything, let alone words.** *Trends in Cognitive Sciences,* 26(12), 1054-1055. https://doi.org/10.1016/j.tics.2022.08.010

Proix T, Delgado Saa J, Christen A, Martin S, Pasley BN, Knight RT, Tian X, Poeppel D, ... Giraud A-L (2022). **Imagined speech can be decoded from low- and cross-frequency intracranial EEG features.** *Nature Communications,* 13, 48. https://doi.org/10.1038/s41467-021-27725-3

Qi G, Zhang J, Bird AD (2022). **Editorial: Unveiling the structure and function of brain microcircuits: Experiments, algorithms and simulations.** *Frontiers in Neural Circuits,* 16, 991137. https://doi.org/10.3389/fncir.2022.991137

Qubad M, Barnes-Scheufler CV, Schaum M, Raspor E, Rösler L, Peters B, Schiweck C, Goebel R, ... Bittner RA (2022). **Improved correspondence of fMRI visual field localizer data after cortex-based macroanatomical alignment.** *Scientific Reports,* 12, 14310. https://doi.org/10.1038/s41598-022-17909-2

Raccah O, Doelling KB, Davachi L, Poeppel D (2022). **Acoustic features drive event segmentation in speech.** *Journal of Experimental Psychology: Learning, Memory, and Cognition,* 48(9), 1494-1504. https://doi.org/10.1037/xlm0001150

Rimmele JM, Sun Y, Michalareas G, Ghitza O, Poeppel D (2023). **Dynamics of functional networks for syllable and word-level processing.** *Neurobiology of Language,* 4(1), 120-144. https://doi.org/10.1162/nol_a_00089

Rimmele JM, Kern P, Lubinus C, Frieler K, Poeppel D, Assaneo MF (2022). **Musical sophistication and speech auditory-motor coupling: Easy tests for quick answers.** *Frontiers in Neuroscience,* 15, 764342. https://doi.org/10.3389/fnins.2021.764342

Schaworonkow N, Nikulin VV (2022). **Is sensor space analysis good enough? Spatial patterns as a tool for assessing spatial mixing of EEG/MEG rhythms.** *NeuroImage,* 253, 119093. https://doi.org/10.1016/j.neuroimage.2022.119093

Schrenk-Siemens K, Pohle J, Rostock C, Abd El Hay M, Lam RM, Szczot M, Lu S, Chesler AT, Siemens J (2022). **Human stem cell-derived TRPV1-positive sensory neurons: A new tool to study mechanisms of sensitization.** *Cells,* 11(18), 2905. https://doi.org/10.3390/cells11182905

Sierra F, Muralikrishnan R, Poeppel D, Tavano A (2022). **A perceptual glitch in serial perception generates temporal distortions.** *Scientific Reports,* 12, 21065. https://doi.org/10.1038/s41598-022-25573-9

Singer W (2022a). **Nachwort.** In: Unseld J (Ed.): Warum müssen wir träumen? Der Traum als psychologische Notwendigkeit (pp. 81-86). Frankfurt am Main: *Frankfurter Verlagsgesellschaft.*

Singer W (2022b). **Unterschiede zwischen natürlichen und künstlichen kognitiven Systemen.** In: Fink H, Rosenzweig R (Eds.): Wo sitzt der Geist? Von Leib und Seele zur erweiterten Kognition (pp. 19-40). *Kortizes.*

Spyropoulos G, Saponati M, Dowdall JR, Schölvinck M, Bosman CA, Lima B, Peter A, Onorato I, ... Vinck M (2022). **Spontaneous variability in gamma dynamics described by a damped harmonic oscillator driven by noise.** *Nature Communications,* 13, 2019. https://doi.org/10.1038/s41467-022-29674-x

Stauch BJ, Peter A, Ehrlich I, Nolte Z, Fries P (2022). **Human visual gamma for color stimuli.** *eLife,* 11, e75897. https://doi.org/10.7554/eLife.75897

Stavropoulos A, Lakshminarasimhan KJ, Laurens J, Pitkow X, Angelaki DE (2022). **Influence of sensory modality and control dynamics on human path integration.** *eLife,* 11, e63405. https://doi.org/10.7554/eLife.63405

Stürner T, Ferreira Castro A, Philipps M, Cuntz H, Tavosanis G (2022). **The branching code: A model of actin-driven dendrite arborization.** *Cell Reports,* 39(4), 110746. https://doi.org/10.1016/j.celrep.2022.110746

Tang-Wright K, Smith JET, Bridge H, Miller KL, Dyrby TB, Ahmed B, Reislev NL, Sallet J, ... Krug K (2022). **Intra-areal visual topography in primate brains mapped with probabilistic tractography of diffusion-weighted imaging.** *Cerebral Cortex,* 32(12), 2555-2574. https://doi.org/10.1093/cercor/bhab364

Tavano A, Maess B, Poeppel D, Schröger E (2022). **Neural entrainment via perceptual inferences.** *European Journal of Neuroscience,* 55(11-12), 3277-3287. https://doi.org/10.1111/ejn.15630

Terzic L, Voegtle A, Farahat A, Hartong N, Galazky I, Nasuto SJ, Andrade A de O, Knight RT, ... Sweeney Reed CM (2022). **Deep brain stimulation of the ventrointermediate nucleus of the thalamus to treat essential tremor improves motor sequence learning.** *Human Brain Mapping,* 43(15), 4791-4799. https://doi.org/10.1002/hbm.25989

Tosato T, Rohenkohl G, Dowdall JR, Fries P (2022). **Quantifying rhythmicity in perceptual reports.** *NeuroImage,* 262, 119561. https://doi.org/10.1016/j.neuroimage.2022.119561

Uhlhaas PJ, Singer W (2013). **High-frequency oscillations and the neurobiology of schizophrenia.** *Dialogues in Clinical Neuroscience,* 15(3), 301-313. https://doi.org/10.31887/DCNS.2013.15.3/puhlhaas

Uran C, Peter A, Lazar A, Barnes W, Klon-Lipok J, Shapcott KA, Roese R, Fries P, ... Vinck M (2022). **Predictive coding of natural images by V1 firing rates and rhythmic synchronization.** *Neuron,* 110(7), 1240-1257.e8. https://doi.org/10.1016/j.neuron.2022. 01.002

Voegtle A, Terlutter C, Nikolai K, Farahat A, Hinrichs H, Sweeney-Reed CM (2022). **Suppression of motor sequence learning and execution through anodal cerebellar trans-cranial electrical stimulation.** *The Cerebellum.* https://doi.org/10.1007/s12311-022-01487-0

Wianny F, Dzahini K, Fifel K, Wilson CRE, Bernat A, Dolmazon V, Misery P, Lamy C, ... Vezoli J (2022). **Induced cognitive impairments reversed by grafts of neural precursors: A longitudinal study in a macaque model of Parkinson's disease.** *Advanced Science,* 9(10), 2103827. https://doi.org/10.1002/advs.202103827

Yusuf PA, Lamuri A, Hubka P, Tillein J, Vinck M, Kral A (2022). **Deficient recurrent cortical processing in congenital deafness.** *Frontiers in Systems Neuroscience,* 16, 806142. https://doi.org/10.3389/fnsys.2022.806142

Zrenner C, Kozák G, Schaworonkow N, Metsomaa J, Baur D, Vetter D, Blumberger DM, Ziemann U, Belardinelli P (2023). **Corticospinal excitability is highest at the early rising phase of sensorimotor μ-rhythm.** *NeuroImage,* 266, 119805. https://doi.org/10.1016/j.neuroimage.2022.119805

2023

Adam KCS, Rademaker R, Serences JT (2023). **Dynamics are the only constant in working memory.** *Journal of Cognitive Neuroscience*, 351, 24–26. https://doi.org/10.1162 jocn_a_ 01941

Adolfi F, Bowers JS, Poeppel D (2023). **Successes and critical failures of neural networks in capturing human-like speech recognition.** *Neural Networks*, 162, 199–211. https://doi.org/10.1016/ j.neunet.2023.02.032

Adolfi F, Wareham T, van Rooij I (2023). **A computational complexity perspective on segmentation as a cognitive subcomputation.** *Topics in Cognitive Science*, 15(2), 255–273. https://doi.org/10.1111/ tops.12629

Batista-Brito R, Majumdar A, Nuño A, Ward C, Barnes C, Nikouei K, Vinck M, Cardin JA (2023). **Developmental loss of ErbB4 in PV interneurons disrupts state-dependent cortical circuit dynamics.** *Molecular Psychiatry*. https://doi.org/10.1038/s41380-023-02066-3

Bittner RA, Reif A, Qubad M (2023). **The ever-growing case for clozapine in the treatment of schizophrenia: an obligation for psychiatrists and psychiatry.** *Current Opinion in Psychiatry*, 36(4), 327–336. https://doi.org/10.1097/YCO.000000000 0000871

Davidesco I, Laurent E, Valk H, West T, Milne C, Poeppel D, Dikker S (2023). **The temporal dynamics of brain-to-brain synchrony between students and teachers predict learning outcomes.** *Psychological Science*, 34(5), 633–643. https://doi.org/ 10.1177/0956797623116 3872

Dorman R, Bos JJ, Vinck M, Marchesi P, Fiorilli J, Lorteije JAM, Reiten I, Bjaalie JG, … Pennartz CMA (2023). **Spike-based coupling between single neurons and populations across rat sensory cortices, perirhinal cortex, and hippocampus.** *Cerebral Cortex*, 33(13), 8247–8264. https://doi.org/10.1093/cercor/bhad111

Dowdall JR, Schneider M, Vinck M (2023). **Attentional modulation of inter-areal coherence explained by frequency shifts.** *NeuroImage*, 277, 120256. https://doi.org/10.1016/j.neuroimage.2023. 120256

Dowdall JR, Vinck M (2023). **Coherence fails to reliably capture inter-areal interactions in bidirectional neural systems with transmission delays.** *NeuroImage*, 271, 119998. https://doi.org/10.1016/j.neuroimage.2023. 119998

Edwards LJ, McColgan P, Helbling S, Zarkali A, Vaculčiaková L, Pine KJ, Dick F, Weiskopf N (2023). **Quantitative MRI maps of human neocortex explored using cell type-specific gene expression analysis.** *Cerebral Cortex*, 33(9), 5704–5716. https://doi.org/10.1093/ cercorbhac453

Farahat A, Effenberger F, Vinck M (2023). **A novel feature-scrambling approach reveals the capacity of convolutional neural networks to learn spatial relations.** *Neural Networks*, 167, 400–414. https://doi.org/10.1016/j.neunet. 2023.08.021

Fries P (2023). **Rhythmic attentional scanning.** *Neuron*, 111(7), 954–970. https://doi.org/10.1016/j.neuron.2023.02.015

Haenelt D, Trampel R, Nasr S, Polimeni JR, Tootell RBH, Sereno MI, Pine KJ, Edwards LJ, … Weiskopf N (2023). **High-resolution quantitative and functional MRI indicate lower myelination of thin and thick stripes in human secondary visual cortex.** *eLife*, 12, e78756. https://doi.org/10.7554/ eLife.78756

Jendritza P, Klein FJ, Fries P (2023). **Multi-area recordings and optogenetics in the awake, behaving marmoset.** *Nature Communications*, 14, 577. https://doi.org/ 10.1038/s41467-023-36217-5

Katsanevaki C, Bastos AM, Cagnan H, Bosman CA, Friston KJ, Fries P (2023). **Attentional effects on local V1 microcircuits explain selective V1-V4 communication.** *NeuroImage*, 120375. https://doi.org/10. 1016/j.neuroimage.2023. 120375

Kazanina N, Poeppel D (2023). **The neural ingredients for a language of thought are available.** *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2023.07.012

López-Jury L, García-Rosales F, González-Palomares E, Wetekam J, Pasek M, Hechavarria JC (2023). **A neuron model with unbalanced synaptic weights explains the asymmetric effects of anaesthesia on the auditory cortex.** *PLOS Biology*, 21(2), e3002013. https://doi.org/10.1371/journal. pbio.3002013

Lu Y, Singer W (2023). **Dynamic signatures of the Eureka effect: an EEG study.** *Cerebral Cortex*, bhad150. https://doi.org/10.1093/cercor/bhad150

Lubinus C, Keitel A, Obleser J, Poeppel D, Rimmele JM (2023). **Explaining flexible continuous speech comprehension from individual motor rhythms.** *Proceedings of the Royal Society B: Biological Sciences*, 290(1994), 20222410. https://doi.org/10.1098/rspb. 2022. 2410

Mittag M, Mediavilla L, Remy S, Cuntz H, Jedlicka P (2023). **Modelling the contributions to hyperexcitability in a mouse model of Alzheimer's disease.** *The Journal of Physiology*, 601(15), 3403–3437. https://doi.org/10.1113/JP283401

Psarou E, Vezoli J, Schölvinck M, Ferracci P-A, Zhang Y, Grothe I, Roese R, Fries P (2023). **Modular, cement-free, customized headpost and connector-chamber implants for macaques.** *Journal of Neuroscience Methods*, 393, 109899. https://doi.org/10.1016/j.jneumeth.2023.109899

Qubad M, Bittner RA (2023). **Second to none: rationale, timing, and clinical management of clozapine use in schizophrenia.** *Therapeutic Advances in Psychopharmacology*, 13, 204512532311581. https://doi.org/10.1177/204512532311 58152

Rimmele JM, Sun Y, Michalareas G, Ghitza O, Poeppel D (2023). **Dynamics of functional networks for syllable and word-level processing.** *Neurobiology of Language*, 4(1), 120–144. https://doi.org/10.1162/nol_a_00089

Rößler N, Jungenitz T, Sigler A, Bird A, Mittag M, Rhee JS, Deller T, Cuntz H, … Jedlicka P (2023). **Skewed distribution of spines is independent of presynaptic transmitter release and synaptic plasticity, and emerges early during adult neurogenesis.** *Open Biology*, 13(8), 230063. https://doi.org/10.1098/rsob.230063

Saponati M, Vinck M (2023). **Sequence anticipation and spike-timing-dependent plasticity emerge from a predictive learning rule.** *Nature Communications*, 14, 4985. https://doi.org/10.1038/s41467-023-40651-w

Sauer A, Grent-'t-Jong T, Zeev-Wolf M, Singer W, Goldstein A, Uhlhaas PJ (2023). **Spectral and phase-coherence correlates of impaired auditory mismatch negativity (MMN) in schizophrenia: A MEG study.** *Schizophrenia Research*, 261, 60–71. https://doi.org/10.1016/j.schres.2023.08.033

Schneider M, Bird AD, Gidon A, Triesch J, Jedlicka P, Cuntz H (2023). **Biological complexity facilitates tuning of the neuronal parameter space.** *PLOS Computational Biology*, 19(7), e1011212. https://doi.org/10.1371/journal.pcbi.1011212

Schneider M, Tzanou A, Uran C, Vinck M (2023). **Cell-type-specific propagation of visual flicker.** *Cell Reports*, 42(5), 112492. https://doi.org/10.1016/ j.celrep.2023.112492

Sotomayor-Gómez B, Battaglia FP, Vinck M (2023). **SpikeShip: A method for fast, unsupervised discovery of high-dimensional neural spiking patterns.** *PLOS Computational Biology*, 19(7), e1011335. https://doi.org/10.1371/journal.pcbi.1011335

Sun Y, Poeppel D (2023). **Syllables and their beginnings have a special role in the mental lexicon. Proceedings of the National Academy of Sciences of the United States of America**, 120(36), e2215710120. https://doi.org/10.1073/pnas.2215710120

Süß AM, Hug M, Conradi N, Kienitz R, Rosenow F, Rampp S, Merkel N (2023). **Lateralization of delta band power in magnetoencephalography (MEG) in patients with unilateral focal epilepsy and its relation to verbal fluency.** *Brain and Behavior*, e3257. https://doi.org/10.1002/brb3.3257

Vessel EA, Pasqualette L, Uran C, Koldehoff S, Bignardi G, Vinck M (2023). **Self-relevance predicts the aesthetic appeal of real and synthetic artworks generated via neural style transfer.** *Psychological Science*, 34(9), 1007–1023. https://doi.org/10.1177/ 09567976231188107

Wiesman AI, Donhauser PW, Degroot C, Diab S, Kousaie S, Fon EA, Klein D, Baillet S, … Quebec Parkinson Network (2023). **Aberrant neurophysiological signaling associated with speech impairments in Parkinson's disease.** *npj Parkinson's Disease*, 9, 61. https://doi.org/10.1038/s41531-023-00495-z

Yiling Y, Shapcott K, Peter A, Klon-Lipok J, Xuhui H, Lazar A, Singer W (2023). **Robust encoding of natural stimuli by neuronal response sequences in monkey visual cortex.** *Nature Communications*, 14, 3021. https://doi.org/10.1038/s41467-023-38587-2

Zrenner C, Kozák G, Schaworonkow N, Metsomaa J, Baur D, Vetter D, Blumberger DM, Ziemann U, Belardinelli P (2023). **Corticospinal excitability is highest at the early rising phase of sensorimotor μ-rhythm.** *NeuroImage*, 266, 119805. https://doi.org/10.1016/j.neuroimage.2022.119805

IMPRINT

Images
Ernst Strüngmann Institute for Neuroscience,
Frankfurt am Main

Further Resources
Page 02: private/D. Poeppel
Pages 65, 68, 71, 78: private/N. Schaworonkow
Page 72: private/P. Donhauser
Pages 80, 82, 85: private/R. Rademaker
Page 108: private/W. Singer
Pages 112, 116: Unsplash
Page 122: private/M. Vinck

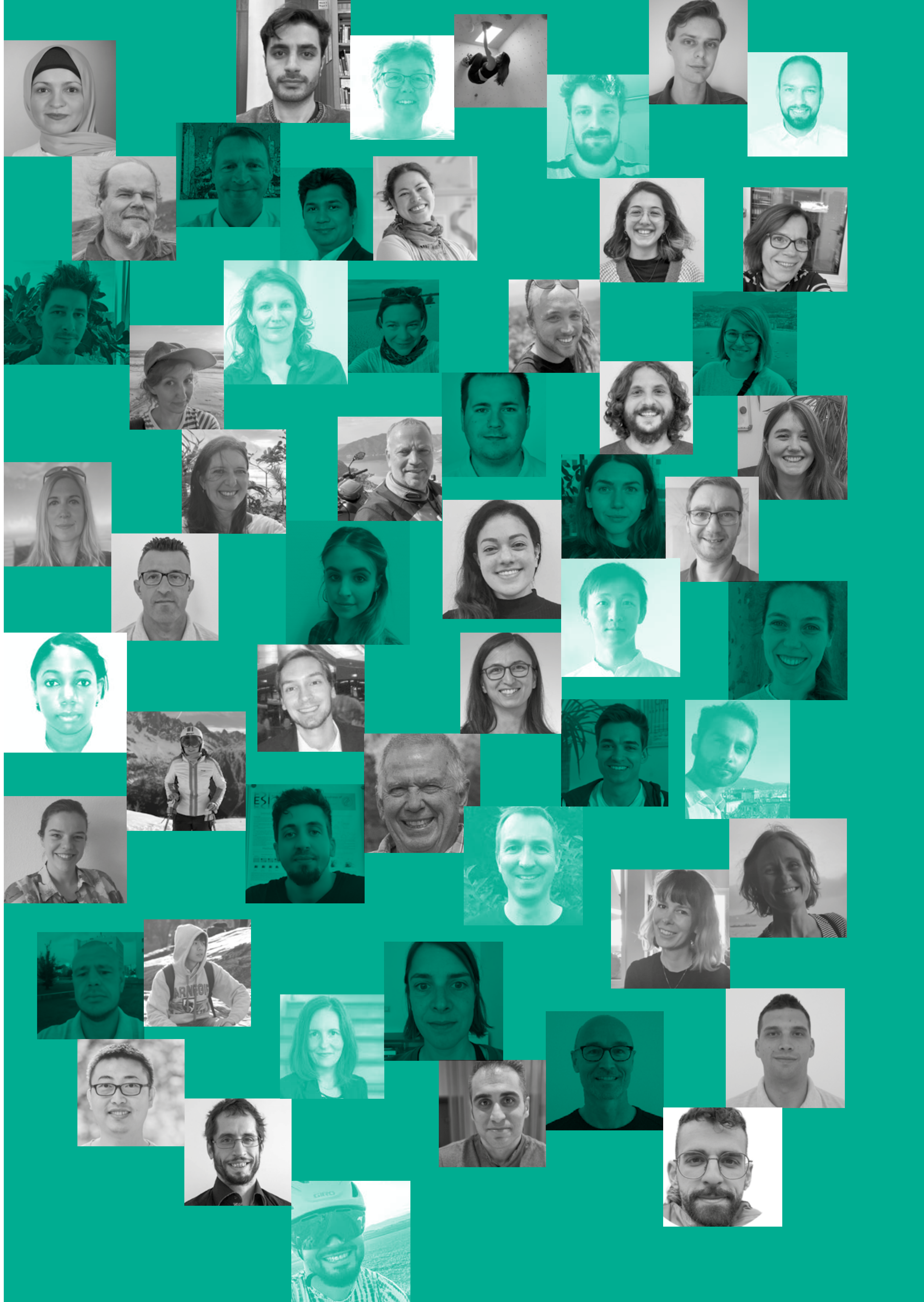
Editor
Ernst Strüngmann Institute for Neuroscience,
Frankfurt am Main

Coordination
Julia Trommershäuser

Design
Claudia Kernberger

Print
Druck- und Verlagshaus Zarbock GmbH & Co.KG

RECYCLED
Papier aus Recyclingmaterial
Paper made from recycled material
FSC® C003425




Ernst Strüngmann Institut


kinder Riegel
Welcome
To the Poeppel Lab
Work hard & be nice to people


TUESDAY 17/10
09:00
10:15

Ernst Strüngmann Institute (ESI) gGmbH
for Neuroscience
in Cooperation with Max Planck Society
Deutschordenstraße 46
60528 Frankfurt am Main
Germany

www.esi-frankfurt.de