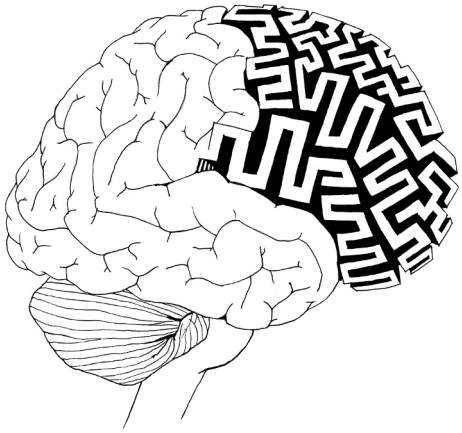
AREADNE 2018

Research in Encoding and Decoding of Neural Ensembles

Nomikos Conference Centre, Santorini, Greece

20-24 June 2018



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Research in Encoding and Decoding of Neural Ensembles
Nomikos Conference Centre, Santorini, Greece, 20-24 June 2018
Nicholas G. Hatsopoulos, John S. Pezaris, editors

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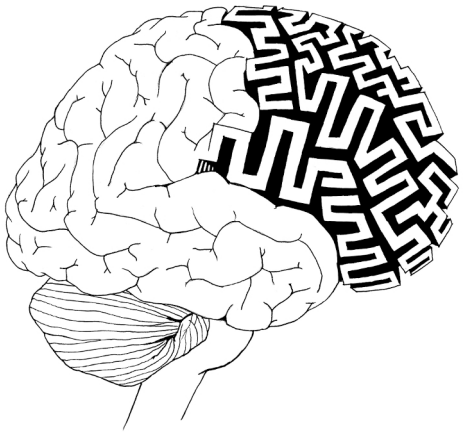

WELCOME

Welcome

Welcome to AREADNE 2018, the seventh AREADNE Conference on Research in Encoding and Decoding of Neural Ensembles, and a celebration of a decade of AREADNE meetings.

One of the fundamental problems in neuroscience today is to understand how the activation of large populations of neurons gives rise to the higher order functions of the brain including learning, memory, cognition, perception, action and ultimately conscious awareness. Electrophysiological recordings in behaving animals over the past forty years have revealed considerable information about what the firing patterns of single neurons encode in isolation, but it remains largely a mystery how collections of neurons interact to perform these functions.

Recent technological advances have provided a glimpse into the global functioning of the brain. Such tools include functional magnetic resonance imaging, optical imaging methods, high-density electroencephalography and magnetoencephalography, and multi-microelectrode electrophysiology. These methodological advances have expanded our knowledge of brain functioning beyond the single neuron level.

At the same time, our understanding of how neuronal ensembles carry information has allowed the development of brain-machine interfaces (BMI) to enhance the capabilities of patients with sensory and motor deficits. Knowledge of how neuronal ensembles encode sensory stimuli has made it possible to develop perceptual BMIs for the hearing and visually impaired. Likewise, research in how neuronal ensembles decode motor intentions has resulted in motor BMIs by which people with severe motor disabilities can control external devices.

Conference Mission Statement

There are three major goals of this conference. First and foremost, this conference is intended to bring scientific leaders from around the world to present their recent findings on the functioning of neuronal ensembles. Second, the meeting will provide an informal yet spectacular setting on Santorini in which attendees can discuss and share ideas outside of the presentations at the conference center. Third, this conference continues our long term goals to promote systems neuroscience within Greece by providing a forum for scientists from around the world to interact with Greek researchers and students.

Organizing Committee

The AREADNE 2018 conference was organized by Nicholas Hatsopoulos and John Pezaris (Co-Chairs), along with Dora Angelaki, Yiota Poirazi, Thanos Siapas, and Andreas Tolias.

Local Organizers

Local organization effort has been provided by Nike Makres with assistance from Ariadne Pangalos and Voula Patinioti.

Sponsors and Support

Our conference is being sponsored with generous gifts from Dr. and Mrs. George Hatsopoulos through the NIMA Foundation and the University of Chicago, and Peter and Yayi Pezaris, to The AREADNE Foundation, a non-profit organization that runs the AREADNE Conferences. In

addition, for 2018, the conference is being administered by the Massachusetts General Hospital, with financial or in-kind support from The Gatsby Charitable Foundation (grant number GAT3506), Simons Foundation, The William M. Wood Foundation, Foley & Lardner, LLC, and the University of Chicago..

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The Myth of Ariadne

The conference name AREADNE is a combination of the conference title, Research in Encoding and Decoding of Neural Ensembles, and the name of the mythological figure Ariadne. Our brain-to-maze logo was inspired by the central role Ariadne played in the myth of Theseus and the Labyrinth.

In Greek Mythology, Ariadne was the daughter of Minos, king of Crete. King Minos built a large, intricate maze called the Labyrinth to house the Minotaur, a fearsome creature that was half bull, half human. Any who attempted to face the Minotaur perished, either by becoming lost in the maze or from the Minotaur's vicious attack. When the hero Theseus came from Athens to slay the Minotaur, Ariadne gave him a sword and a ball of silk thread. Theseus tied one end of the thread at the Labyrinth entrance and unwound it as he went along, so that after he had found and slain the Minotaur, he could escape from the maze by following the thread back out.

LOCAL INFORMATION

We have assembled a small selection of local information on Fira and the island of Thera. For more information, select among the many guidebooks written for travel in Santorini.

Restaurant Information

Greeks normally eat their evening meal quite late, with restaurants being busiest 10 PM to midnight. The largest meal of the day is often lunch, leading naturally to the habitual afternoon siesta. Tipping at restaurants is not expected, as the cost of service is normally included in the price of the meal. Each euro symbol in the list below is about € 10.

Restaurants in Fira and Firostefani

Assyrtiko	+30-22860-22463	€ € €	caldera view, wine restaurant
Kapari	+30-22860-21120	€ €	taverna, set back from main road
Koukoumavlos	+30-22860-23807	€ € € €	caldera view, nouvelle cuisine
Mama Thira	+30-22860-22189	€ €	caldera view, taverna
Nick the Grill	+30-22860-23492	€	souvlaki stand, near the main square
Sphinx	+30-22860-71450	€ € € €	caldera view, Greek cuisine
The Greeks	+30-22860-22989	€ €	taverna, near the cable car
To Ouzeri	+30-22860-21566	€ €	Greek tapas, near main square

Restaurants in Oia

Iliovassilema	+30-22860-71614	€ €	fresh fish
Thalami	+30-22860-71485	€ €	ouzo bar
1800	+30-22860-71485	€ € € €	nouvelle cuisine

Restaurants in Perivolos-Vlychada

Taverna Dimitris	+30-22860-82532	€ €	Greek taverna near the marina
to Psaraki	+30-22869-82783	€ € €	fish tavern overlooking the marina
The Net	+30-22860-82818	€ € € €	fish tavern by the sea, local cuisine

Recommended Activities

Santorini offers not just sweeping vistas, but excellent nightlife, a respectable wine industry, beaches with white, black, or red sand, ancient excavations, and fantastic sunsets. Also, we have optional tours to the Akrotiri archaeological site and to the volcano island at the center of the caldera, although these may not be able to accommodate everyone. Beyond these two excursions (which can be taken on your own, although without the benefit of our invited experts), there are plenty of other activities on the island. A few suggestions to scratch the surface are listed below.

Santozeum
open daily 10.00–18.00, tel +30 22860 21722, www.santorzeum.com, Fira

Archaeological Museum at Fira
open 08.00–15.00 (closed Mondays), tel +30-22860-22217, Ypapantis Street, Fira

Museum of Prehistoric Thera
open 08.30–15.00 (closed Mondays), tel +30-22860-23217, Mitropoleos Street, Fira

Folk Art Museum
open 10.00–14.00 tel +30-22860-22792, Kondohori, near Fira

Wine Museum
open daily 12.00–20.00, tel +30-22860-31322, located in Vothonas village

Santo Winery
www.santowines.gr, tel +30-22860-22596, located in Pyrgos

Oia at sunset
sunset is at approximately 8 pm in late June; once at Oia, follow the crowds westward

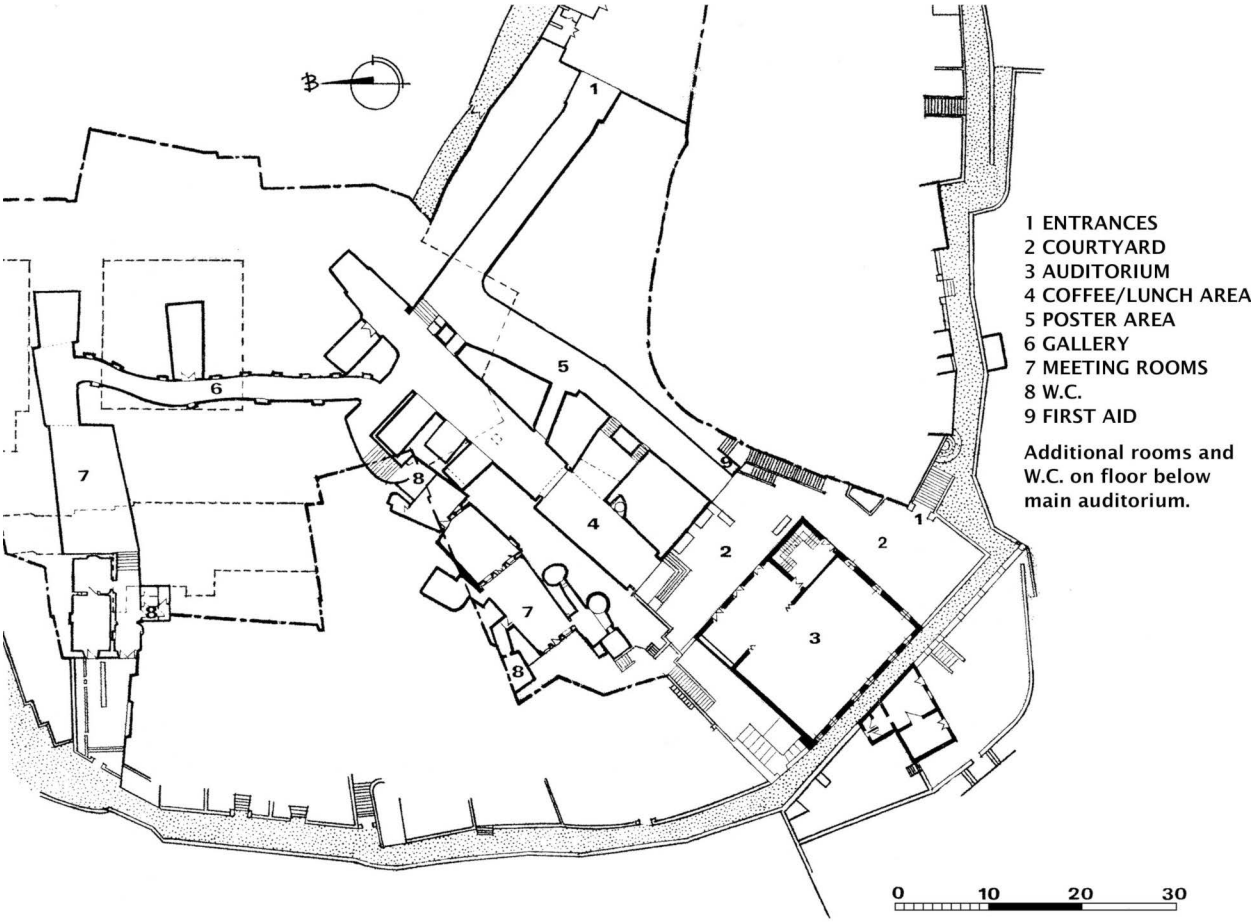
Monastery of Profitis Ilias
in Pyrgos, at the mountain peak; museum open 09.00–20.15; modest dress required

Main Beaches

The beaches on Santorini are beautiful and varied, with white, red, and black sand depending on location. However, swimming must be done with care as the water gets deep quickly and rip currents are not uncommon. Flip-flops are a must as the dark sand can get extremely hot in the sun. SCUBA diving is available with trips to wrecks, the volcano, and the underwater caldera face. Beaches are at Perivolos (13 km from Fira), Perissa (13 km), Vlychada (12 km), and Kamari (10 km).

Conference Centre Map

Oral presentations will be held in the main auditorium of the Centre. Coffee breaks will be in the reception area and courtyard. Posters will be hung on the walls of the main tunnel. A first aid station is available off the main tunnel, while restrooms are in the lower level. Please refer to the map below for more details.



DAILY SCHEDULE AND PROGRAM

Overall Schedule

The schedule for the four-day conference follows the Greek lifestyle of having a long lunch, with the afternoon free for siestas or swimming, and a late dinner.

Wednesday
19:30–22:00 welcome reception and registration

Thursday
08:30–09:30 registration
09:30–09:45 opening remarks
09:45–12:30 lectures and coffee break
12:30–14:00 lunch
17:00–21:30 lectures and coffee break, posters

Friday
09:00–12:30 lectures and coffee break
12:30–14:00 lunch
17:00–21:30 lectures and coffee break, posters

Saturday
09:00–12:00 optional excursions (no lunch provided)
17:00–21:30 lectures and coffee break, posters

Sunday
09:00–12:30 lectures and coffee break
12:30–14:00 lunch
17:00–19:45 lectures and coffee break
19:45–20:00 closing remarks
21:00–24:00 banquet dinner at Selene Restaurant in Pyrgos

WEDNESDAY, 20 JUNE 2018

19:30–22:00 welcome reception at Nomikos Centre

THURSDAY, 21 JUNE 2018

08:30–09:30 registration

09:30–09:45 opening remarks

MORNING SESSION Kenny Blum, moderator

09:45–10:30 **Mala Murthy** (Princeton University)
Neural mechanisms for dynamic acoustic communication in flies, 36

10:30–11:00 coffee break

11:00–11:45 **Jennifer F. Linden** (University College London)
Putting sounds in context, 31

11:45–12:30 **Kerry Walker** (University of Oxford)
Representations of complex sound features in subpopulations of auditory cortical neurons, 44

12:30–14:00 lunch

AFTERNOON SESSION Georgia Gregoriou, moderator

17:00–17:45 **David Freedman** (University of Chicago)
Circuit mechanisms of short-term working memory in biological and artifical neural networks, 28

17:45–18:15 coffee and light snacks

18:15–19:00 **Nicole Rust** (University of Pennsylvania)
Remembering what we see, 40

19:00–19:20 **Desmond Patterson** (University of Texas, Austin)
Bubble or boom? Why volcanoes erupt the way they do, 38

19:20–19:40 **Andronike Makres** (Hellenic Education and Research Center)
The prehistoric (possibly Minoan) settlement of Akrotiri and the Ancient Greek city-state of Ancient Thera: what is so great about them?, 34

20:00–21:30 posters, presenting author

Panagiotis Artemiadis (Arizona State University)
Novel approach to decoding neural activity to multi-degree of freedom bci: Methods and metrics of mutual adaptation in humans and machines, 48

Carlos Brito (Gatsby Computational Neuroscience Unit)
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Jongrok Do (Institute for Basic Science)
Choice-dependent neural trajectory of human decision making, 56

Alexander Ecker (University of Tübingen)
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Kang Yong Eo (Institute for Basic Science)
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Ainhoa Hermoso-Mendizabal (Institut d'Investigacions Biomèdiques August Pi i Sunyer)
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Luca Mazzucato (Columbia University)
Expectation-induced modulation of metastable activity drives faster coding of sensory stimuli, 79

Mariangela Panniello (University of Oxford)
Neural coding principles of somatosensory perception and behaviour revealed through multiplexed two photon imaging, 82

Matthew Perich (University of Geneva)
Decoding locomotor events from motor cortex enables a brain-spine interface to alleviate gait deficits of Parkinson's disease, 83

Konstantinos Evangelos Petousakis (IMBB-FORTH)
A tale of two trees: Modeling apical and basal tree contribution to L2/3 V1 pyramidal cell orientation selectivity, 84

Chris Rodgers (Columbia University)
The sensorimotor strategies and cortical coding that mediate curvature discrimination by active whisker touch, 85

FRIDAY, 22 JUNE 2018

MORNING SESSION Leslie Osborne, moderator

09:00–09:45 **Camillo Padoa-Schioppa** (Washington University in St Louis)
A neural circuit for economic decisions, 37

09:45–10:30 **Joni D. Wallis** (University of California, Berkeley)
Dynamics of prefrontal computations during decision-making, 45

10:30–11:00 coffee break

11:00–11:45 **Alan A. Stocker** (University of Pennsylvania)
Optimal perceptual decision-making with limited representational resources, 42

11:45–12:30 **Barry J. Richmond** (NIMH/NIH)
Using chemogenetic tools (DREADDs) to help identify circuitry for ranking reward values, 39

12:30–14:00 lunch

AFTERNOON SESSION Robert Desimone, moderator

17:00–17:45 **Marlene R. Cohen** (University of Pittsburgh)
Understanding the relationship between neuronal variability and behavior, 26

17:45–18:15 coffee and light snacks

18:15–19:00 **Alex Huk** (University of Texas, Austin)
Encoding and decoding of 3D motion in visual area MT, 30

19:00–19:45 **Jason N. MacLean** (University of Chicago)
Decoding functional networks in cerebral cortex, 33

20:00–21:30 posters, presenting author

Shay Ben-Sasson (Ben Gurion University of the Negev)
Dynamical implications of optimal temporal infrpomation encoding in recurrent spiking networks, 94

Rob Cao (Gatsby Computational Neuroscience Unit)
From multistable phenomena to optimal models of decision-making, 52

Anita Devineni (Columbia University)
Population coding and temporal dynamics in the fruit fly taste system, 55

Abhilash Dwarakanath (Max Planck Institute for Biological Cybernetics)
Perisynaptic activity in the prefrontal cortex reflects spontaneous transitions in conscious visual perception, 57

SATURDAY, 23 JUNE 2018

09:00–13:00 optional excursions (no lunch provided)

AFTERNOON SESSION Stephanie Palmer, moderator

17:00–17:45 **Karel Svoboda** (HHMI Janelia Research Campus)
Biophysics of motor planning and short-term memory, 43

17:45–18:15 coffee and light snacks

18:15–19:00 **Julijana Gjorgjieva** (Max Planck Institute for Brain Research)
Spontaneous and sensory-driven activity shape neural circuits in the developing brain, 29

19:00–19:45 **Sydney S. Cash** (Massachusetts General Hospital)
New perspectives on seizures incorporating single neurons, networks, slow and fast activity, 25

20:00–21:30 posters, presenting author

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Philipp Berens (University of Tuebingen)
Simple recombination of retinal output channels yields highly diverse visual representations in mouse dLGN, 50

Angus Chadwick (Gatsby Computational Neuroscience Unit)
Feature-specific inhibition enables flexible control of neuronal selectivity in an attractor model of visual cortex, 53

James Cotton (Shirley Ryan AbilityLab)
Scaling of information in large sensory populations, 54

Moein Esghaei (German Primate Center)
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Emmanouil Froudarakis (Baylor College of Medicine)
Object representations in the mouse visual system, 63

Xu Han (Neuro-Electronics Research Flanders)
Source-specific projections between specialized visual cortical areas, 110

SUNDAY, 24 JUNE 2018

MORNING SESSION Daniel Margolias, moderator

09:00–09:45 **Nikos K. Logothetis** (Max Planck Institute for Biological Cybernetics)
Concurrent multisite recordings and brain imaging: a study of events related system and synaptic memory consolidation, 32

09:45–10:30 **Alcino J. Silva** (University of California, Los Angeles)
Molecular, cellular, and circuit mechanisms that open and close the window for memory linking across time, 41

10:30–11:00 coffee break

11:00–11:45 **Elizabeth A. Buffalo** (University of Washington)
Bridging the gap between the spatial and mnemonic views of the hippocampus, 23

11:45–12:30 **David J. Foster** (University of California, Berkeley)
Mechanisms and functions of hippocampal place cell sequences, 27

12:30–14:00 lunch

AFTERNOON SESSION Tatiana Pasternak, moderator

17:00–17:45 **Davi D. Bock** (HHMI Janelia Research Campus)
Order versus randomness in the fly mushroom body, 22

17:45–18:15 coffee and light snacks

18:15–19:00 **Sophie Caron** (University of Utah)
Biased randomness, a connectivity mechanism for associative brain centers, 24

19:00–19:45 **Gero Miesenböck** (University of Oxford)
Dendritic integration of sensory evidence in perceptual decision-making, 35

19:45–20:00 closing remarks

21:00–24:00 banquet dinner at Selene Restaurant in Pyrgos

INVITED SPEAKER ABSTRACTS
(in alphabetical order by speaker)

ORDER VERSUS RANDOMNESS IN THE FLY MUSHROOM BODY

Zhihao Zheng, Feng Li, J. Scott Lauritzen, Matthew Nichols, Corey Fisher, Nadiya Sharifi, Steven Calle-Schuler, Lucia Kmecova, Jawaid Ali, Davi D. Bock[*]

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The mushroom body (MB) of the Drosophila brain is critical for olfactory learning and memory. The MB on each side of the brain contains about 2,000 Kenyon cells (KCs) that receive olfactory input in the MB calyx from about 150 projection neurons (PNs). Light microscopy data pooled across many animals [1, 2], as well as theoretical arguments [3], have suggested that the PN-to-KC synaptic network is completely random. However, the distributions of PN arbors in the MB calyx are highly structured [4, 5] and KCs have been reported to oversample three specific PN subtypes labeled by the MZ19 driver line [6]. These data suggest that a thorough examination of the PN-to-KC network, within a single animal, may reveal previously unrecognized order in network structure reflecting an underlying olfactory stimulus space [7].

To compare intra-animal PN-to-KC network structure to random null models, we used a whole-brain electron microscopy dataset [8] to map all olfactory PN inputs to the MB, as well as about 280 randomly sampled KCs. We found that KCs tend to get multiple inputs from a specific subset (a *community*) of olfactory PNs, at levels well beyond those predicted by a purely random PN-to-KC model. The community PNs mostly arose from antennal lobe glomeruli encoding food odors, suggesting preferential integration of inputs of ethologically relevant odorants. We also traced input to a tightly cofasciculated set (a *bundle*) of about 170 KCs. The bundle KC dendrites arborized in a restricted territory in MB calyx, and received above-chance input from the community PNs. A random model in which traced KCs claws were allowed to select randomly from locally neighboring PN boutons largely reproduced the observed network structure, suggesting that developmentally determined fine-scale precision in axonal and dendritic arbor overlap is responsible for the PN-to-KC network structure we observe.

References

1. Murthy, *et al.*, 2008
2. Caron, *et al.*, 2013
3. Litwin-Kumar, *et al.*, 2017
4. Tanaka, *et al.*, 2004
5. Jefferis, *et al.*, 2007
6. Gruntman, Turner, 2013, *Nat Neurosci*, 16(12):1821–1829
7. Koulakov, *et al.*, 2011
8. Zheng, *et al.*, 2017

BRIDGING THE GAP BETWEEN THE SPATIAL AND MNEMONIC VIEWS OF THE HIPPOCAMPUS

Elizabeth A. Buffalo

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While it has long been recognized that medial temporal lobe structures are important for memory formation, studies in rodents have also identified exquisite spatial representations in these regions in the form of place cells in the hippocampus and grid cells in the entorhinal cortex. Spatial representations entail neural activity that is observed when the rat is in a given physical location, and these representations are thought to form the basis of navigation via path integration. One striking difference between rodents and primates is the way in which information about the external world is gathered. Rodents typically gather information by moving to visit different locations in the environment, sniffing and whisking. By contrast, primates chiefly use eye movements to visually explore an environment, and our visual system allows for inspection of the environment at a distance. In this lecture, I will discuss recent work from my laboratory that has examined neural activity in the hippocampus and adjacent entorhinal cortex in monkeys performing behavioral tasks including free-viewing of complex natural scenes and memory tasks in a virtual environment. These data suggest that spatial representations including place cells, grid cells, border cells, and direction-selective cells can be identified in the primate hippocampal formation even in the absence of physical movement through an environment. I will also discuss new research involving chronic, large-scale recordings throughout the primate brain and other areas of opportunity for future research to further our understanding of the function of the hippocampal formation.

BIASED RANDOMNESS, A CONNECTIVITY MECHANISM FOR ASSOCIATIVE BRAIN CENTERS

Elom Amematsro[1], *Daniel Zavitz*[2], *Emerson Arehart*[1,2], *Fred Adler*[1,2], *Alla Borisyuk*[2], *Sophie Caron*[1,*]

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Uncovering fundamental mechanisms of neuronal connectivity that enable associative brain centers to learn efficiently is an important goal of neuroscience. In the *Drosophila melanogaster* mushroom body, the constituent Kenyon cells receive input from olfactory projection neurons. Each projection neuron connects to one of the fifty glomeruli in the antenna lobe, the primary olfactory processing center. We and others have shown that these connections are random in that there are no sets of glomeruli converging preferentially onto a given Kenyon cell [1–3]. However, we found that the glomeruli are not represented with equal frequency among Kenyon cell inputs. Certain glomeruli form many more connections than expected under a uniform distribution, whereas other glomeruli form far fewer connections than expected. We are testing the idea that this non-uniform distribution, which we termed *biased randomness*, serves an important biological function, namely to predispose the learning ability of the mushroom body towards certain ethologically pertinent stimuli. To test this idea, we built two mathematical models of the mushroom body: one model was built using the biased distribution of input that we measured experimentally, while the other model uses a uniform distribution of input. Both models generate very similar representations for most of the tested odors. However, we found that each model generates strikingly different representations for a few ethologically relevant odors. Odors activating over-represented glomeruli activate many more Kenyon cells than odors activating underrepresented glomeruli do. Consequently, although both models show overall similar learning performance, they perform differently in tasks involving these ethologically relevant odors. We are proposing that over-representation serves a biological function, namely to enable odors that must be learned in many different contexts, pheromones for instance, to be represented by a large number of Kenyon cells. In contrast, under-representation might be used as a strategy to prevent the mushroom body from representing — and possibly learning — odors with strong innate valence. We are currently testing this idea further by measuring the biases in connectivity in the mushroom body of other *Drosophila* species, namely *Drosophila sechellia*, that have evolved in different ecological niches and therefore have different olfactory preferences. Our preliminary data suggests that biases shift in a predictable manner, reflecting the expected olfactory ecology of a species. Altogether, our work supports the idea that biased randomness is a wiring mechanism that predisposes associative brain centers to learn efficiently.

References

1. Caron, Ruta, Abbott, Axel, 2013, *Nature*
2. Gruntman, Turner, 2013, *Nat Neurosci*
3. Murthy, Fiete, Laurent, 2008, *Neuron*

NEW PERSPECTIVES ON SEIZURES INCORPORATING SINGLE NEURONS, NETWORKS, SLOW AND FAST ACTIVITY

Sydney S. Cash

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Our understanding of the pathophysiology which underlies epilepsy and ictogenesis is becoming increasingly nuanced. Over the last decade we have come to appreciate that seizure initiation, spread and termination represents an interplay of activities which encompass different spatial and temporal scales and different neuronal types and functions. In this presentation, I will discuss some of those events which lead up to seizure initiation and characterize the spread of a focal seizure as well as its termination. The spotlight will be on the role of single neurons, both excitatory and inhibitory, during this process based on data obtained from a variety of different types of high density microelectrode array recordings performed in patients with intractable focal epilepsy undergoing surgery. In particular, we will discuss the dynamics of excitation and inhibition before overt (EEG) seizure activity, and through the remainder of the seizure dynamic evolution. This information will be placed in the context of ongoing larger scale activity and the multiscale functional networks which underlie such activity. We find a distinction in many of these characteristics between seizures with different large-scale signatures — seizures characterized by spike-wave discharges versus low voltage fast activity in particular. We will also explore how the dynamics of activity outside the canonical seizure focus impact seizure spread and the way the dynamics of that spread may inform our ability to control seizure activity. Ultimately, we are using these types of data to create a hypothetical model of seizure dynamics which incorporates the physiological characteristics of different neuronal classes at the level of individual neurons and small populations — a model framework whose implications we hope will allow for better seizure prediction and control.

UNDERSTANDING THE RELATIONSHIP BETWEEN NEURONAL VARIABILITY AND BEHAVIOR

Amy M. Ni[1,2], *Douglas A. Ruff*[1,2], *Marlene R. Cohen*[1,2,*]

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[2] Center for the Neural Basis of Cogntion, Pittsburgh, PA USA
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The responses of pairs of neurons in visual cortex to repeated presentations of the same visual are typically correlated, but the importance of this correlated variability has been the subject of much debate. We took a practical approach, reasoning that if correlated variability is important for perception, it should be closely associated with visually guided behaviors. I will discuss results showing that correlated variability in visual cortex 1) has a consistent relationship to performance on perceptual tasks, regardless of whether performance is affected by cognitive factors that change quickly (*e.g.*, attention), slowly (*e.g.*, learning), or for reasons outside experimental control, 2) is oriented along the same dimensions in population response space that are most predictive of behavior on individual trials, and 3) is selectively communicated to downstream areas involved in decision making. These results suggest that animals behave suboptimally in a particular way, such that correlated variability has an outsized impact on performance. We propose that even in well-practiced behavioral tasks, animals optimize the way they use sensory information for the very large range of stimuli and tasks they encounter in the natural world, making correlated variability a critical limit on performance.

Acknowledgments

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MECHANISMS AND FUNCTIONS OF HIPPOCAMPAL PLACE CELL SEQUENCES

David J. Foster

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A major role of hippocampal neurons is to take part in coordinated spiking events across ensembles of neurons. In my laboratory, we investigate both the mechanisms underlying the generation of these events, and their possible functions. In the first part of the talk, I will describe recent unpublished work in which we have used optogenetic methods to silence one component of the hippocampal circuitry, area CA3, in order to assess its contribution to activity patterns in hippocampal output area CA1. Surprisingly, in addition to suppressing rest-associated population events, removal of CA3 input had a drastic effect on CA1 place field responses even in a familiar environment, suggesting that in contrast to recent literature, CA3 is the predominant driver of CA1 under normal conditions. In the second part of my talk, I will share very preliminary data from a study of hippocampal ensemble activity patterns recorded while rats navigate an environment with complex barrier structure. We find evidence that replays are exquisitely sensitive to the transition structure of the environment. Moreover, hippocampal replay demonstrates extraordinary plasticity, in adapting to daily changing environmental structure even after very many days of continual environmental change. These data support the notion that replay plays a critical role in navigational learning and decision-making.

CIRCUIT MECHANISMS OF SHORT-TERM WORKING MEMORY IN BIOLOGICAL AND ARTIFICAL NEURAL NETWORKS

David J. Freedman[1,2,*], *Guangyu R. Yang*[3,4], *Francis Song*[3,5], *Xiao-Jing Wang*[3], *Nicolas Y. Masse*[1]

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Solving complex behavioral tasks often requires storage or manipulation of task-relevant information in short-term or *working* memory. A widely-held view is that information in working memory is maintained in persistent neuronal spiking activity, which is often observed in the delay period of short-term memory based tasks—particularly in cortical areas such as the prefrontal cortex (PFC) and posterior parietal cortex (PPC). However, recent studies from multiple groups have reported a surprising lack of persistent delay activity in both PPC and PFC in monkeys performing several delay-based tasks. This raises questions about the precise function of persistent activity, and about the mechanisms used by neural networks to represent mnemonic information in an activity silent manner. To address these questions, this study examines the prevalence of, and information encoded by, persistent activity in PFC and/or PPC ensembles in monkeys performing four delay-based tasks which vary in their short-term memory demands.

We also explore the circuit computations underlying working memory by examining the activity and circuit motifs of recurrent neural networks (RNNs) trained to perform a similar set of delay-based tasks as in the experimental work. Recent modelling studies have suggested a plausible mechanism by which neural networks can maintain information in the absence of persistent activity—short term plasticity (STP) in the synaptic efficacies between neurons. STP time constants (hundreds to thousands of ms) are well suited for the time range of working memory. Thus, we endowed RNNs with STP (depression and facilitation) and a metabolic constraint to encourage reduced spiking, to assess RNN capacity to maintain task-relevant information in working memory without relying on persistent activity. We show that STP can support activity-silent maintenance of information in delay-based tasks of varying complexity, but that most tasks were solved by a hybrid of STP and neural activity. However, in tasks requiring active manipulation of remembered information as opposed to passive maintenance, we observed a greater dependence on neuronal activity. These results suggest that STP can support activity-silent maintenance of information in short-term memory, although persistent neuronal activity is required to support the cognitive processes involved in manipulating information in working memory.

Acknowledgments

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SPONTANEOUS AND SENSORY-DRIVEN ACTIVITY SHAPE NEURAL CIRCUITS IN THE DEVELOPING BRAIN

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The emergence of flexible and stable neural circuits requires the coordination and appropriate timing of multiple mechanisms acting at the single neuron and network level. While molecular guidance cues and chemoaffinity gradients establish the initial coarse connectivity patterns at early developmental stages, activity-dependent plasticity mechanisms based on developmental activity patterns continue the refinement of this initially imprecise connectivity into functional circuits that can execute diverse tasks in adulthood. We use quantitative data analysis, theory and modeling to understand how neural circuits are built and organized during early postnatal development into functional units, and how they are modified by intact and perturbed sensory-evoked activity. I will show a quantitative analysis of longitudinal recordings of single neuron and network activity spontaneously generated in the visual cortex before eye opening recorded by our collaborators. I will first discuss how specific patterns of this activity drive connectivity refinements from novel adaptive mechanisms of plasticity. After eye opening, the visual system is faced with a different challenge as sensory-evoked activity continues to refine circuit connectivity. I will then show how cortical activity patterns are modified following a significant sensory perturbation that affects the correlation structure of sensory inputs, and present theoretical work that links cellular and synaptic changes to network activity patterns. Our work characterizes the statistical nature of changing spontaneous and early sensory-evoked activity patterns in early development, and demonstrates the utility of these patterns in guiding different aspects of circuit organization.

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ENCODING AND DECODING OF 3D MOTION IN VISUAL AREA MT

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From visual orientation in primate V1 to wind velocity in cricket cercal cells, neuronal tuning almost always follows a bell-shaped function. Here we report that a basic visual property (3D motion direction) is encoded with tuning that is strikingly non-Gaussian — characterized by distinct plateaus separated by steep cliffs, or, *terraced* tuning [1].

We first examined how this terraced encoding scheme might arise from tuning to basic 2D motion signals. We found that canonical forms of frontoparallel velocity tuning interact with the geometry of 3D space and binocularity to yield these 3D direction tuning shapes. The resulting environmentally-centered encoding model takes MT's canonical log-gaussian tuning to monocular velocities, adds the two monocular responses, and then performs the requisite trigonometric transformations to extract 3D direction from the differential velocities in the two eyes.

We then considered how 3D direction can be decoded from such tuning curves. Modeling estimation and discrimination of 3D directions revealed three insights: (*i*) Ocular dominance likely underlies coarse direction discrimination, rather than differential velocity tuning across the eyes; (*ii*) Estimation of 3D direction is more precise for motions roughly towards/away than motions closer to frontoparallel; (*iii*) If 3D motion perception relies on MT tuning, performance on 3D motion direction discrimination tasks should change dramatically as a function of viewing distance. In summary, our model of 3D direction encoding in MT captures the drastically non-Gaussian tuning curves observed empirically, makes testable predictions for the consequences of these for perceptual performance, and allows for quantitative inquiry into the impact of referencing neural responses to real environmental variables.

Acknowledgments

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PUTTING SOUNDS IN CONTEXT

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The linearly-weighted receptive field has been used to describe central auditory responses to complex stimuli for decades, and one or more linearly-weighted fields also lie at the heart of more recent linear-nonlinear (LN) approaches to analysis of neuronal responses to complex sounds. However, the crucial assumption of linear weighting—that the sensitivity of the neuron to a local element of the stimulus is independent of the rest of the stimulus—is challenged by long-standing reports of nonlinear combination sensitivity in the central auditory system. Such nonlinearities include forward suppression of the response to the second tone in a pair and more complex combination effects for spectrally offset tone pairs. How do these and perhaps other contextual nonlinearities combine over frequency and time to shape neuronal responses to sounds more complex than tone pairs? And how might the larger behavioral context in which sounds appear affect their neuronal representation?

In this talk, I will discuss the impact of local acoustic context on auditory cortical and thalamic responses to complex sounds, as determined through experiments that involved recording neuronal responses to spectrotemporally rich dynamic random chord stimuli in two subdivisions of the mouse auditory thalamus and two auditory cortical fields. We found that in both auditory cortex and thalamus, elements of a complex sound modulate neuronal responsiveness more effectively when they coincide with sounds at distant frequencies, and less effectively when they are preceded by sounds at similar frequencies. Such local-context-driven lability in receptive fields may be a widespread motif in sensory processing.

Input-specific gain modulation is evident in awake as well as anaesthetised animals, but its sensitivity to behavioral context is still unknown. At the end of the talk, I will briefly describe a new method for monitoring behavioral state in unrestrained mice, which we are using to explore the impact of behavioral context as well as acoustic context. We developed an ultralight head-mounted camera system combined with head-movement sensors and multichannel electrode implants, to simultaneously monitor eye position, pupil dilation, whisking, and pinna movements along with head motion and neuronal activity in freely moving mice engaged in natural behaviors. The power of the combined technology is demonstrated by initial observations linking sound stimulation to whisker movements, pupil diameter to behavioral state, and sensory cortical activity to volitional head movements in freely moving mice.

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CONCURRENT MULTISITE RECORDINGS AND BRAIN IMAGING: A STUDY OF EVENTS RELATED SYSTEM AND SYNAPTIC MEMORY CONSOLIDATION

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Experimental work in animals and humans suggests that various oscillatory patterns, including single or multiple cycle short-lasting episodes, reflect state-changes in self-organizing large-scale networks. For instance, patterns like K-complexes, spindles, hippocampal sharp wave ripples, and PGO waves, are thought to reflect state-changes in networks regulating cognitive capacities, such as learning, memory encoding and consolidation, and memory-guided decision making . Although studied in detail with neurophysiological methods, the global effects of the aforementioned events on the entire brain remained elusive. The use of multishank-multichannel (MS-MC) electrical recordings of activity in different structures *per se* permits both the detection and the contextual identification of structure-specific neural events, for that matter also of their interrelationships. Combining MS-MC recordings with spatiotemporally resolved fMRI evidently offers a unique opportunity to study the cooperative patterns of a large number of brain structures either leading or responding to recorded events. In an effort to do so, we developed so-called neural event triggered fMRI (NET-fMRI), and used it to study the dynamics of the networks related to ripples and PGO events.

Initial recordings in hippocampus with ripple-triggered functional magnetic resonance imaging, showed that most of the cortex is selectively activated during the ripples, whereas most diencephalic, midbrain and brainstem regions are strongly inhibited [3]. Other regions, such as the parabrachial nucleus in pons were up or down-modulated and so were the low frequency field potentials in the peri-event intervals. Analysis of the temporal alignment between the SPW and ripple components revealed well-differentiated SPW-R subtypes in the CA1 LFP . Well defined PGO-subtypes were also evident in pons, with phasic events often occurring together with ripples and brief oscillations occurring exclusively in REM periods characterized by high hippocampal theta activity. The co-occurrence of ripples and PGO waves is the first evidence for a sequential occurrence of synaptic tagging and local plasticity changes potentially induced by the cholinergic PGO activity, that is related to synaptic consolidation. In the talk I will present new results related to such event interactions, and the global NET-fMRI patterns associated with them.

Acknowledgments

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DECODING FUNCTIONAL NETWORKS IN CEREBRAL CORTEX

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Visual cortical neuronal population activity is selectively modulated by particular visual stimulus parameters, such as the direction of a moving bar of light, resulting in well-defined trial averaged tuning properties. However, given any single stimulus parameter, a large number of neurons in visual cortex remain unmodulated, and the role of this untuned population is not well understood. Here, we use two-photon calcium imaging to record, in an unbiased manner, from large populations of layer 2/3 excitatory neurons in mouse primary visual cortex to describe co-varying activity on single trials in neuronal populations consisting of both tuned and untuned neurons. Specifically, we summarize pairwise covariability with an asymmetric partial correlation coefficient, allowing us to analyze the resultant population correlation structure, or functional network, with graph theory. Using the graph neighbors of a neuron, we find that the local population, including both tuned and untuned neurons, are able to predict individual neuron activity on a moment to moment basis, while also recapitulating tuning properties of tuned neurons. Variance explained in total population activity scales with the number of neurons imaged, suggesting larger sample sizes are required to fully capture local network interactions. We also find that a specific functional triplet motif in the graph results in the best predictions, suggesting a signature of informative correlations in these populationsIn summary, we show that unbiased sampling of the local population can explain single trial response variability as well as trial-averaged tuning properties in V1, and the ability to predict responses is tied to the occurrence of a functional triplet motif.

THE PREHISTORIC (POSSIBLY MINOAN) SETTLEMENT OF AKROTIRI AND THE ANCIENT GREEK CITY-STATE OF ANCIENT THERA: WHAT IS SO GREAT ABOUT THEM?

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Santorini is home to two very important archaeological sites:

1. The Bronze Age (possibly Minoan) site of Akrotiri that dates to the 2nd Millennium B.C. and

2. Ancient Thera, a Greek city-state (*polis*) that flourished in the 4th and 3rd centuries B.C.

In my presentation I shall discuss these two entirely different ancient societies and show how each is of relevance to modern western civilization. I will discuss how the first society—Bronze Age Akrotiri—appears so exotic because of how little we know about it, given the absence of historical texts and writing, and because of its well-known climactic end. I will also discuss how the second society—classical 4th/3rd century Thera—appears so familiar because its values, to a great extent, reflect the fundamental values of modern western democracies. Yet despite the familiarity with classical civilizations, such as 4th/3rd century Thera, we are more fascinated by the Bronze Age Civilizations, such as the Minoans and Mycenaeans. Why is that so?

In the case of the classical Greek city-states it is easy to understand the relevance: These states used the alphabet for the first time, the citizens spoke and wrote Greek, they trusted the potential for excellence of simple individuals and enjoyed political freedom. It is in this socio-political context that, in addition to philosophy, geometry, athletics, etc., democratic practices and values also emerged with the seminal example of the Ancient Athenian Democracy.

DENDRITIC INTEGRATION OF SENSORY EVIDENCE IN PERCEPTUAL DECISION-MAKING

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Perceptual decisions require the accumulation of sensory information to a response criterion. Most accounts of how the brain performs this process of temporal integration have focused on evolving patterns of spiking activity. We report that subthreshold changes in membrane voltage can represent accumulating evidence before a choice. αβ core Kenyon cells ($\alpha\beta_c$ KCs) in the mushroom bodies of fruit flies integrate odor-evoked synaptic inputs to action potential threshold at time scales matching the speed of olfactory discrimination. The forkhead box P transcription factor (FoxP) sets neuronal integration and behavioral decision times by controlling the abundance of the voltage-gated potassium channel Shal (K_V4) in $\alpha\beta_c$ KC dendrites. Manipulations that advance or delay the first $\alpha\beta_c$ KC spike have corresponding consequences for reaction times. $\alpha\beta_c$ KCs thus tailor, through a particular constellation of biophysical properties, the generic process of synaptic integration to the demands of sequential sampling.

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NEURAL MECHANISMS FOR DYNAMIC ACOUSTIC COMMUNICATION IN FLIES

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Social interactions require continually adjusting behavior in response to sensory feedback. For example, when having a conversation, sensory cues from our partner (*e.g.*, sounds or facial expressions) affect our speech patterns in real time. Our speech signals, in turn, are the sensory cues that modify our partner's actions. What are the underlying computations and neural mechanisms that govern these interactions? To address these questions, my lab studies the acoustic communication system of Drosophila. To our advantage, the fly nervous system is relatively simple, with a wealth of genetic tools to interrogate it. Importantly, Drosophila acoustic behaviors are highly quantifiable and robust. During courtship, males produce time-varying songs via wing vibration, while females arbitrate mating decisions. We discovered that, rather than being a stereotyped fixed action sequence, male song structure and intensity are continually sculpted by interactions with the female, over timescales ranging from tens of milliseconds to minutes — and we are mapping the underlying circuits and computations. We have also developed methods to relate song representations in the female brain to changes in her behavior, across multiple timescales. Our focus on natural acoustic signals, either as the output of the male nervous system or as the input to the female nervous system, provides a powerful, quantitative handle for studying the basic building blocks of communication.

A NEURAL CIRCUIT FOR ECONOMIC DECISIONS

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Economic choice behavior entails the computation and comparison of subjective values. A central contribution of neuroeconomics has been to show that subjective values are represented explicitly at the neuronal level. This result at hand, the field has increasingly focused on the difficult question of where in the brain and how exactly values are compared to make a decision. I will describe a series of results suggesting that good-based decisions emerge from a neural circuit within the orbitofrontal cortex (OFC). The main lines of evidence are (*i*) the fact OFC lesions specifically disrupt value-guided behavior, (*ii*) the fact that during economic choice different groups of neurons in OFC encode the input and the output of the decision process, (*iii*) the fact that these groups of cells are computationally sufficient to generate decisions and (*iv*) the fact that activity fluctuations in each group of neurons correlate with choice variability. I will also discuss a newly developed theory of optimal coding for economic decisions. Its central concept is that neuronal tuning functions are optimal if they insure maximal expected payoff. In this framework, I will show that value coding in OFC is functionally rigid (quasi-linear tuning) but parametrically plastic (range adaptation with optimal gain).

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BUBBLE OR BOOM? WHY VOLCANOES ERUPT THE WAY THEY DO

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Geologically fascinating and visually stunning, the island of Santorini ranks amongst the world's classic volcanoes. Santorini is the result of two volcanic processes occurring repeatedly over the past 400,000 years: the accumulation of volcanic material from numerous eruptions, and the collapse of the central region to form the present day caldera with soaring cliffs and spectacular harbor. As a preliminary to the mid-conference field trip to the Kameni Islands (the result of historical eruptions over the last 2000 years) this presentation will address one of the questions most commonly asked of volcanologists—"Why do volcanoes erupt the way they do?"

The underlying control on the nature of an eruption is the composition of the source magma beneath (or within) the volcano. Specifically, on the interplay of two composition-dependent parameters: the volatile content and the viscosity. Put more simply: how much gas is dissolved in the magma, and how rapidly can that gas escape? Gas-rich high viscosity magmas produce catastrophically violent explosive eruptions. Gas-poor and/or low viscosity magmas typically produce gentler eruptions.

As magma ascends, the associated decrease in pressure allows dissolved gases (primarily CO_2 and H_2O) to form bubbles within the magma. In the lowest viscosity magmas (such as the basalts of Hawaii and Iceland), these bubbles buoyantly migrate upwards through the magma towards the surface. The typical result is a relatively gentle eruption characterized by a bubbling (actively out-gassing) lava lake and the gentle effusion of runny and now *flat* lava. The upper regions the underlying magma chamber may comprise up to 90% gas in a foam-like structure, and it is the complex formation and collapse of this foam (in a process showing characteristics of self-organized criticality) that determines the specific nature of the surface eruption. The recent eruptions of Kilauea (Hawaii) are a classic example of this *gentle* style of eruption.

In contrast, higher viscosity magmas (such as fed the major Santorini eruption of about 3600 years ago) hinder such upward migration and gas loss. Instead, the magma reaches near surface levels with much (if not most) the original inventory of volatiles. When the constraining pressure drops below a critical value, the gas rich magma ruptures to the surface and explosively liberates the entrapped gases. The violence of this process is such to completely fragment the magma resulting in airborne volcanic ashes. The eruption ceases or diminishes as the source magma goes flat. Commonly, the centre of the volcano will collapse downwards into the emptying upper magma chamber resulting in a large caldera structure such as the harbour of Santorini.

A common final stage for this style of eruption is for slow, gentle, toothpaste-like extrusion of the residual high viscosity but relatively gas-poor magma to form small lava domes and flows in the floor of the volcanic crater or caldera—it is this process that is responsible for the young Kameni islands of Santorini that we will be visiting.

USING CHEMOGENETIC TOOLS (DREADDs) TO HELP IDENTIFY CIRCUITRY FOR RANKING REWARD VALUES

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An obvious feature of normal behavior is that sensory stimuli such as visual images are used to predict the outcome of current behavior. The values of the stimuli and the ranks of the values are inferred by observing how avidly the animal pursues the outcome. We have been asking where in the brain information about visual images becomes associated with the relative outcome values, and where the ranking might be learned and remembered. To this end we have carried out experiments wherein we inactivate brain areas of interest. We have used three inactivation methods: classical tissue removal, muscimol inactivation, and a chemogenetic tool, the DREADD (designer receptor exclusively activated by designer drug). We find that area TE is the last of area in the ventral stream cascade that carries information about the identity of images, and that inactivating rhinal, orbitofrontal, or lateral prefrontal cortices, or the rostromedial ventral striatum affect learning the ranks of the values predicted by a set of visual images. Included will be some experiences with DREADDs.

REMEMBERING WHAT WE SEE

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Our visual memory percepts of whether we have encountered specific objects or scenes before are hypothesized to manifest as decrements in neural responses in inferotemporal cortex (IT) with stimulus repetition. To evaluate this proposal, we recorded IT neural responses as monkeys performed a single-exposure visual memory task designed to measure the rates of forgetting with time. We found that a weighted linear read-out of IT was a better predictor of the monkeys' forgetting rates and reaction time patterns than a strict instantiation of the repetition suppression hypothesis, expressed as a total spike count scheme. Behavioral predictions could be attributed to visual memory signals that were reflected as repetition suppression and were intermingled with visual selectivity, but only when combined across the most sensitive neurons.

MOLECULAR, CELLULAR, AND CIRCUIT MECHANISMS THAT OPEN AND CLOSE THE WINDOW FOR MEMORY LINKING ACROSS TIME

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Studies of the molecular, cellular and circuit mechanisms of learning and memory have focused almost exclusively on how single memories are acquired, stored and edited. By comparison, very little is known about the mechanisms that integrate and link memories across time. Recently, we have used state of the art *in vivo* imaging methods, chemogenetic and optogenetic approaches in the hippocampus and retrosplinial cortex, to uncover mechanisms that open and close the window for memory linking across time. Interestingly, we showed that aging disrupts these mechanisms and that this results in age dependent decline in memory linking.

OPTIMAL PERCEPTUAL DECISION-MAKING WITH LIMITED REPRESENTATIONAL RESOURCES

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Bayesian inference has been a successful and principled model framework for explaining perceptual behavior. However, in many cases it has been difficult to convincingly justify the choices of the model parameters (*i.e.*, the likelihood functions and prior beliefs) needed to explain the data. I will demonstrate how we used the efficient coding hypothesis to derive a new and better constrained formulation of the Bayesian observer model. The new model makes a set of rather surprising and counter-intuitive predictions that, however, are supported both by neural and psychophysical data. I will discuss the general implications of the new framework for our understanding of perceptual behavior.

BIOPHYSICS OF MOTOR PLANNING AND SHORT-TERM MEMORY

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Our goal is to uncover the principles by which mammalian neural circuits perform fundamental computations, from perception to action. Cortex is parcellated into areas with distinct functions, each of which contains complex local circuits. Cortical areas in turn associate into mesoscale circuits with other cortical and subcortical areas via long-range connections. Information is represented by action potentials in widely distributed ensembles of neurons. What are the mechanisms shaping neural representations, and how do the representations drive behavior? We are only in the beginning stages of mapping the complexity of mammalian neural circuits. Can we extract principles in the absence of complete information about neural circuits? We have begun to address these questions in behaving mice in the context of motor planning and short-term memory.

Many movements are too rapid for online corrections. Movements that are preceded by periods of motor planning, which preprograms movement parameters, are faster and more accurate than in the absence of planning. In addition to its role in motor control, motor planning is also a prospective form of short-term memory, linking past events or instructions (*e.g.*, “throw a curveball”) and future movements (the actual pitch). During motor planning, neurons in motor cortex show slow dynamics (also referred to as persistent preparatory activity) related to specific movements, long before movement onset, in the absence of sensory input [1].

I will show that populations of neurons in the anterior lateral motor cortex collectively direct future movements [2]. Neuronal populations are shaped by attractor dynamics, with one attractor per movement [3]. The underlying neural circuits involve a cortico-thalamocortical loop [4, 5].

Acknowledgments

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REPRESENTATIONS OF COMPLEX SOUND FEATURES IN SUBPOPULATIONS OF AUDITORY CORTICAL NEURONS

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Pitch is our perception of the tonal quality of sounds on a low-to-high scale. It underlies our experience of musical melody, our interpretation of speech, and the ability to attend to one voice in a crowded room, yet the brain mechanisms that support this key percept remain unclear. To better understand these mechanisms across species, we compare the pitch discrimination of ferrets and humans on 2-alternative forced choice tasks. These experiments show that both species use harmonic and temporal envelope cues to make pitch judgments, but the relative weighting of these cues differs across species. We use high-channel-count microelectrode recordings in behaving ferrets to examine the cortical codes that underlie pitch judgments. These experiments demonstrate that inhibition can shape neural representations of pitch when animals are actively engaged in a discrimination task, compared to when they are passively listening to the same sounds. Furthermore, distinct subpopulations of neurons in secondary auditory cortex may be specialized for representing pitch. Our current experiments use 2-photon calcium imaging to measure the response properties of large numbers of neurons in ferret auditory cortex, while classifying their cell type and precise spatial position. This approach allows us to better understand how and where pitch is extracted within the cortical microcircuit, and to isolate the contributions of pyramidal and inhibitory neurons to feature encoding.

DYNAMICS OF PREFRONTAL COMPUTATIONS DURING DECISION-MAKING

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A major challenge to understanding the neural mechanisms underlying cognitive processes is that these processes cannot be directly observed, but rather must be inferred from behavioral measures. Furthermore, there could be considerable variability in these processes from one iteration to the next. Because neuronal responses are inherently stochastic, studies of cognitive processes typically average activity across many repeated trials. However, when the dynamics of those processes vary, this approach can obscure critical mechanistic details. In the first part of my talk, I will describe recent studies in my lab which have uncovered the dynamics of decision-making in orbitofrontal cortex with single trial resolution by leveraging the power of decoding ensemble activity by recording from many orbitofrontal neurons simultaneously. During individual choices, neural representations alternate between states associated with each available option, as if the network were considering them in turn. In the second part of my talk, I will discuss the relationship between dynamics at different neural scales, specifically single neurons and field potentials, and the implication that this has for the interpretation of macro-level measures of neural activity, such as fMRI and EEG.

POSTER ABSTRACTS

(in alphabetical order by first author)

NOVEL APPROACH TO DECODING NEURAL ACTIVITY TO MULTI-DEGREE OF FREEDOM BCI: METHODS AND METRICS OF MUTUAL ADAPTATION IN HUMANS AND MACHINES

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Objective: This work proposes a novel adaptive method for Brain Computer Interface (BCI), using online-learning via visual feedback to the user. The method uses electroencephalographic (EEG) signals and combines motor with speech imagery to provide a multiple DoF BCI system.

Approach: The approach utilizes the covariance matrix descriptor as a feature, which lies in the Riemannian manifold, and the Relevance Vector Machines (RVM) classifier. The novel contributions are that, (*i*) we propose a new method to select representative data points collected during the online-learning for updating the RVM model, and (*ii*) the online classifier is an adaptively-weighted mixture of RVM models to account for the users' exploration and exploitation processes during the learning phase, as illustrated in Figure 1. Instead of evaluating the subjects' performance solely based on the conventional metric of accuracy, we analyze their skill improvement based on 3 other criteria, namely the quality of the confusion matrix, the separability of the data and their stability.

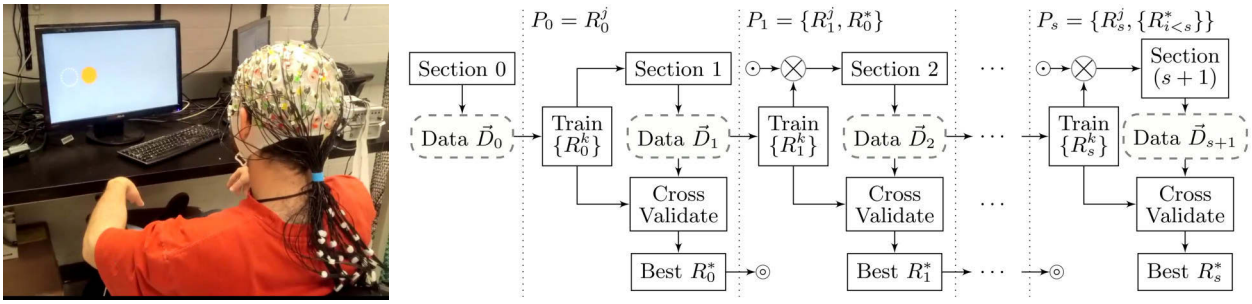

Figure 1. Procedure of the Co-Adaptive learning BCI system with Visual Feedback.

Main results: After collecting calibration data for 8 minutes in the first section of the experiment, 8 participants were able to control the system while receiving visual feedback in the subsequent sections. All participants demonstrated statistically significant improvements based on the confusion matrix quality criterion, including two of them who fell into the BCI illiteracy category. 5 of total 8 subjects also significantly improved their skills of using the BCI based on the separability of data criterion. Furthermore, the instability of data is used as the indication of the exploration and exploitation learning process.

Significance: Our proposed BCI system complements the existing approaches in several aspects. First, the co-adaptation paradigm is proved successful in allowing not only the classifiers, but also the users to actively discover their own way to use the BCI through their exploration and exploitation processes. Furthermore, the auto-calibration system can be used immediately with a minimal calibration time. Finally, we combine motor and speech imagery in order to increase the degrees of freedom for BCI control applications. We received very positive feedback from users, which once again emphasizes the importance of early feedback on BCI applications.

HUMAN-LEVEL SACCADE AND MICROSACCADE DETECTION USING CONVOLUTIONAL NEURAL NETWORKS

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Saccades are ballistic eye movements that rapidly shift gaze from one location of visual space to another. Even during gaze fixation, the eyes are not perfectly still, but they continuously exhibit microsaccadic movements separated by slow ocular position drifts. Studying the neuronal processes that underlie eye movements and fixation maintenance requires detecting saccades in large-scale eye position data. However, this can be a daunting task, particularly when such saccades are generated in coordination with other tracking eye movements, like smooth pursuit, and also when saccade amplitude is close to eye tracker noise levels. In such cases, human labeling is required, but this is a tedious task that is also prone to variability.

Here, we used a convolutional neural network (CNN) to detect saccades. We trained the network on human-labeled saccades and microsaccades collected from humans and monkeys, using either video-based eye tracking (for the human data) or scleral search coil measurements (for the monkey data). The training data also included catch-up saccades embedded within smooth pursuit eye movements. The CNN was able to detect saccades based on estimates of horizontal and vertical eye velocity. It reached near-human performance in saccade detection while being much faster. The approach does not require any parameter tuning and can accurately detect microsaccades and saccades occurring even in noisy signals.

Algorithms for automated saccade detection such as the one we present here will facilitate, and render more objective, studies of neurophysiological processes underlying saccade generation and visual processing.

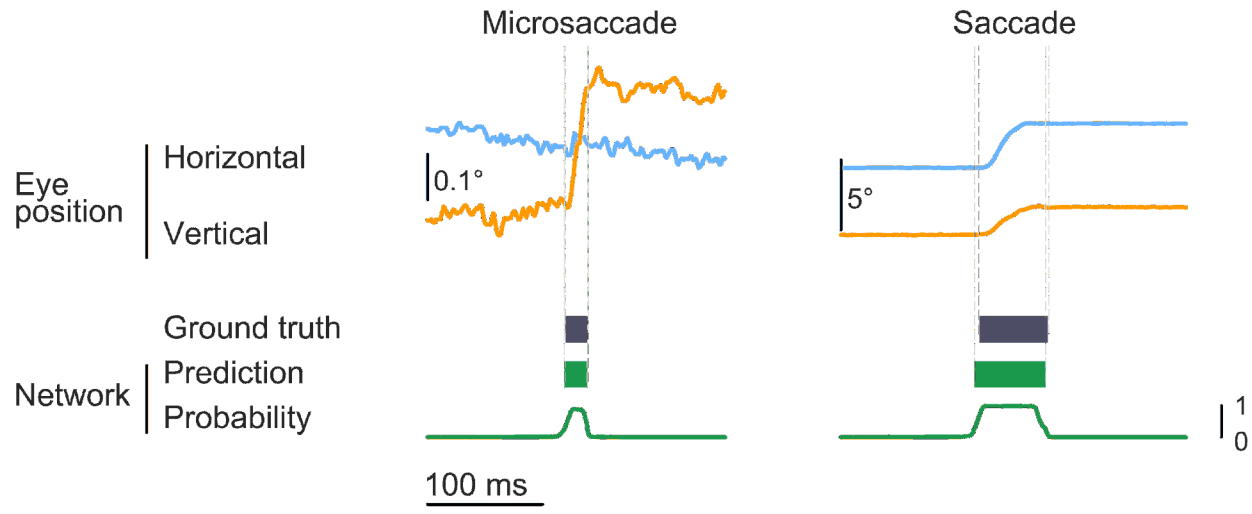

Figure 1. Two example saccades of different amplitudes (from a video-based tracker) with human-labeled ground truth shown in grey and prediction by convolutional neural network shown in green.

SIMPLE RECOMBINATION OF RETINAL OUTPUT CHANNELS YIELDS HIGHLY DIVERSE VISUAL REPRESENTATIONS IN MOUSE dLGN

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More than 30 functional types of retinal ganglion cells (RGCs) compute distinct features of the visual world in parallel and send this information to the brain. Little is known, however, about which RGC types project to the dorsolateral geniculate nucleus (dLGN) of the thalamus, and the principles underlying their recombination. Here, we functionally characterized dLGN-projecting RGCs and developed a model of how dLGN responses arise from retinal input channels.

To this end, we selectively labelled dLGN-projecting RGCs via dLGN-injections of a retrograde virus for conditional Ca^{++}-indicator expression, followed by *in vitro* retinal 2P Ca^{++} imaging of light-evoked responses. We assessed the functional types of dLGN-projecting RGCs based on the RGC classification from Baden and colleagues [1], and, using their stimulus set, assigned each cell to the best-matching functional RGC type. While overall most RGC types seem to innervate the dLGN, certain types like ON- and OFF alpha cells or OFF suppressed cells are clearly overrepresented.

In a separate set of experiments, we recorded the responses of dLGN neurons to the same visual stimuli using *in vivo* extracellular multi-electrode recordings in awake, head-fixed mice. To extract visual response features, we applied sparse non-negative matrix factorization (NNMF). Interestingly, this showed that dLGN cells exhibit a much higher diversity of response dynamics than previously thought. We then modelled dLGN cell responses as a sparse linear combination of retinal input types. Surprisingly, we found that this simple feedforward model sufficed to explain the majority of dLGN cell responses sparsely with 3–5 RGC input types very well (average correlation: 0.71).

Our study reveals that most mouse RGC types project to dLGN, which yields an unexpectedly diverse representation that can be modelled by a sparse feedforward model.

Acknowledgments

Supported by the Collaborative Research Center 1233 “Robust Vision” (DFG) and the Bernstein Award to PB (BMBF).

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PLASTICITY OF ADAPTATION REGULATES NEURAL ACTIVITY AND TEMPORAL CORRELATION FOR ARBITRARY INPUT STATISTICS

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Spike-triggered adaptation regulates the activity level in single neurons and has been associated with an efficient encoding of information. It has been observed that adaptation currents act at multiple time scales, matching the statistics of the neuron's input, leading to temporal decorrelation at various time scales [1]. This tuning of adaptation to input properties raises the question of whether adaptation can be learned.

We show how an interval dependent plasticity model (IDP) of adaptation allows for the self-organization of a neuron's activity. Similar to synaptic plasticity models, the amplitude of the adaptation current is modified at each spike, modulated by a trace of previous spikes, with a short time scale for potentiation and a long time scale for depression. Stability is reached when the auto-correlation of the spiking activity is equal at these two time scales (Fig. 1 a–b).

When injecting strong excitatory input currents, adaptation became up-regulated, and the output activity transitions from repetitive to irregular spiking, with a balance between excitation and the effective adaptation current. For inputs with power-law statistics, multiple adaptation currents with distinct time-scales were considered, leading to the learning of near power-law adaptation and consequent temporal whitening of the output activity (Fig. 1 c), as observed *in vivo* [1].

While activity dependent intrinsic plasticity has been observed experimentally, the underlying mechanisms are still unknown. Our model proposes very specific dependencies between adaptation change and spiking activity that may be tested in *in vitro* experiments. These findings indicate how instrinsic plasticity may be implemented in cortical neurons, allowing for stable activity regimes and an efficient temporal coding that is flexible to diverse input statistics.

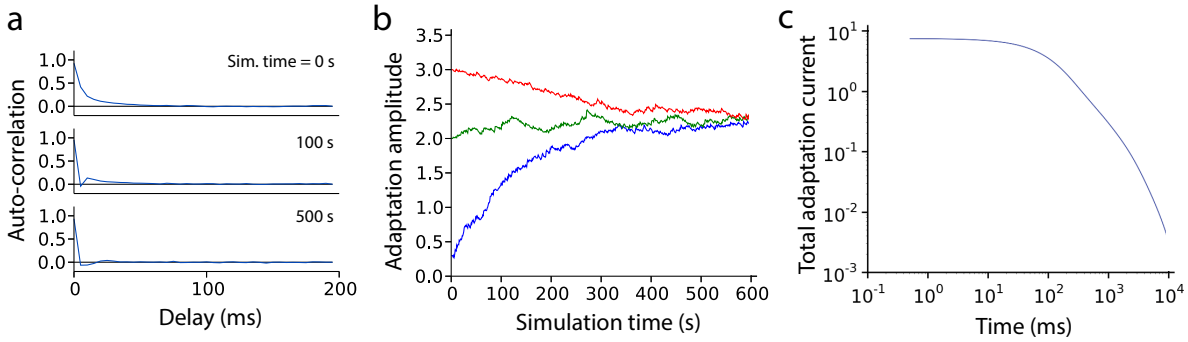

Figure 1. (**a**) Auto-correlation as a function of delay τ, for different simulation times. At the end, the auto-correlation function is nearly flat. (**b**) Different initial adaptation values converge to the same final adaptation magnitude. (**c**) Total adaptation current learned for a power-law input when including multiple plastic adaptation currents.

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FROM MULTISTABLE PHENOMENA TO OPTIMAL MODELS OF DECISION-MAKING

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The stochastic timing of perceptual events reveals much about the dynamical properties of underlying neural populations. In particular, computational models of sensory evidence accumulation, such as the drift-diffusion framework, have shed light on important aspects of perceptual decision-making. Here, we propose an extension of this framework to the study of multistable perception. In this simplified setting, some well-established statistical features of multistable phenomena are sufficient to fully constrain a hierarchical model of stochastic evidence accumulation.

The complex dependencies of average reversal times on competing inputs — also known as Levelt's propositions — are accurately reproduced for all combinations of stimulus strength, and are shown to rely on comparatively simple qualitative mechanisms. The stereotypical Gamma-like shape of reversal time densities, as well as the peculiar relationships between mean and higher-order moments — also known as the scaling property — are also closely obtained and qualitatively accounted for [1, 2]. In addition, our model correctly predicts non-stationary features of empirical reversal sequences, such as the effect of average stimulus strength on the group structure of short and long dominance periods.

We further notice that the model's characteristic exploratory dynamics, where new sensory evidences are accumulated while old sensory evidences are simultaneously discarded, can match that of normative models of optimal decision-making in changing environments [3]. We speculate that its hierarchical structure, which allows different levels of representation to interact via sensory-driven (bottom-up) influences and perceptually-driven (top-down) influences, makes it suitable to perform optimal decisions in a volatile world.

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FEATURE-SPECIFIC INHIBITION ENABLES FLEXIBLE CONTROL OF NEURONAL SELECTIVITY IN AN ATTRACTOR MODEL OF VISUAL CORTEX

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Feature-specific neuronal connectivity is a hallmark of sensory cortex, and has been observed across a wide variety of species and cortical areas [1]. However, while feature-specific connectivity between pyramidal cells is ubiquitous, the relationship between inhibitory connectivity and neuronal tuning varies considerably between cortical areas and species [1–3]. Even within individual animals, interactions between excitatory and inhibitory cells may be modified by experience [4]. Attractor models of cortical circuits suggest that neuronal tuning emerges as a consequence of feature-specific connectivity within the local network, but the majority of previous models have lacked separate excitatory and inhibitory populations [5], or have considered networks with nonspecific inhibition. Thus, the functional consequences of feature-specific inhibitory connectivity remain poorly understood. Here, we study how connectivity between excitatory and inhibitory neurons impacts neuronal tuning, population dynamics and the selectivity of population responses for sensory inputs in an attractor model of orientation tuning in visual cortex. We show that feature-specific connections between interneurons and pyramidal cells can either sharpen or broaden the tuning curves of pyramidal cells. Relative to networks with uniform inhibition, tuning curves are sharpened when interneurons preferentially target pyramidal cells with orthogonal orientation preferences to their own (ortho-inhibition), but are instead broadened when interneurons target pyramidal cells with similar orientation preferences to their own (iso-inhibition). Beyond this sharpening of single-cell tuning, the ortho-inhibition network further enhances the ability of the pyramidal population to discriminate between similar orientations by suppressing the translational variability of the attractor bump, thereby reducing the overlap between signal and noise dimensions in the population response. Finally, feature-specific connectivity between excitatory and inhibitory neurons fundamentally changes the way in which tuning can be modulated by top-down inputs, allowing the selectivity of responses to specific stimuli to be dynamically modulated by top-down inputs to the relevant subpopulation of interneurons. Our findings suggest plausible inhibitory connectivity motifs and top-down inputs that can account for changes in neuronal selectivity with learning and behavioural context [4], and make testable predictions for the changes in neuronal tuning curves when the behavioural relevance of stimuli change.

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SCALING OF INFORMATION IN LARGE SENSORY POPULATIONS

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How effectively does the brain encode information across large numbers of neurons? Many models predict that shared variability (or, *noise correlations*) will cause information to saturate for even moderately sized population, although empirical evidence in this regime is severely lacking. We studied this prediction using a novel 3D high-speed *in vivo* two-photon microscope to record nearly all of the hundreds of neurons in a small volume of the mouse primary visual cortex. We presented full field grating with five closely spaced orientations and measured how encoded information grows with population size.

Contrary to numerous predictions, we find that information continues to increase for population sizes of several hundred neurons with little sign of saturation. In addition, a decoder ignoring correlations between neurons can still decode the majority of the information in the population. The growth of information with population size is well described by an equation motivated by models of information limiting correlations [1],

$$I(n) = I_o n/(1 + \varepsilon\, n),$$

with ε a consistently low value across numerous anesthetized and awake animals, demonstrating that the magnitude of information-limiting correlations is quite small. Finally, we find the empiric correlation structure is consistent with numerous eigenvectors weakly aligned to the population tuning, $\dot{f}(\theta)$, which can give rise to similar growth.

Our results suggest that sensory neural populations represent information in a truly distributed manner and pooling of neural activity within local circuits may be much more effective than previously anticipated. The representation in early sensory areas does not appear to be impaired substantially by shared sensory noise.

Acknowledgment

Supported by NIH

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POPULATION CODING AND TEMPORAL DYNAMICS IN THE FRUIT FLY TASTE SYSTEM

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The taste system controls feeding behaviors by promoting the consumption of nutritious foods and preventing the ingestion of toxins. From invertebrates to mammals, neural encoding of taste is typically described as a labeled-line system, in which different neuronal populations respond to different categories of tastants and elicit specific innate behaviors. Sugar-sensing neurons, for example, drive appetitive feeding behaviors, whereas bitter-sensing neurons induce aversion. Our studies of the fruit fly (*Drosophila melanogaster*) taste system suggest that taste coding goes beyond a simple labeled-line system: specifically, we show that different populations of taste neurons interact and that information is encoded in their temporal dynamics.

In nature, fruit flies frequently encounter acetic acid, a naturally occurring product of fruit fermentation that provides calories but can also be toxic. We observed that acetic acid elicits opposing behaviors depending on hunger: fed flies show taste aversion to acetic acid, whereas starved flies show a robust appetitive response. Calcium imaging revealed that, unlike other tastants, acetic acid activates both sugar- and bitter-sensing neurons. Genetically targeted silencing experiments showed that bitter-sensing neurons mediate the aversive response in fed flies, whereas sugar-sensing neurons drive the appetitive response in starved flies. We found that the sugar and bitter pathways compete to determine the behavioral response to acetic acid, and hunger shifts the balance from aversion to attraction by upregulating the sugar pathway and downregulating the bitter pathway. Imaging experiments suggest that this hunger modulation occurs downstream of sensory neurons, implying that central taste processing transforms invariant sensory responses into flexible motor outputs.

While performing calcium imaging of taste sensory neurons, we discovered striking differences in their temporal dynamics. Two classes of taste neurons, sugar- and water-sensing neurons, showed a sustained response throughout the stimulus presentation that rapidly diminished upon stimulus removal. By contrast, bitter-sensing neurons showed strong, transient responses at both the onset and offset of the stimulus. These temporal dynamics were preserved in a set of downstream bitter-responsive neurons, the PPL1 dopaminergic neurons (DANs). PPL1 DANs are essential for aversive olfactory learning, in which pairing an odor with an aversive unconditioned stimulus (US) causes subsequent aversion to the odor. In this paradigm, PPL1 DANs encode the US and mediate learning by inducing plasticity at synapses onto odor-responsive neurons. We found that pairing odor with bitter taste induced plasticity at these synapses. The bitter onset and offset responses in PPL1 DANs contributed differently to this plasticity and, in some paradigms, had opposing effects. The distinct effects induced by bitter onset and offset responses are likely due to their different temporal relationships with odor during odor-bitter pairing. The temporal dynamics of taste responses thus have implications for learning.

Together, our results suggest that taste coding is more complex than previously appreciated. They reveal state-dependent interactions between different populations of taste neurons as well as pronounced temporal dynamics in their responses. These features of taste coding are likely to influence both innate and learned behaviors.

CHOICE-DEPENDENT NEURAL TRAJECTORY OF HUMAN DECISION MAKING

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Decision making is a dynamic process that involves an interplay among multiple regions of the brain and a sequence of multiple processing stages. However, our current understanding of neural underpinnings of decision making process is mostly based upon precise but spatially-limited intracortical neuronal responses recorded at single-cell level.

We recorded electroencephalography (EEG) while observers performed a self-ordered task that consists of three increasingly difficult steps in a trial lasting 3 seconds [1]. In the first step, observers voluntarily chose one of three different categories of pictures (face, object, and building) presented at any of three of the six possible positions equidistant from the central fixation by pressing a button corresponding to the chosen category. In the second step, observers had to choose one of the two remaining categories. In the last step, they had to choose the one remaining category. In each step, three new pictures of the same three categories were presented at a new subset of positions for 500 ms and followed by 500 ms inter-stimulus interval. This task allowed us to tease apart all six possible behavioral trajectories of choices that observers made.

We investigated the existence of neural trajectory corresponding to behavioral trajectory of three steps of choices by using a demixed Principal Component Analysis (dPCA) [2] that can extract task condition-responsive subspace. Task condition was defined by the chosen category at each step. We split each 3-second trial into three 1-second segments and used all segments when calculating the weight for dPCA in order to extract pure choice space irrespective of step order. Using this weight, we projected responses of the entire 3-second trial onto dPCA axes that are most responsive to categorical choice of observers.

In neural state space, we found three separate regions corresponding to three categorical choices even though the same visual information was presented. We also found that neural trajectory passed through these three category-specific regions in the same order of behavioral choice. Thus, we were able to identify six unique neural trajectories corresponding to the six different combinations of sequential decisions. Our results support the idea that there are generalized cognitive search processes and may advance our understanding of the neural codes that link the brain and such cognitive maps.

Acknowledgments

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PERISYNAPTIC ACTIVITY IN THE PREFRONTAL CORTEX REFLECTS SPONTANEOUS TRANSITIONS IN CONSCIOUS VISUAL PERCEPTION

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In binocular rivalry, our perception alternates spontaneously between mutually exclusive or mixed interpretations, although the physical stimulus remains constant. This enables us to study visual consciousness, as it allows for a dissociation between sensory processing and conscious perception [1]. Previous imaging studies in humans have implicated the role of the fronto-parietal network in mediating perceptual alternations [2]. However, whether this frontal activation is indeed related to the percept, or, rather is confounded by, or reflects the consequences of perception *viz*. decision-making, introspection or motor-output, is still a matter of debate [3, 4]. Moreover, the degree of modulation in the frontal regions at the spiking and perisynaptic activity timescales is yet unclear.

Because of the above-mentioned considerations, two male macaques were trained to maintain fixation within a window and follow the motion of the stimulus for up to 12 seconds in a specifically designed no-report paradigm. They were implanted with Utah Arrays (10 × 10) in the ventro-lateral prefrontal cortex. Spontaneous switches in the percept were identified from the Optokinetic Nystagmus traces. Trials where the stimulus was experimentally switched acted as a control. Sites on the array were sorted according to their preference for either an upward-moving or a downward-moving stimulus based on the spiking activity.

In the high-frequency regime, *i.e.* the Gamma band (80–150 Hz), the power followed the pattern of selectivity displayed by the neural discharges including adaptation as reported previously [4]. Activity preceding a spontaneous switch revealed epochs of power modulations in the low-frequencies, *i.e.* the Delta Band (1–4 Hz) and the Theta Band (4–8 Hz), whereas this activity manifested itself strongly post-switch during physical alternation, pointing towards a role of slow cortical states in refreshing the content of conscious visual perception. Moreover, this burst-like activity was stronger when a preferred stimulus switched to a non-preferred stimulus implicating these slow cortical states in specifically overcoming an energy barrier required to transition from a preferred to a non-preferred stimulus. Taken together, these results strongly suggest that oscillatory activity in the prefrontal cortex plays a central role in the spontaneous transitions in conscious visual perception.

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SPECTRALLY MULTIPLEXED REPRESENTATIONAL DYNAMICS OF ENSEMBLE AVERAGE OF SIMULTANEOUSLY PRESENTED OBJECTS

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We are constantly bombarded with an enormous amount of ever-changing stream of information that overwhelms its processing capacity. One way the visual system copes with this problem is to use a dimension reduction mechanism known as ensemble representation, wherein a central tendency is extracted from a set of stimuli that vary along one or more feature dimensions. Behavioral studies have shown that ensemble average of similar stimuli can be extracted and the accuracy of ensemble average decreases as the inter-stimulus variability increases. However, neural mechanisms underlying such properties of ensemble representation remain poorly understood.

Here we hypothesize that ensemble average of a specific feature is a coarse-grained representation in which high-dimensional neural population activity is projected into a low-dimensional subspace linearly spanned by the basis feature channels. To test this hypothesis, we used an inverted encoding model-based decoding analysis to reconstruct neural representation of ensemble average orientation from full electroencephalography (EEG) signals that were recorded while an array of 36 randomly oriented Gabor patches was presented at the center of the screen. In Experiment 1, we examined if ensemble average is effortlessly encoded in the brain regardless of whether observers were required of computing ensemble average or not. In Experiment 2, we tested whether the accuracy of the reconstructed ensemble average orientation decreases as orientation variability among Gabor patches increases.

In Experiment 1, we found that theta band activity pattern encoded ensemble average orientation for initial 500 ms after an array onset regardless of task demand. Furthermore, after the disappearance of initial theta band activity, alpha band activity pattern maintained the neural representation of ensemble average orientation for about 800 ms only when observers were required of computing ensemble average. In Experiment 2, ensemble average orientation recovered from initial theta band activity pattern gradually deteriorated as orientation variability increased. This task-dependent oscillatory multiplexing of ensemble average information through theta and alpha band activities may index the change of neural computation, which translates into the precision of behavioral performance.

Acknowledgments

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EMPIRICAL SELECTION OF EFFECTIVE STIMULI FOR MOUSE VISUAL CORTEX

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Large-scale studies of neuronal circuits require sensory stimuli that elicit rich population responses in a short time. Here, we provide the *neural response gamut*, a metric to empirically evaluate the ability of visual stimuli to evoke strong, repeatable, and diverse responses in large populations of recorded neurons. We use the metric to compile stimulus ensembles that quickly and efficiently interrogate circuit function.

Intuitively, the neural response gamut estimates the volume in the neural response space occupied by the repeatable component of the population responses to a given stimulus ensemble. In this way, it parallels in form and meaning the entropy of a multivariate normal distribution with a given covariance matrix, but with no direct equivalence. Let vectors $\boldsymbol{x}$ and $\boldsymbol{y}$ be the instantaneous responses of a population of neurons to two repeats of the same stimulus. Let $\langle\cdot\rangle_{\mathcal{S}}$ denote the empirical average over an ensemble of stimuli $\mathcal{S}$. Then the mean neuronal activity is $\mu_{\mathcal{S}} = ½\langle \boldsymbol{x} + \boldsymbol{y}\rangle_{\mathcal{S}}$ and the cross-covariance matrix is

$$C_{\mathcal{S}} = \frac{1}{2}\langle \boldsymbol{x}\otimes\boldsymbol{y} + \boldsymbol{y}\otimes\boldsymbol{x}\rangle_{\mathcal{S}} - \mu_{\mathcal{S}}\otimes\mu_{\mathcal{S}},$$

where $\otimes$ denotes the outer product. Although noise in the responses contaminates and biases the cross-covariance matrix, it remains useful as a sample estimate of the signal covariance matrix of the neuronal population, *i.e.* the covariances of the repeatable components of neuronal responses. We computed the response gamut as the log determinant (*i.e.* sum of the logarithms of eigenvalues) of the cross-covariance matrix

$$E_{\mathcal{S}} = \sum_{i=1}^{m} \log \lambda_i(C_{\mathcal{S}} + \alpha I),$$

where α is a regularization parameter and $\lambda_i(\cdot)$ is the i-th largest eigenvalue. For robustness, the calculations were limited to m largest eigenvalues, *e.g.* m = 10% of the number of neurons. The metric rewards stimulus ensembles that evoke strong, repeatable, and diverse responses: when $E_{\mathcal{S}} > E_{\mathcal{R}}$, then the stimulus ensemble $\mathcal{S}$ may be judged superior to ensemble $\mathcal{R}$ of the same duration for the study of properties of population responses.

We collected two-photon simultaneous imaging in four $1200\times1100\ \mu m^2$ planes spanning 400 µm in depth (6.4 Hz sampling rate). Deconvolved calcium activity traces from over five thousand neurons in response to natural movie visual stimuli (2 repeats of 15 minutes, composed of 10 second clips) were used to calculate cross-covariance matrices. A simulated annealing algorithm was used to perform global search for a subset of movie clips that maximized the response gamut. We then trained a deep recurrent network to predict the deconvolved Ca^{++} activity of simultaneously recorded neurons to the selected videos using a combination of convolutional layers, gated recurrent units, and spatial transformers. The network simultaneously receives the pupil position, dilation, and movement speeds of the animal to account for receptive field shifts and brain state changes of the animal. The response gamut of the training set significantly and positively correlated with model performance, as measured by test correlation between recorded and predicted activity for withheld test data.

DYNAMIC THEORY OF CORTICAL NETWORKS WITH ACTIVE DENDRITIC PROPERTIES

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Activity-dependent calcium influx into dendritic structure initiated by spikes in the soma (so-called active dendritic properties) is an essential component of neuronal dynamics. The importance of this active property has been highlighted in many single-cell studies [1] and also incorporated in the large-scale simulation of multicompartmental neurons of cortical circuits [2]. However, up to date, there has been no theory developed to study the role of the active dendrites on the collective dynamics of recurrent networks. In the present study, we develop a dynamic theory of the cortical microcircuits, in which neurons integrate input via active dendrites. The theory includes an effective self-excitation due to the spike-dependent activation of calcium influx, in addition to the canonical model of the balanced recurrent network [3]. Our analysis shows that a slow-dynamic asynchronous state, with timescales of hundred of milliseconds, emerges due to the dendritic properties as it has been observed in large-scale simulations of cortical columns [2]. We further study a simulation of spiking neurons [4] in the balanced state of excitation and inhibition. Our simulations confirm the prediction of the analytical results consistently and suggest a physiologically plausible tuning of the timescales of the dynamics by changing the distribution of inhibitory inputs into distal and proximal dendrites of pyramidal neurons. Our results indicate that the active dendritic properties allows a slow collective cortical dynamics.

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EXPLORING SHARP-WAVE RIPPLE DYNAMICS IN THE REPTILIAN BRAIN

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Sharp-wave ripples (SWRs) are highly synchronized population events that have been proposed to underlie the transfer of mnemonic representations in rodents, and to drive synaptic changes as memories are consolidated into cortical long-term stores. As such, SWRs play a prominent role in theories of episodic memory consolidation and may serve cognitive functions more generally; yet, key questions remain open and an understanding of how exactly SWRs are generated or affect downstream circuits at a synaptic level remains elusive.

The identification of functional principles necessitates a comparative approach, and the recent discovery of SWRs in the brain of a sleeping dragon (*Pogona vitticeps*) is thus of particular interest, offering the opportunity to study the function of these dynamics in the relatively simple reptilian brain and its three-layered cortex. To this end, we investigated the possibility of studying SWRs *ex vivo* — in whole-brain and slice preparations — while taking advantage of the reptilian brain's resilience and experimental tractability. Using a combination of whole-cell and extracellular recordings, guided by transcriptomic and anatomical tracing data, we find SWR dynamics that closely resemble those recorded *in vivo* and during periods of slow-wave sleep. Neurons in the vicinity of the putative site of SWR origin frequently show sub- and suprathreshold depolarizations and receive barrages of excitatory and inhibitory inputs, locked to the trough of individual sharp waves. Neuromodulatory tone and ionic composition of the extracellular milieu can be used to regulate SWR properties and their frequency of occurrence.

Our preliminary results demonstrate the utility of this system for gaining insight into cellular and network mechanisms underlying the generation of SWRs and open the door for future studies exploring the potential role of SWRs as fundamental units of communication, supporting information transfer and storage in the vertebrate brain.

THE ROLE OF FAST NOISE CORRELATIONS IN ENCODING DYNAMIC STIMULI IN THE RETINA

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A major challenge in sensory neuroscience is to understand how complex stimuli are encoded by neural circuits. In the retina, several layers of neurons process the visual stimulus, which is ultimately encoded by the spiking activity of ganglion cells. It is still unclear how the visual scene is encoded by the collective activity of ganglion cells.

Here we recorded large populations of ganglion cells with multi-electrode array on rat retinas responding to complex stimuli, such as videos of moving objects. We found that neighbouring cells exhibit fast correlations, that cannot be explained by the joint activation due to the stimulus. The time scale of these noise correlations is fast enough to be mediated by gap junctions, and they were present specifically for cells of the same type.

In order to investigate the role of these noise correlations in the encoding of the visual scene we have constructed a model capable of predicting both the response of individual single cells (PSTH) and the observed noise correlations. This model is composed of a cascade of two layers of processing, and equipped with a recurrent interaction network among the ganglion cells to reproduce specifically noise correlations.

We are currently using this model to measure how noise correlations impact the coding of these complex stimuli, and test if they are helpful or detrimental to the encoding capacity of the retinal network.

Further information about the inference method is available in pre-print form [1].

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OBJECT REPRESENTATIONS IN THE MOUSE VISUAL SYSTEM

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Object recognition is a hallmark of visual perception and despite years of research we still do not have a complete mechanistic understanding of how populations of neurons across different brain regions give rise to invariant object representations. Primates are an ideal animal model to study object recognition given their rich visual capabilities. However, recent advancements in techniques available for recording and manipulating neuronal populations and high throughput behavioral training of rodents allow us to study how objects are represented in the activity of large populations of neurons across the entire visual hierarchy.

Here we used a large field of view two-photon microscope, that allows us to record the calcium activity of thousands of neurons from all visual areas of the mouse simultaneously. We quantified the linearly decodable information available across the mouse cortical visual hierarchy. Using support vector machine classification, we decoded the identity of different objects undergoing numerous nuisance transformations such as rotation, scale and translation. We found that two lateral visual areas LM and LI carry progressively more information about objects compared to V1, similarly to what has been shown in the rat [1] and which maybe analogous to the primate ventral stream. The increase in decoding performance across the visual areas correlated with the linear separation of their activity trajectories in the reduced space (Figure 1). Additionally, the population dynamics differ across the visual hierarchy where the information about object identity evolves faster in more selective visual areas.

Our results point to a specific object processing pathway in the mouse with areas that have linearly separable object identity manifolds and distinct temporal dynamics.

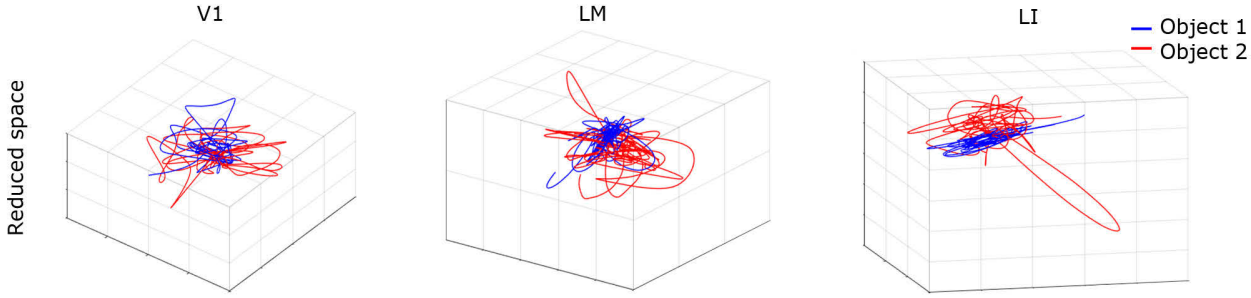

Figure 1. Low dimensional representation of the neural activity space with locally linear embedding, illustrating the wider separation of neural trajectories for two objects when transitioning from V1 to higher visual areas.

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TWO PHOTON IMAGING REVEALS SALT AND PEPPER TONOTOPY IN FERRET AUDITORY CORTEX

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Tonotopic organisation has been a widely accepted property of the primary auditory cortex (A1) for over 50 years. Electrophysiological studies have described it in a wide range of mammals, including rodents, cats, ferrets, and primates. However, the spatial resolution of microelectrode recordings is limited, and do not offer fine-scale mapping of cortical responses. Two photon (2p) calcium imaging, on the other hand, can measure the sensory responses of much large numbers of single neurons within a local area of the neocortex. Recent studies using 2p calcium imaging to investigate the spatial organization of frequency preferences in the mouse A1 have shown that although tonotopic organisation is visible at a large scale, neighbouring neurons can have vastly different frequency preferences [1–3].

To date, it remains unclear whether this local variability of responses is a general feature of the mammalian A1, or a peculiarity of rodents. To address this controversy, we have carried out 2p calcium imaging in the auditory cortex of anaesthetised ferrets (*Mustela putorius furo*). Each ferret ($n = 6$) was injected in A1 with an AAV1 viral vector encoding the calcium indicator GCaMP6m. Four weeks later, we imaged the neuronal responses to pure tones (1.2–41 kHz; 40–100 dB SPL) in cortical layers 2/3.

Our results show that although a large scale tonotopy is present in layers 2/3, neurons within one imaging field can widely vary in their frequency preferences. Pairwise correlations and BF variability quantification confirm that the local variation in neuronal best frequency is similar in mice and ferrets. Therefore, a salt-and-pepper local organisation of frequency preference seems to be a shared feature of the auditory cortex across mammalian species.

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RATS USE BEHAVIORAL OUTCOMES TO FLEXIBLY ADAPT HOW INTERNAL MODEL OF THE ENVIRONMENT INFLUENCE THEIR DECISIONS

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Prior experiences shape the way we perceive the world by creating expectations, a reference frame for future decisions and judgements. Little is known however about how these expectations are adjusted to the environment changing conditions. We trained rats in a reaction time two-alternative forced-choice (2AFC) task where the probability to repeat the previous stimulus category (left or right) was varied in blocks of 200 trials. Rats adapted their behavior to the stimulus serial correlations by developing a positive (negative) repeating choice bias after correct (alternations). The repeating bias built-up after each correct response but vanished to almost zero after error trials independently of the number of previous correct trials. GLM analysis revealed that this repeating bias contained two history-dependent factors: (*i*) a lateral bias towards (away from) the side of recently rewarded (unrewarded) responses, *i.e.* a win-stay-lose-switch strategy; (*ii*) a novel and strong transition bias that reinforced recent correct repetitions and alternations. We found that the transition bias was absent after error trials, when the reliability of the internal model was possibly questioned, and recovered after the subsequent correct trial. This ability to rapidly activate and inactivate bias was captured by a non-linear latent generative model of rat behavior (Fig. 1a), whereby a reward-driven modulatory signal gated the influence from accumulated transition evidence on the current decision. The modulation allowed the transition bias to reset after errors while maintaining the transition evidence, and a single correct trial was sufficient to recover the accumulated choice bias. We conducted neural population recordings in dorsomedial striatum. Preliminary analyses showed that several neurons were selective to rats' present choice, present outcome and previous trial transition type (repetition *vs.* alternation; Fig. 1b), suggesting that the region might be accumulating behaviorally-relevant information from recent trial history in order to guide perception. Overall, our findings reflect that rats use behavioral outcomes to flexibly adapt the influence of internal models of the environment on their decisions.

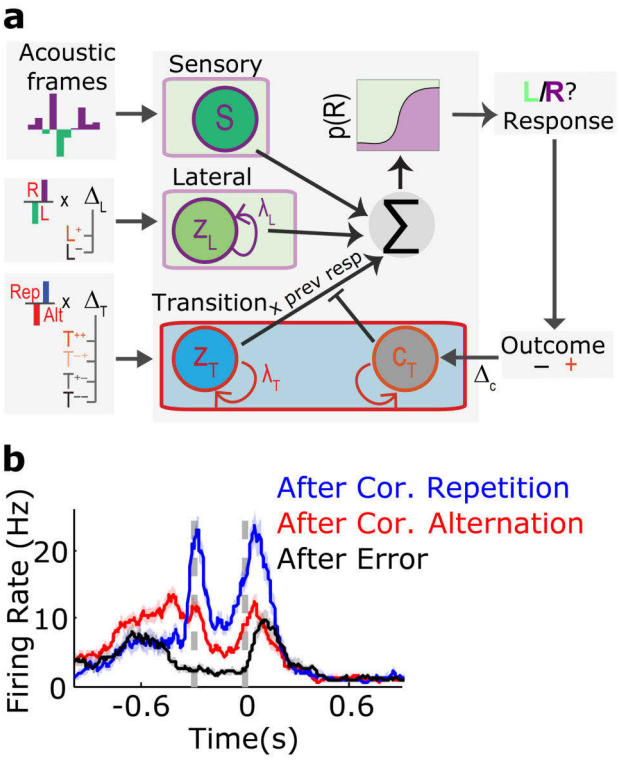

Figure 1. (a) Diagram of the latent generative model. **(b)** Firing rate of an example neuron aligned to the center poking and stimulus presentation. The neuron is selective to the previous transition type.

NOMINALLY NON-RESPONSIVE FRONTAL AND SENSORY CORTICAL CELLS ENCODE BEHAVIORAL VARIABLES VIA ENSEMBLE CONSENSUS-BUILDING

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Spike trains recorded from the cerebral cortex of behaving animals can be complex, highly variable from trial-to-trial, and therefore challenging to interpret. A fraction of recorded cells typically exhibit trial-averaged responses with obvious task-related features and can be considered *classically responsive*, such as neurons with tonal frequency tuning in the auditory cortex or orientation tuning in the visual cortex. However, a substantial number of cells (including cells in primary sensory cortex) do not appear to fire in a task-related manner and are often neglected from analysis [1]. Even classically-responsive cells lose their stimulus representation during task-engagement without impairing behavioral performance [2, 3]. These results suggest that nominally non-responsive cells may play an underappreciated role in sensory processing and cognition.

To understand their role, we devised a novel single-trial spike-timing-based decoding algorithm to unlock the hidden coding capacities of these neurons recorded from the auditory and frontal cortex of trained rats. Specifically, we used multielectrode arrays to record neural ensembles while animals performed a go/no go auditory frequency recognition task. We found that nominally non-responsive cells reveal hidden task information complementary and comparable to that of responsive cells.

Historically, the capacity to predict behavioral errors on single trials using responsive cells has been limited. Using our novel decoder, we demonstrate that including non-responsive cells significantly improved predictions of behavioral errors in both auditory and frontal cortex indicating that these neglected cells can provide missing insights into behavioral variability. Surprisingly, we found that stimulus category information is more prevalent and pervasive in frontal cortical ensembles suggesting it may be critical for extracting task-relevant stimulus information. This was accomplished by ensembles of non-responsive cells coordinating the behavioral meaning of their activity, essentially achieving consensus on the representation of task variables on correct but not error trials. These results demonstrate that non-responsive cells not only contain task relevant information, but also may play an essential and underappreciated role in behavior.

Acknowledgments

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POSTTRAUMATIC STRESS DISORDER: NEURONAL POPULATION CODING OF SUDDEN TRAUMATIC EVENTS

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Posttraumatic stress disorder (PTSD) is the only psychological disorder with known etiology, namely, exposure to a traumatic event. Despite extensive study, the mechanisms underlying the development of the disorder are not well understood. We have previously shown that trauma exposure is dealt with in healthy controls by decorrelating brain networks proportionally to trauma intensity; by contrast, in PTSD no decorrelation is observed [1]. Here, we offer a new theory of PTSD based on neuronal population coding. Specifically, we propose that intense sensory convergence resulting from massive engagement of sensory modalities during exposure to trauma leads to fixed, highly correlated downstream frontal, temporal and ultimately limbic neural networks [2], reflecting encoding of salient sensory inputs. Furthermore, we postulate that PTSD is the involuntary outcome of behavioral decoding of those highly correlated neural ensembles manifested by prominent re-experiencing of traumatic events through intrusive memories, nightmares, and flashbacks.

To test this theory we evaluated fMRI data from 36 subjects (15 PTSD, 21 healthy controls). We found that, indeed, zero-lag crosscorrelations increased progressively in PTSD, relative to the controls, from primary sensory areas to successive areas of multisensory convergence and final limbic pathways, along the cortical organization plan described by Jones and Powell [2]. We postulate that this hard-wired plan channels sensory inputs in specific ways such that intense and simultaneous multisensory stimulation leads to spatially progressive hypercorrelation, a condition which, in healthy people, gradually reverts to the normal, uncorrelated state but which, in the case of PTSD, remains in the hypercorrelated state. The factors underlying the persistence of this hypercorrelated state in PTSD as well as potential interventions aimed at facilitating decorrelation remain to be investigated.

Acknowledgments

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SIGNAL PROPAGATION THROUGH INTER-AREAL BALANCED AMPLIFICATION IN A LARGE-SCALE CIRCUIT MODEL OF THE PRIMATE CORTEX

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Stable transmission of signals in a multi-area feedforward network represents a long-standing challenge: as a signal propagates across areas, it may either die out or explode [1–3]. Previous studies on signal transmission regard cortical areas as identical nodes and do not constrain inter-areal connectivity based on data [1–3].

We reexamine this long-standing problem using a large-scale cortical network framework, based on recently published anatomical data of the macaque cortex [4], including the natural heterogeneity found in both inter-areal projections and local circuit connectivity. Our computational model incorporates, for the first time in a signal propagation analysis, complex long-range projections across cortical areas with an abundance of feedback connections. This leads to the emergence of reverberatory inter-areal excitatory loops, posing a unique challenge to signal transmission.

We propose a novel mechanism, based on strong long-range excitation stabilized by lateral inhibition, to boost signal transmission in our large-scale framework. Our mechanism is inspired by the balanced amplification phenomenon [5], extending its central idea from local-circuits to a large-scale system; balanced amplification follows from strong local recurrent excitation balanced by local inhibition.

We demonstrate the effectiveness of our mechanism across a range of computational models, including recently examined population rate models. We build a large-scale spiking network model and validate our mechanism in both the asynchronous and synchronous propagation modes. Finally, we use our large-scale spiking network model to examine the emergence of global activity patterns associated with subliminal, preconscious and conscious processing [6]. Our findings demonstrate our model as an anatomically realistic platform for investigations of the global primate cortex dynamics.

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THE PATHOCONNECTOMICS OF CIRCUIT REMODELING IN RETINAL DEGENERATION

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The retina is a complex, heterocellular tissue with most/all retinal cell classes becoming altered in retinitis pigmentosa (RP) and age-related macular degeneration (AMD) in a process called retinal remodeling [1, 2]. Defining disease and the stage-specific cytoarchitectural and metabolic responses in RP and AMD is critical for highlighting targets for intervention. We now know that negative plasticity and neural retinal remodeling occurs regardless of retinal insult in models of retinal degeneration as well as in human RP and in human AMD, revealing that no retinal disease fails to trigger remodeling and reprogramming.

Remodeling associated with retinal degeneration is intimately linked with insults that cause photoreceptor stress and eventually photoreceptor cell death. These phenomena result in reprogramming of cell types in retina followed by progressive neural degeneration akin to CNS neural degenerations involving both neuronal and glial classes. No cell class in the retina is spared from the effects of remodeling. The earliest cell classes involved in remodeling are horizontal, bipolar and Müller cells and the Müller glia are the last cell class left in the remodeling retina.

Our efforts are focused on elucidating the precise wiring changes in retina, through the creation of pathological connectomes, or *patho-connectomes* to study precisely what the aberrant circuit topologies are, compared to normal topologies derived from Retinal Connectome 1 (RC1) [3]. Because temporal windows are critical to understanding when interventions may be possible, we are exploring when circuit topology revisions occur to understand their impact on information flow in the retina and their impact on rescues of vision loss. Precise circuit topologies in early retinal degenerative events is our first area of exploration with ultrastructural reconstructions of outer retinal neurons, bipolar cells and horizontal cells. Müller glia are also of intense interest as we are tracking the earliest metabolic and morphological changes in glia in response to retinal degenerations.

Acknowledgments

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ESTIMATING AVERAGE SINGLE NEURON RECEPTIVE FIELD SIZES IN HUMAN PRIMARY VISUAL CORTEX

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The retinotopic organization of visual cortex has been extensively studied in primates and other mammals with the notion of the receptive field (RF) playing a major contribution to neuroscientific research in general. Although a wealth of information has been acquired from studies in cats, non-human primates, *et cetera*, which led to explicit understanding of the organization of primary visual cortex and the development of analytical formulations to describe the projection from the retina to the cortical space, RF sizes have not been accurately estimated in human V1.

Recent studies substantially advanced this field of research by using novel neuro-computational methods. A prime example of such methods is the estimation of population receptive fields (pRFs) in retinotopically organized visual areas. However, pRFs are only estimates of aggregate voxel-based averages of ten to hundreds of thousands of neurons within fMRI voxels and are a function of: (i) the receptive field properties of single units belonging to a voxel, (ii) the scatter in the location of receptive field centres across units, and (iii) the interactions between nearby connected units.

Here, we present a novel approach to estimate the average single-neuron receptive field sizes in human primary visual cortex. To this end, we exploit the spatial-frequency dependent fMRI responses of visual RFs modeled as Gabor functions. Furthermore, we validate non-invasive RF size estimates obtained using the same fMRI method in non-human primates by comparing them directly with RF sizes obtained via intracranial electrophysiological recordings.

Acknowledgments

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ROUTING INFORMATION FLOW BY SEPARATE NEURAL SYNCHRONY FREQUENCIES ALLOWS FOR FUNCTIONALLY LABELED LINES IN HIGHER PRIMATE CORTEX

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The efficiency of neural processing in the sensory cortices, as well as their communication with motor/associative areas is crucial to transform sensory input into behavioral actions. To optimally perform visuo-motor behavior, the coordination of the activity of single neurons is crucial. Here we find in the macaque dorsal visual pathway, that the synchronized firing of neurons relative to the phase of high-gamma (180–220 Hz) local field potentials predicts the animal's behavioral speed in a visual attention task. An enhanced synchrony is observed with fast reaction times, but only among neurons where the target stimulus falls within their receptive fields. The absence of any significant high-gamma synchrony in slow reaction time trials suggests a mechanistic role of the phase of high-gamma oscillatory activities in coordinating the inputs with the stochastically generated spikes of area MT. Given a different frequency range (gamma, 40–70 Hz) for a similar phenomenon in the ventral visual pathway, we hypothesize that neural activity within different frequency bands may implement information-routing through distinct channels (here, the dorsal vs. the ventral visual pathway). We further used modeling to examine how well the source of incoming information could be maintained in associative areas. Our observations suggest that high-level cortical areas may use functional labeled lines to distinguish the sources of input information.

Acknowledgments

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MOTION SENSITIVITY IN THE PRIMATE LATERAL GENICULATE NUCLEUS

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It is commonly believed that motion sensitivity does not appear in the early visual system of primates until the spatial integration of non-direction-selective lateral geniculate nucleus (LGN) afferents occurs in the primary visual cortex [1]. However, several studies have described weak orientation-sensitive or direction-selective responses in primate LGN neurons, chiefly in New World monkey species [2]. Here, we show that direction-selectivity is apparent at multiple spatiotemporal scales in receptive fields (RFs) of LGN neurons in awake, behaving Old World monkeys (*Macaca mulatta*).

To study the dynamics of LGN RFs, we developed wide-field chromatic naturalistic (fractal) noise stimuli and ultra-thin multi-channel electrode arrays for high-throughput extracellular recording. Many neurons had RFs with spatial asymmetry (and thus presumed to exhibit orientation tuning) that dynamically changed shape (and thus presumed to exhibit motion sensitivity). Two temporally-distinct motion response types were observed. First, primarily in magnocellular layers, early narrowly-tuned responses to stimulus movement along a preferred direction occurred from about 100 to 20 msec before spike occurrence. Preferred directions often changed between temporally-adjacent excitatory and inhibitory components, but with matching chromaticity. The second type of motion response occurred later, within 20 msec of the LGN output signal, and represented broadly-tuned outward motion with respect to the RF center. The late response was seen in all cell types and all cell layers (parvocellular, magnocellular, and koniocellular). In general, motion sensitivity was enhanced when considering the aggregate activity of many local neurons, such as through the wideband field potential.

A variety of potential mechanisms may give rise to the observed patterns, including retinal circuitry, convergence of retinal inputs within LGN, and cortical feedback. The late response is particularly reminiscent of starburst amacrine cells that form direction-selective retinal ganglion cell circuitry in the rabbit and mouse [3], which may have analogs in the primate retina [4]. The enhancement observed when analyzing local neural ensembles suggests that the LGN may be organized into discrete motion-sensitive subunits. These anatomical clusters might provide a substrate for the development of functional structures in visual cortex.

Acknowledgments

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NEURAL SYSTEM IDENTIFICATION FOR LARGE POPULATIONS: SEPARATING WHAT AND WHERE

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Neuroscientists classify neurons into different types that perform similar computations at different locations in the visual field. Traditional methods for neural system identification do not capitalize on this separation of *what* and *where*. Learning deep convolutional feature spaces that are shared among many neurons provides an exciting path forward, but the architectural design needs to account for data limitations: While new experimental techniques enable recordings from thousands of neurons, experimental time is limited so that one can sample only a small fraction of each neuron's response space.

Here, we show that a major bottleneck for fitting convolutional neural networks (CNNs) to neural data is the estimation of the individual receptive field locations — a problem that has been scratched only at the surface thus far. We propose a CNN architecture with a sparse readout layer factorizing the spatial (where) and feature (what) dimensions. The feature dimensions can also be used for neural cell type classification.

Our network scales well to thousands of neurons and short recordings and can be trained end-to-end. We evaluate this architecture on ground-truth data to explore the challenges and limitations of CNN-based system identification. Moreover, we show that our network model outperforms current state-of-the art system identification models of mouse primary visual cortex.

Acknowledgments

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SPARSE REDUCED-RANK REGRESSION FOR EXPLORATORY VISUALIZATION OF SINGLE CELL PATCH-SEQ RECORDINGS

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In recent years, single cell RNA sequencing has become an important tool for identifying cell types in various brain areas [1–3]. However, it is challenging to link transcriptomically defined types to classically known electrophysiological or morphological properties. To this end, a recently introduced *patch-seq* technique allows recording electrophysiological activity of single neurons via patch-clamping before extraction of cell contents for RNA sequencing [4, 5].

One can use egularized regression to construct sparse models that pre electrophysiological properties (such as action potential width or threshold) from the expression data [4]. However, electrophysiological properties form highly correlated groups that can be predicted together, simplifying the overall model and possibly gaining power. Here we introduce reduced-rank regression (RRR) regularized with an elastic net penalty as a tool to predict all electrophysiological properties using a small number of latent components. The approach yields a sparse model where only a small number of genes contribute to each component, facilitating interpretation. Our technique can be seen as a variant of canonical correlation analysis (CCA).

For example data [4], the optimal number of components was two, yielding matching visualization of both RNA-seq and electrophysiological data. Cross-validation indicated that fewer than 10 genes per component sufficed. The first component (cross-validated correlation, CVC, of 0.8) separates the two cell types, identifying a set of marker genes similar to the earlier report [4]. The second component is weaker (CVC 0.5) but carries information about action potential threshold. Our results indicate that sparse reduced-rank regression is viable for exploratory analysis of single cell patch-seq datasets.

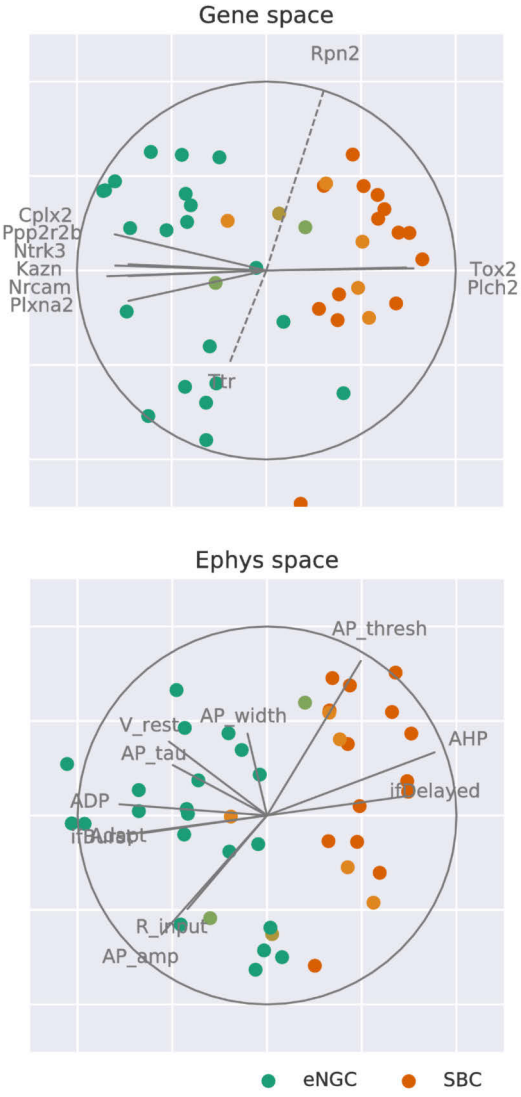

Figure 1. Reduced-rank regression biplots in the transcriptomic and electrophysiological spaces.

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TASK REPRESENTATION IN THE MACAQUE POSTERIOR PARIETAL CORTEX DURING VIRTUAL NAVIGATION

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Much of what we know about how the brain computes comes from highly controlled tasks that use stimuli with stationary statistics and a limited set of actions (usually two). Such tasks may be inadequate to fully reveal the rich structure of neural representations and computations that mediate fluid behaviour. To understand dynamic neural processing underlying natural behaviour, we trained two macaque monkeys on a continuous-time foraging task in which they used a joystick to steer freely and catch targets in a two-dimensional virtual environment devoid of landmarks. At the beginning of each trial, a circular target blinked briefly and monkeys had to use a joystick to steer to the memorized target location by integrating optic flow generated by their own movements (Figure 1a). The ground plane was composed of transient elements to prevent them from serving as landmarks, and targets appeared briefly at a random location on the ground plane within the field of view. Distance and angular eccentricity of the targets varied randomly across trials, prompting monkeys to use a variety of trajectories (Figure 1b). We implanted multi-electrode arrays to sample the activity of a large number of neurons in the posterior parietal cortex (PPC). Fitting a generalized additive model to the neural activity revealed that a majority of neurons encoded multiple task-relevant variables ranging from the monkeys' instantaneous linear and angular velocity to more abstract, integrated variables such as distance moved, direction of heading, and distance to target. We then inferred the structure of neural interactions by extending our model to include coupling between neurons. We found that there was sparse but indiscriminate flow of information between neurons encoding different task variables, and that the coupled model provided a better account of neural responses. To understand how task variables are represented at the population level, we used canonical correlation analysis and found that the dimensionality of task-relevant neural subspace was as high as possible. Similar analyses on uncoupled and coupled model populations showed that coupling between neurons was responsible for broadening the task representation. These results demonstrate that recurrent connections in the primate PPC facilitate processing and integration of sensory inputs in dynamic environments.

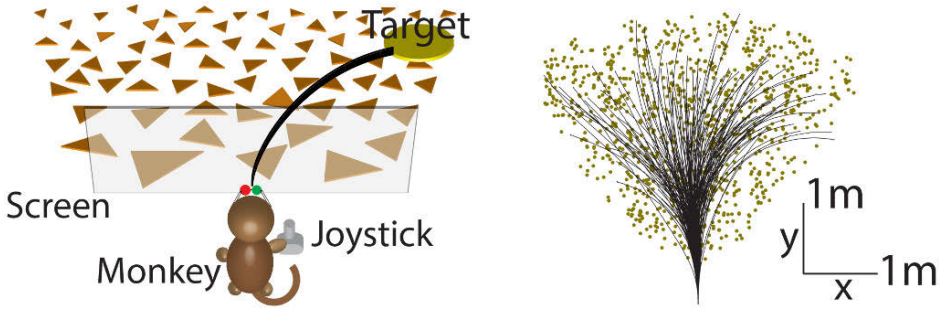

Figure 1. (left) Task overview showing an example path to the memorized target location. **(right)** Suite of paths taken for randomly placed targets.

NEURAL SIGNATURES OF VARIABLE BELIEFS INCREASE WITH TASK LEARNING IN V1

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Previous work has suggested that top-down, especially task-dependent, sources of variability are some of the dominant modes of trial-to-trial variability in sensory neuron responses. It has also been hypothesized that such top-down modulators can be understood as representing *variable beliefs* about task-relevant features of the stimulus in a probabilistic inference (PI) framework of perception, where task-based expectations act as a prior [1].

A stronger test of this hypothesis would be to measure (*i*) the emergence of task-dependent correlations over the course of learning a task, and (*ii*) a change in the correlation structure on short time scales as the task context is changed [2]. The PI framework predicts the task-dependent component of correlations should be proportional to the product of neural sensitivities to the stimulus. This means that such correlations would *increase* over the course of learning, while a purely feedforward framework would predict the opposite trend (assuming perceptual learning reduces these information-limiting correlations [3]).

We present preliminary results from two macaque monkeys learning two versions of an orientation-discrimination task. V1 neurons were recorded over the course of training. Training included four phases: cardinal discrimination, oblique discrimination, interleaved task-switching, and finally task-switching with V2 reversibly inactivated by cooling each day.

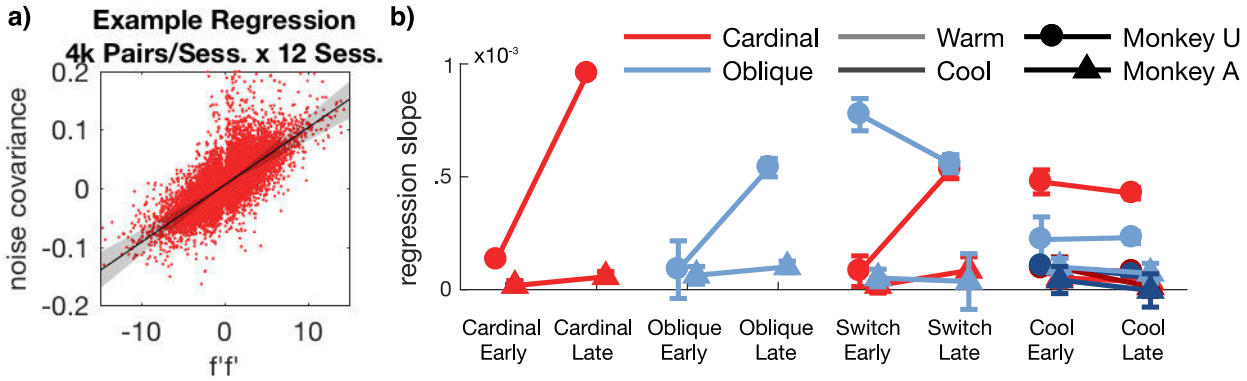

Figure 1. (**a**) We quantify the amount of task-dependent correlations as the slope of the relationship between pairs of neurons' noise-covariance and the product of their sensitivities. (**b**) Amount of task-dependent correlations increases from early to late half of cardinal and oblique phases, and again when monkeys re-learn the cardinal task, indicating a consistent positive relationship between performance and differential correlations across learning. Difference in effect magnitude between monkeys may be explained by laminar differences (ongoing).

Acknowledgments

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LINEAR AND NONLINEAR ANALYSIS OF NEURONAL CONNECTIVITY FROM SPIKE TRAINS

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An important problem in the understanding of neuronal ensembles is the reconstruction of the connectivity between neurons based on multi-unit recordings of their spike trains. Different methods have been developed to address this question. The simplest approach is to use linear techniques, such as the cross-correlogram, to study the presence of precise spike correlation. The nonlinear nature of the coupling between neurons, that are themselves nonlinear dynamics, led to the development of nonlinear techniques. For example, the approach of Chicharro and Andrzejak [1], *measure L*, was developed for time-continuous signals from nonlinear dynamics. Later on an extension was introduced for the application to point processes [2]. There are model systems, like Hindmarsh-Rose dynamics, in which nonlinear techniques have been proved to have a better sensitivity to small couplings and robustness to noise [3]. We study to what extent nonlinear techniques improve the understanding of the system in real-world data. In this case, there are problems such as nonstationarity in the firing rate of the neurons that can easily lead to false positive detections of direct couplings. We illustrate the occurrence of these problems based on real neuronal data, including spiking data from intracranial recordings from epilepsy patients. Furthermore, we underline the importance of applying surrogates. These are Monte Carlo resampling techniques that help to avoid false positive detections of connectivity. The implementation of the measure L is available online [4]. In closing, we show that it is recommendable to apply different coupling detection techniques at the same time, in order to extract complementary information which can provide a deeper understanding of neural systems.

Acknowledgment

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TRANSGENERATIONAL EPIGENETIC INHERITANCE OF ANCESTRAL TRAUMA

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Recent experiments have revealed that environmental changes can result in alterations of gene expression in the liver, that appear to be maintained in both parent and offspring, despite the fact that the offspring have never been exposed to parental environments. This phenomenon, known as transgenerational epigenetic inheritance, can potentially prepare offspring to accommodate changes in the environment of their parents. Other studies suggest that transgenerational epigenetic inheritance is also observed for learned behaviors. Specifically, these studies showed an increase in number of neurons responsive to the odor, and an increase in sensitivity that is also prevalent in the F1 population. We have initiated experiments to determine a mechanism for an increase in sensory neuron number, with remarkable specificity in both parent and offspring. We have condition male mice to a novel odor, paired with a light foot shock. After olfactory conditioning, we remove the main olfactory sensory epithelium, which contains the olfactory sensory neurons (OSNs), and the main olfactory bulb (MOB), which contains the terminals of the OSNs. Using the immunolabeling-enabled three-dimensional imaging of solvent-cleared organs (iDISCO) tissue clearing method in tandem with immunohistochemistry, we stain for neurons that express a receptor for the paired odor in conditioned and unconditioned animals. Using light sheet microscopy to image the entire epithelium and bulb, we observed changes in cell number in response to the conditioned odor. We have verified experience-dependent structural changes in the main olfactory epithelium (MOE), showing an increased number of neurons that recognize the salient odor. Furthermore, we have confirmed that these changes are observed in the F1 generation. The offspring of conditioned mice also displayed a heighten number of cells specific to the paired odor, despite the fact that they have never experienced the odor. We now wish to determine the mechanism responsible for the specific increase in cell sensory neuron number in response to learning, and how an increase in neuron number contributes to the behavior of the offspring.

Acknowledgments

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EXPECTATION-INDUCED MODULATION OF METASTABLE ACTIVITY DRIVES FASTER CODING OF SENSORY STIMULI

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Sensory stimuli are processed faster when their presentation is expected, compared to when they are unexpected. The neural correlate of anticipation is a faster encoding of sensory stimuli when they are preceded by an anticipatory cue (the same cue for all stimuli), as observed in the gustatory cortex of alert rats [1]. However, the specific computational process mediating this coding acceleration is unknown. Here, we demonstrate that anticipatory neural activity is driven by pre-stimulus modulations of the network dynamics induced by the anticipatory cue. We propose a biologically plausible model of anticipation based on a recurrent network of spiking neurons with clustered architecture. In the absence of stimulation, the model temporal dynamics unfold through sequences of metastable states, each state being a population vector of firing rates, reproducing the ongoing activity observed in the data [2]. We modeled several taste stimuli and one anticipatory cue as afferent inputs targeting subsets of excitatory neurons. The cue-triggered input induced excited and inhibited responses with similar proportions across neurons in single trials, as observed in experiment [3]. Stimuli evoked specific state sequences, characterized in terms of stimulus-coding states. When stimulus presentation was preceded by the anticipatory cue, coding states showed a faster onset. This led to a faster decoding of expected stimuli compared to unexpected ones, even though the cue was the same for all stimuli.

We elucidated this anticipatory effect as a cue-induced modulation of the network energy landscape. Network states, or attractors, are represented as potential wells in the energy landscape. Cue presentation lowers the barriers between the wells, leading to faster transition rates between attractors and shorter timescales of network dynamics. In the presence of a stimulus, this acceleration drives a shorter onset latency of coding states, explaining the anticipation effect. The opposite result was obtained in the presence of a distracting cue, which recruited the network's recurrent inhibition, slowing down stimulus coding. Anticipatory and distraction were unrelated to changes of firing rates in stimulus-selective neurons, and absent in homogeneous networks without clusters (unable to generate metastable states). Our results suggest that observed state sequences are a consequence of the combinatorial and temporal coding properties of metastable cortical states and demonstrate a novel mechanism for speeding up sensory coding in cortical circuits.

Acknowledgments

NIDCD Grant K25-DC013557 (LM); the Swartz Foundation Award 66438 (LM); NIDCD Grant R01-DC010389 (AF); Klingenstein Foundation Fellowship (AF); NSF Grant IIS-1161852 (GLC).

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BAYESIAN WEIGHT UPDATES STABILIZE AND IMPROVE LOCAL LEARNING IN A RECURRENT NEURAL NETWORK

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Neural networks in the brain must be capable of not only producing time-varying signals but also learning how to produce them. A typical approach to this problem is to build a chaotic recurrent neural network (RNN) and train a set of weights w_j so that a linear readout of the neural firing rates $\sum_j w_j r_j(t)$ produces the desired signal $f(t)$ [1]. By feeding back this readout to all neurons, the RNN will stabilize, so long as the readout stays close to $f(t)$. This can be easily achieved using powerful but non-local learning rules such as recursive-least-squares (RLS).

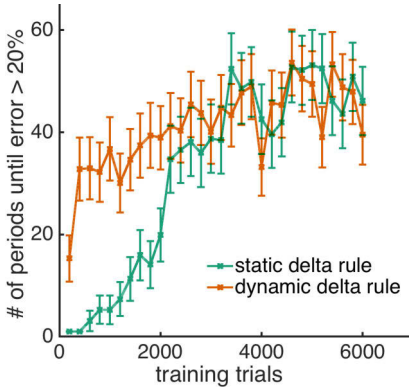

Figure 1. The number of periods of $f(t)$ until readout error (mean squared error normalized by variance of $f(t)$) exceeds 20%, using readout weights at different points throughout training. Error bars designate S.E.M.

Local learning rules, however, struggle to solve this problem due to the instabilities inherent to the chaotic dynamics of the RNN. Even a slight deviation from the optimal set of weights can prevent the network from stabilizing, thus producing a readout that diverges from its target within even one or two periods of $f(t)$. Indeed, a standard delta-rule will produce readouts that can maintain low error for only 10 periods or less after 1000 trials of training (Fig. 1). One reason for this is that the learning rate must be very low for the delta-rule to maintain stability throughout training, meaning that the readout weights will take a long time to align with their optimum. This contrasts with RLS, which typically makes large updates early in training and then slows down. This suggests the learning rate should adapt over time, so it can start big and then get small.

But how quickly should the learning rate decrease? A principled approach to this question arises from considering the fact that any weight update should take into account the uncertainty in the true value of the weight [2]. Framing the learning problem as Bayesian inference, under certain assumptions we derive the following dynamic delta-rule with a history-dependent decaying learning rate:

$$\Delta w_i(t) = \frac{1}{\beta + \sum_{t'=1}^{t} r_i(t')^2} \left(f(t) - \sum_j w_j r_j(t) \right) r_i(t).$$

We find that these learning rate dynamics help attenuate the instabilities described above, by allowing the network to start with a large learning rate that quickly brings the readout weights closer to the optimal ones. This results in a stable solution within 1000 trials (fig 1), meaning that fixing the weights and running the network at this point will result in a readout with less than 20% error for over 30 periods of $f(t)$.

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INVESTIGATING THE CONTRIBUTION OF DENDRITES IN PATTERN COMPLETION BY MEANS OF COMPUTATIONAL MODELLING

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Pattern completion describes the ability of the brain to retrieve an entire memory representation from partial or degraded inputs [1]. Malfunctions of this process due to neurodegenerative diseases are often accompanied by structural changes at dendritic spines and can severely impair cognition as well as memory in both mouse models and human patients.

Many theoretical models, based on empirical data, predict that the extensive auto-associative network within the CA3 region of the hippocampus provides the necessary substrate for pattern completion to occur [1, 2]. However, a more detailed understanding of the mechanisms underlying the phenomenon remains to be established. Inspired by previous work characterizing dendrites as contributors to pattern separation [3], along with recent experimental findings [1], we sought the components of pattern completion machinery within the dendrites of CA3 pyramidal neurons.

Towards this goal, we developed a simplified spiking model of the CA3 region, which comprises pyramidal cells with dendrites along with inhibitory cell populations. In addition, the network can integrate excitatory inputs from the dentate gyrus (DG) and the medial entorhinal cortex (ECLII). To ensure its biological validity, a large amount of electrophysiological data was taken into consideration. Our model enables simulations of pattern storage and recall, and estimation of pattern completion capacity [4] under diverse sets of conditions. The incorporation of dendrites in CA3 pyramidal neurons facilitates the investigation of how dendritic morphology and nonlinearities contribute to the emergence and robustness of pattern completion.

Acknowledgments

This work was supported by the ERC Starting Grant “dEMORY: dissecting the role of dendrites in memory” ERC-2012-StG-311435.

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NEURAL CODING PRINCIPLES OF SOMATOSENSORY PERCEPTION AND BEHAVIOUR REVEALED THROUGH MULTIPLEXED TWO PHOTON IMAGING

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How neuronal activity in different layers of the neocortex contributes to sensory processing and perception is a fundamental question in neuroscience. Neuronal population codes are commonly studied by comparing signal correlations (trial-averaged responses) and noise correlations (trial-by-trial variability), with the latter thought to be critical for generating efficient, sparse codes. Until recently, we have been lacking methods for recording neuronal responses with the high spatial and temporal resolution required to study signal and noise correlations in identified neurons in different cortical layers *in vivo*.

Here, we present a novel strategy for spatio-temporally multiplexed 2-photon calcium imaging to address this need. Our method allows us to simultaneously image neuronal activity in two z-planes within layers II, III, and IV of the vibrissal somatosensory cortex in head-fixed, moving mice. Animals were trained to perform a rewarded whisker-dependent discrimination task and expressed a genetically encoded calcium sensor and inhibitory interneuron-specific fluorescent markers.

Using dimensionality reduction methods, including canonical polyadic tensor decomposition, we examine neuronal representations of task variables in two simultaneously recorded neuronal populations, both within and between different cortical layers. Our data confirm feedforward inputs from layer III to layer II and specifically suggest a recruitment of layer II inhibition during sensory stimulation. This mechanism may be critical in the shaping of layer II-III output in sensory guided behaviour. Ongoing work focuses on determining the specific contribution of different interneuronal subclasses.

DECODING LOCOMOTOR EVENTS FROM MOTOR CORTEX ENABLES A BRAIN-SPINE INTERFACE TO ALLEVIATE GAIT DEFICITS OF PARKINSON'S DISEASE

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Parkinson's Disease (PD) disrupts the transmission of neural motor commands to lumbar spinal circuits that control leg movements by causing the death of dopaminergic neurons in the basal ganglia. While levodopa and deep brain stimulation therapies alleviate most motor symptoms of PD, gait disorders are less responsive to these treatments. People with PD typically exhibit short and slow steps, balance deficits, and freezing of gait. These symptoms arise when cortical commands meant to activate and modulate spinal locomotor centers are rendered dysfunctional. Yet, the underlying mechanisms of PD remain poorly understood, limiting our ability to develop effective clinical interventions. Using nonhuman primates treated with MPTP — a chemical that selectively kills dopaminergic cells in the substantia nigra — we studied the impact of PD on the interactions between the cortical and spinal circuits that control locomotion. We then developed a novel neuroprosthetic intervention that uses intracortically-recorded brain activity to synchronize the delivery of epidural electrical stimulation of the spinal cord with descending cortical movement commands.

We surgically implanted two 48-channel Utah arrays bilaterally in the leg motor cortex, intramuscular EMG electrodes in muscles of both legs, and two spinal electrode array implants covering the dorsal aspects of the lumbar and sacral spinal cord. We recorded neural, EMG, and kinematic signals wirelessly during unrestrained locomotion. We found that motor cortical activity could be used to accurately decode gait events during attempted movements before and after the development of PD symptoms. We then evaluated the therapeutic potential of cortically controlled spinal stimulation to alleviate these symptoms. We applied the neural decoder in real-time to control an implanted pulse generator that delivered spatially-selective electrical stimulation protocols to the spine, activating specific motoneuron pools enabling flexion and extension muscle synergies. Our neuroprosthesis not only increased the stability and speed during basic overground walking, but also restored skilled locomotor control on a horizontal ladder task. This experiment reveals the therapeutic potential of our neuroprosthesis to alleviate PD motor deficits, and may help to understand how PD impacts the coordination between cortical and spinal motor circuits.

A TALE OF TWO TREES: MODELING APICAL AND BASAL TREE CONTRIBUTION TO L2/3 V1 PYRAMIDAL CELL ORIENTATION SELECTIVITY

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Pyramidal neurons, a mainstay of cortical regions, receive a plethora of inputs from various areas. Afferent synapses are received by either the apical or basal dendritic trees, which are morphologically distinct. Both trees differentially contribute to the somatic response, although their exact functional roles remain unclear. Inputs to apical dendrites are integrated en-masse at the apical trunk and propagate to the soma. Basal dendrites, on the other hand, branch out from the soma, with inputs being integrated semi-independently. Thus, these trees define distinct anatomical and possibly functional sub-units.

To assess the latter, we modeled the complex response pattern of the L2/3 V1 pyramidal neuron to spatially tuned synaptic input. Our goal was to elucidate the contribution of each tree to the response pattern of the neuron [1], namely its orientation tuning curve. Towards this goal, we created a morphologically detailed computational model of a single cell in the NEURON simulation environment. The model was validated against electrophysiological data recorded *in vitro* and *in vivo*. We investigated the role of dendritic integration at the basal and apical trees, and its contribution in shaping cell responses.

Results indicate that somatic action potentials are generated only when input coincides bilaterally, as unilateral stimuli are unable to evoke an adequate response at the soma. In addition, given equal synaptic drive, the responses of the neuron appear to be initiated by the apical tree, as its dendritic spiking activity temporally precedes somatic spike-like activity. Finally, basal tree activity, in the form of either depolarization or spiking, is essential for producing somatic activity, despite occurring in close temporal proximity to the somatic spike-like events. This model provides evidence for distinct computations taking place in the basal and apical trees of the neuron.

Acknowledgments

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THE SENSORIMOTOR STRATEGIES AND CORTICAL CODING THAT MEDIATE CURVATURE DISCRIMINATION BY ACTIVE WHISKER TOUCH

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Humans and other animals can identify objects by active touch - coordinated exploratory motion and tactile sensation. For example, we precisely scan our fingertips over objects in order to identify them, integrating input from each finger into a holistic representation of shape. Similarly, mice adeptly recognize objects by scanning them with their array of whiskers, and whisker-mediated touch is critical for exploration and navigation. The primary somatosensory cortex (S1) is likely crucial to this processing, but the paucity of suitable behavioral paradigms for whisker-based object recognition has thus far impeded elucidation of the underlying cortical circuits. The goal of this work is to determine the behavioral strategies by which mice recognize objects using their whiskers, and the cortical computations that implement these strategies.

To establish a platform for answering these questions, we first developed a behavioral task for head-fixed mice - curvature discrimination - that challenges them to discriminate concave from convex shapes. We use high-speed videography to track the whiskers and to identify the time and location of every whisker contact made on the stimuli. Mice typically contact the stimuli in multi-whisker bouts lasting 25–50 ms, producing rich spatiotemporal patterns of contacts across the whisker array. To identify which aspects of this sensory stream the brain uses to identify the shapes, we have trained decoding algorithms to classify the object based only on the contact patterns. We are using these models to identify what sensory events are most informative about curvature and about the mouse's choice. This analysis will reveal the feature recognition strategies that mice employ to infer object shape from complex tactile input.

We next asked how S1 is involved in this task. Like all cortex, S1 is structured into anatomically and physiologically distinct layers, which differ especially in their input and output connectivity with the rest of the brain. The computational function of each layer remains a longstanding enigma. Because of the prominent long-range connection in the superficial layer 2/3 (L2/3) that connect different cortical columns, we hypothesize that L2/3 will be crucial for integrating information across whiskers and identifying the contact patterns that are associated with each shape. In order to identify how the cortex encodes and computes shape, we are recording individual neurons using an extracellular linear silicon array that permits the simultaneous recording of dozens of neurons across all layers. Preliminary results with reverse correlation reveal multi-whisker receptive fields in many cells across cortical layers. We hypothesize that this multi-whisker responsivity is generated within L2/3; to test this, we are presently suppressing L2/3 while recording from the rest of the circuit. Taken together, these studies will reveal the algorithmic foundation and circuit implementation of the sensorimotor computations that mediate object recognition.

Acknowledgments

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CLUSTERED INHIBITORY ARCHITECTURE SUPPORTS CORTICAL ATTRACTOR NETWORK DYNAMICS

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Balanced networks of inhibitory and excitatory neurons with random recurrent connectivity are often employed to model cortical circuits. These models exhibit irregular and asynchronous spiking activity similar to that observed *in vivo*. Recent studies [1–3], have extended the balanced random network to incorporate clusters of strongly interconnected excitatory neurons. This clustered topology demonstrates a functionally desired multistability where different clusters become spontaneously activated and inactivated. The model captures a realistic high firing variability of single neurons and a reduction in trial-to-trial variability during stimulation as observed experimentally.

We recently showed that this topology leads to widely separated firing rate states of single neurons and tends quickly towards firing rate saturation, which is inconsistent with experimental observations. To overcome this problem we introduced clusters of inhibitory neurons coupled to each excitatory cluster [4]. This connectivity scheme is not directly supported by experimental findings. However, recent anatomical and physiological studies point to possible inhibitory clustering through connection strengths.

Here we model different architectures of inhibitory circuits, based on recent experimental studies [5–7], and investigate the role of inhibitory clusters on the dynamics of the spiking network when excitatory clusters have increased connection strengths with different portions of the inhibitory population. Our model can be reduced to the case of exclusively excitatory clusters [2], or to a one-to-one correspondence of inhibitory and excitatory clusters [5], but we explore all different architectures in between these extreme cases. Such intermediate scenarios are more consistent with recent experimental observations.

We find that inhibitory clustering is necessary to achieve realistic spiking activity under stimulation in terms of a biologically realistic firing rate, spiking regularity and trial-to-trial spike count variability. Inhibitory clustering achieves the desired attractor dynamics over a wide range of network parameters. Remarkably, when the stimulus is weak, without clustering of inhibitory neurons, the spiking network model fails to capture the reduction of trial-to-trial variability during stimulation.

Acknowledgments

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USING POPULATION RECORDINGS FROM MULTIPLE BRAIN AREAS TO ASK HOW ATTENTION IMPROVES PERCEPTION

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Attention has long been known to both dramatically improve subjects' ability to see attended objects and also to modulate the responses of visual and oculomotor neurons throughout the brain. Work in the field has been guided by two hypotheses about how those neuronal changes might affect perception. The first hypothesis posits that attention improves the amount of visual information that is encoded by populations of neurons. The second posits that attention improves the information that is communicated to downstream areas involved in perceptual decision-making. We measured the relative importance of these two hypothesized mechanisms by recording simultaneously from populations of neurons in middle temporal area of visual cortex (MT, which is involved in motion perception) and in the superior colliculus (SC, which contains neurons whose responses can be described as visual, oculomotor, decision-related, and everything in between; Figure 1A).

We found evidence in favor of both hypotheses (*e.g.*, that attention decreases shared response variability, or noise correlations, within each area but increases correlations between MT and the SC; Figure 1B). However, neither hypothesis provided a satisfactory account of behavioral improvements (*e.g.*, correlated variability between MT and the SC was unrelated to decisions on individual trials). Instead, we find evidence in favor of a third hypothesis, that attention reshapes the neuronal representation of attended stimuli such that attended visual information is used more effectively to guide decisions. By using novel population-level analyses that are constrained both by the monkey's behavior and the measured interactions between neurons in both areas, we found that attention has a larger effect on the sensory information in MT that is both communicated to the SC and used to guide behavior than it does on the total amount of stimulus information that is represented in MT. These data suggest that attention-related behavioral improvements may result from a restructuring of population responses that allow for task-related information to be more effectively communicated between brain areas.

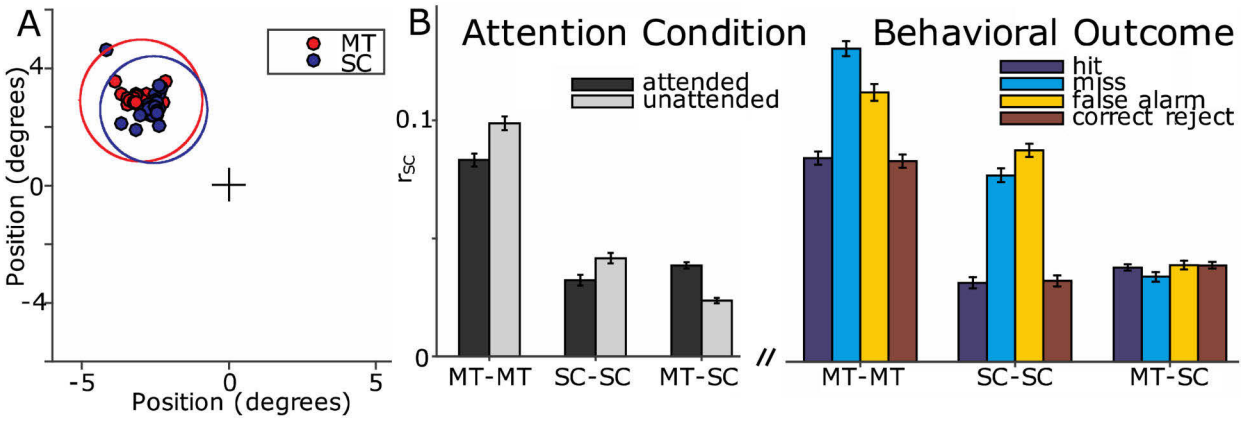

Figure 1. A. Receptive fields centers from population recordings in MT and SC. The circles are an estimate of the size of one receptive field from each area. **B.** Left, attention decreases noise correlations (r_{SC}) within an area and increases r_{SC} between areas. Right, within area, not between area, r_{SC} depend on trial outcome.

GENERALIZED PHASE LOCKING ANALYSIS OF ELECTROPHYSIOLOGY DATA

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Brain information processing likely relies on cooperative interactions between neural populations at multiple scales. Growing evidence suggests that network oscillations, as observed in Local Field Potentials (LFP), are instrumental to the spatiotemporal coordination of these interactions. Therefore, investigating the coupling between spatiotemporal patterns of LFP and spiking activity is instrumental to understand distributed neural information processing.

Common approaches to investigate this coupling are restricted to pairwise spike-LFP interactions, which are suboptimal for modern datasets with hundreds of simultaneous recording sites. Capturing efficiently the overall spike-LFP coupling structure in this high dimensional setting is of paramount importance to exploit the full potential of modern electrophysiology recording techniques.

We develop a Generalized Phase Locking Analysis (GPLA), a multivariate extension of phase locking analysis, by gathering pairwise complex phase locking information in a rectangular matrix and summarize its structure with the largest singular value and the corresponding singular vectors. Singular vectors represent the dominant LFP and spiking patterns and the singular value, called generalized Phase Locking Value (gPLV), characterizes the strength of the coupling between LFP and spike patterns. We further investigate statistical properties of the gPLV and develop a statistical testing framework.

Compared to univariate pairwise approaches, simulations with networks of Leaky Integrate and Fire (LIF) neurons [1, 2] show that GPLA: (*i*) can reliably retrieve the coupling between spikes and LFP with lesser amount of data and (*ii*) exploits optimally the activity of multiple units to increase the statistical power while preserving individual coupling properties. Application to recordings from Utah arrays in macaque prefrontal cortex reveals a previously undetected large-scale coupling through an LFP traveling wave in the beta band (15–30 Hz) synchronized with an array-wide synchronous spiking event. We hypothesize that it reflects a spatially distributed population with enhanced horizontal connectivity that activated by the incoming traveling wave. These results illustrate the interest of GPLA to assess global relationships between spatiotemporal patterns of spikes and network oscillations.

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EXTREMELY SPARSE CODING IN BASAL GANGLIA: MOTOR LEARNING IS FOREVER

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Deep-brain stimulation surgery provides an opportunity for single-unit recording in the basal ganglia and thalamus of humans. Firing rates in the internal globus pallidus (GPi) of adults with Parkinson's disease and in non-human primates are typically 40hz or greater. In GPi and thalamus of children with dystonia due to cerebral palsy (CP), we find firing rates are typically 5–10hz, and there is a large subpopulation of slow-firing cells with rates less than 1hz. Figure 1a shows a typical raster plot of 100 distinct slow-firing cells recorded from a child with spontaneous involuntary dystonic spasms.

Simultaneous firing (within 0.5 msec) is counted for all pairs of neurons and compared to the predicted rate for independent firing. Figure 1b shows the chi-squared statistic for autocorrelation between different cells. The block-diagonal pattern indicates that coincident spikes occur much more frequently within the same region, and are seen most often in GPi, Voa/Vop, and STN. Significant coincidence at 0 delay suggests that simultaneous spikes are due to common inputs to each region.

These findings are consistent with a digital hash code, in which sensory-motor events are encoded in time-locked patterns of firing. There are approximately 350,000 neurons in each human GPi [Hardman et. al. 2002], sufficient to allocate 50 two-neuron pairs for every second, and 17 three-neuron triplets for every *millisecond* of an 80-year life.

This supports an algorithm in which all experience is stored, and learning (through dopaminergic systems) identifies which experiences are rewarded and selected for future repetition. Generalization is predicted to occur only after sufficient repetitive practice of similar sensorimotor tasks, so that variability is experienced and learned. The structure is consistent with common observations of motor learning, including highly context-specific generalization, one-shot learning, minimal interference between dissimilar tasks, and absence of forgetting. I provide simulations of a spike-based persistent memory algorithm for robot control that reflects the human recordings and possesses these properties.

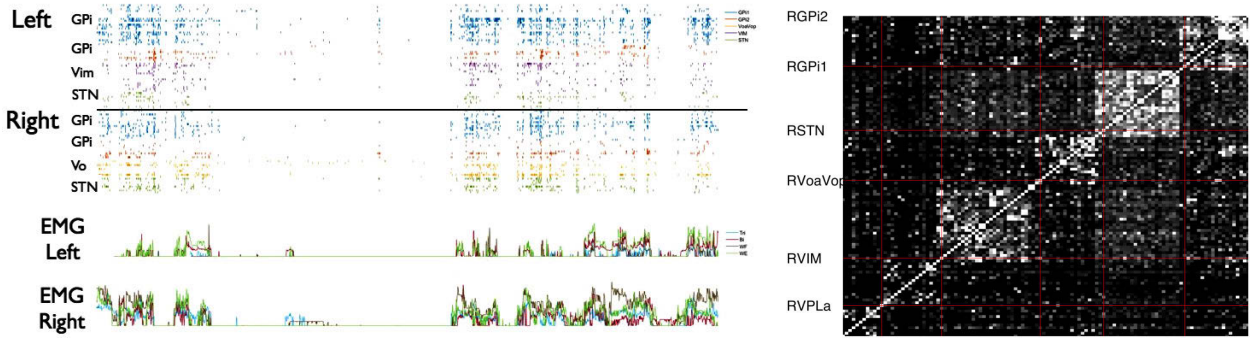

Figure 1. (left) 10-minute recording from GPi, STN, Vim, and Vo during dystonic spasms. Top: spike rasters. Bottom: EMG. **(right)** Autocorrelation matrix at zero time-delay for spike coincidences over 2 hours. White pixels indicate significance $\chi^2 > 12$, $p < 0.002$.

NEURAL MECHANISMS UNDERLYING CONTROL OF JOINT MANIPULATION

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Role asymmetry or specialization (*e.g.*, leader-follower) during dyadic interactions has been previously conceptualized as each agent in a dyad focusing on a subset of the actions to accomplish a common goal, *e.g.*, moving a couch. Such agent-level task allocation may arise from the possibility that such assignments reduce the overall individual responsibility during a given interaction. Role asymmetry in social interactions has been reported in a wide variety of tasks, *e.g.*, finger tapping. It has been shown when there are no explicit leader or follower roles, leader-follower relations may naturally emerge during the interaction. Role asymmetry has been primarily examined through visual coupling between agents, raising the question of whether the same principles drive both coordination and leader-follower interactions during tasks with both a visual and physical coupling *e.g.*, two people carrying a table. Imperatively, what differentiates this scenario from solely visual is the requirement of each agent coordinating forces they exert on a physically-connecting object (*e.g.*, a table).

We used a task that required two people jointly lifting and balancing a U-shaped object to investigate the extent to which role allocation in physical tasks is due mainly to intrinsic or extrinsic (bio-)mechanical factors, and whether roles were stable across interactions. We found that role asymmetry spontaneously emerged and was persistent within a session. The finding that individuals may naturally take on roles during physical interactions raises the question of whether it is merely just an individual factor unrelated to task success or is subservient to a dyadic-level strategy needed to accomplish the task goal.

While these results indicate that role specialization in physical interactions may arise to subdivide labor to achieve the goal, the neural mechanisms underlying the role asymmetry in physical interactions remains unknown. We aimed to further investigate how people self-organize into roles during physical interactions, and how these roles are reflected in each actor's neural dynamics.

We examined how the EEG dynamics of leaders (or followers) differed when they are assigned that role or when it emerges naturally. The experiment involved two participants lifting and balancing a U-shaped object, using one hand each. Dyads of participants were either assigned to a group with either no *a-priori* role assignment (Human-Human; H-H group), or with one person being assigned a role (Leader-Follower; L-F group). Cortical activity was assessed using EEG recorded from both subjects. We found that the involvement of each individual in changing the total moment of the joint manipulation task could be related to the level of EEG power suppression in left centro-parietal region at alpha frequency band. EEG power from followers exhibiting smaller total moment rate (torque corrections) was characterized by greater suppression in left centro-parietal area which is involved in planning and adjusting the dynamics of precision grasping. These factors could have contributed to differences in brain activation as captured by our EEG power analyses between leaders and followers.

Acknowledgments

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PARIETAL AND PREFRONTAL CONTRIBUTIONS TO STIMULUS ENCODING AND MEMORY STORAGE

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Electrophysiological recordings in non-human primates have suggested a prominent role of prefrontal and parietal cortices in the control and storage of behaviourally relevant information in working memory. Working memory processes have been associated with persistent activity frequently observed while animals memorise task relevant parameters over a delay period. However, a direct comparison of persistent activity in prefrontal and parietal areas during encoding and storage of task related information is missing.

We investigated how information about the location and identity of stimuli is represented in the frontal eye fields (FEF) and the lateral intraparietal area (LIP) during the presentation and delay epochs of a visual search and a memory guided saccade task. To this end, we performed simultaneous recordings in the two areas of two macaques with up to four electrodes in each area and estimated the task relevant information carried by the activity of neurons and neural ensembles.

Stimulus selective activity was observed in both areas during target presentation in the search task. However, stimulus identity was encoded in a sustained manner in LIP and only transiently in FEF. Moreover, stimulus related information was higher and reached significance earlier in LIP, indicating differential processing of stimulus identity in the FEF-LIP circuit. In the delay period, stimulus identity information was higher than baseline in both areas, however, selectivity was diminished. In the delay period of the memory guided saccade task, information about target location was higher among LIP neurons compared to FEF. Interestingly, unlike FEF, LIP neurons with significant delay activity carried significantly higher information about the memorized location compared to LIP neurons without delay activity. Finally, in the search task we observed enhanced synchronisation between FEF and LIP in the beta range in the target, delay and search period, whereas modest enhancements in gamma synchronisation were found during the search period. These results suggest frequency specific interactions between the two regions in different task epochs and provide further support for a role of both beta and gamma frequency synchronisation in long-range communication in the brain.

Acknowledgments

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ODOR PERCEPTION ON THE TWO SIDES OF THE BRAIN: CONSISTENCY DESPITE RANDOMNESS

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Olfactory perception involves both discrimination and generalization, respectively the detection of odor differences and similarities. The ability to generalize is vital to performance in any olfactory task because natural variability implies that the exact same stimulus is never experienced twice. This presents a problem, because neurons in the mouse piriform cortex receive input from an apparently random collection of olfactory glomeruli, implying that the representation of odors differs among different individuals and across the brain hemispheres of a single individual. To drive behavior coherently, the two hemispheres must generalize in a similar manner. How is consistency of olfactory generalization possible between different randomly-wired cortices?

We have combined *in vivo* optical imaging of odor responses in piriform cortex with mathematical modeling and observe that many properties of the piriform odor representation are in good accord with predictions of a model with random input. Consistent with previous models, we observe that piriform representations simulated with random input are less correlated than the bulb representations but maintain sufficient correlation between odors to support generalization. Next, we trained two model readout units, each connected to an independent model piriform, on a single odor and find that these trained readouts produce highly correlated output to any novel odor. Thus, consistent generalization across individuals is possible given a single shared experience.

Odor-guided behavior typically involves making a binary choice; for example, to act or not to act. We therefore modeled choices by comparing readout values to a threshold and examined the choice agreement across a large number of odors. Whereas odor discrimination and categorization require far fewer neurons than reside in piriform, we find that the ability of the model to support consistent choices across brain hemispheres requires the full complement of 1 million piriform neurons, a potential answer to why piriform cortex is so large.

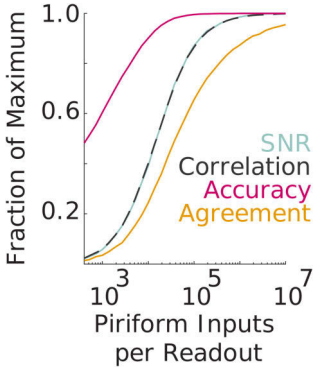

Figure 1. Scaling of different metrics of trained readout performance versus the number of inputs to each readout: readout choice agreement (orange), readout correlation (black), SNR (cyan, occluded by black curve), and accuracy (magenta). Maximizing readout agreement, the ability of multiple readouts to make similar binary choices, requires more inputs than does any other metric of readout performance, saturating only when the number of inputs is in excess of 1 million.

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BEHAVIORAL MODULATION OF VISUAL RESPONSES IN MOUSE SUPERFICIAL SUPERIOR COLLICULUS

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Visual responses in multiple brain regions, including visual thalamus and primary visual cortex (V1), are modulated by non-visual factors such as locomotion and level of arousal. We asked whether this modulation also extends to the superficial layers of superior colliculus (SC), which receive direct visual input from the retina, and if so, where this modulation may originate.

To record the activity of neuronal populations within the top 150 µm of SC, we used two-photon calcium imaging while mice were head-fixed and free to run on a treadmill. To drive visual activity we presented drifting gratings of varying orientations and directions, and to measure spontaneous activity we presented uniform gray screens. To track arousal level, we measured running speed and pupil diameter.

We found that about 50% of neurons in superficial SC were significantly correlated with running and pupil diameter both during spontaneous and visually driven activity. Roughly equal numbers of neurons showed positive and negative correlations. Changes in arousal also had significant effects on direction tuning curves. These effects could be described with a linear model (additive shifts plus multiplicative effects) but were heterogeneous across neurons.

To investigate whether these behavioral effects were inherited from V1, we inactivated V1 by optogenetically stimulating inhibitory neurons, while recording from ipsilateral SC neurons using Neuropixels probes. V1 inactivation decreased average visual responses in SC, but it did not significantly decrease their modulation by locomotion and arousal.

We then tested whether behavioral modulation originates in the retinal input to superficial SC. We expressed GCaMP in retinal ganglion cells (RGCs) and imaged calcium activity of RGC boutons in the superficial SC. To our surprise, bouton activity was correlated with locomotion and arousal and the boutons' direction tuning was modulated to a similar degree as seen in SC neurons. Correlation with locomotion even persisted during complete darkness, excluding the possibility that changing light levels reaching retina due to pupil dilation caused the change in responses.

This observation might be explained by two mechanisms: modulation of RGC output by behavior, *e.g.*, via backprojections from the rest of the brain, or modulation of retinal boutons in the superficial SC, *e.g.*, via neuromodulators causing changes in calcium levels. We are currently testing the first hypothesis by recording from the optic tract to investigate whether retinal firing rates are modulated by running and arousal.

Taken together, our results show that neuronal responses in the superficial layers of SC are not solely driven by visual inputs but are also modulated by locomotion and arousal. This modulation is not inherited from V1, but rather originates as early in the visual pathway as in the retinal input to superficial SC.

DYNAMICAL IMPLICATIONS OF OPTIMAL TEMPORAL INFRPOMATION ENCODING IN RECURRENT SPIKING NETWORKS

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Encoding of information by spike times rather than firing rates can enhance the representational power of neuronal networks. Here, we use an information theoretic framework to develop and study gradient-based learning rules for a recurrent network of integrate-and-fire neurons, which maps high-dimensional input spike trains to output spike trains. Information maximization has been shown to be a useful paradigm in networks of simplified rate-model neurons. Feedforward networks that optimize information representation perform independent component analysis (ICA). In recurrent networks, information maximization results in better amplification of external inputs, which takes advantage of the input statistics and the structure of correlations among neurons [1]. Furthermore, these recurrent networks tend to operate near a critical point in their dynamics, namely, on the border between normal amplification of external inputs and hallucinations [1]. Nevertheless, rate models cannot describe the full rich dynamics found in cortical networks of spiking neurons.

An important basic question is what dynamical properties will emerge in a recurrent network of spiking neurons, which optimizes the representation of the incoming spike trains. Inspired by earlier work on feedforward networks [2], we developed learning rules that maximize the entropy of the output spike trains in networks with both feedforward and recurrent connections. These learning rules effectively maximize the spike-time sensitivity of the network. We simulated the evolution of these networks by exposing them to input spike trains, and analyzed their dynamical behavior. Entropy maximization is expected to lead to irregular Poisson-like firing in single neurons and to low pairwise correlations. Indeed, our simulations show a substantial decrease in the network synchrony and in the correlations among neurons during the learning process, resembling balanced-state networks [3]. Maximizing the susceptibility of the network to small changes in the input spike-times is expected to lead to critical dynamics. Our preliminary findings show that under certain conditions these networks indeed display neuronal avalanches, a hallmark of critical brain dynamics [4]. We believe that the proposed theoretical framework can unify the concepts of balanced-state networks and critical networks, two leading models for cortical dynamics.

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BREAKDOWN OF SPATIAL CODING AND NEURAL SYNCHRONIZATION IN EPILEPTIC MICE

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Epilepsy causes significant cognitive deficits in both humans and rodent models yet the circuit mechanisms leading to cognitive dysfunction remain unknown. We developed a wireless miniature microscope (Miniscope) for *in vivo* calcium imaging to examine the spatial representation of freely behaving epileptic and control mice running on a linear track. The Miniscope is powered by a lithium polymer battery and all data is saved onto a microSD card and allows for recording at least 30 minutes in mice as they run on a linear track.

We found dramatically altered spatial coding in CA1 neurons of chronically epileptic mice. Within a session, CA1 neurons in epileptic mice had reduced spatial information and stability compared to controls. We then isolated only the place cells with significant spatial information, stability, and above chance firing rates within their place field. We found significantly less place cells in epileptic mice, and these place cells have significantly reduced spatial information and stability.

We then decoded the position of the mouse on the linear track from the within session data (training on 2/3 of the data, and testing on the remaining 1/3), and found significantly more decoding error in the epileptic animals. Together, these findings indicate that spatial information is severely disrupted in epileptic mice. We then examined the stability of place cells across various imaging intervals. With just 30 minutes between imaging sessions, epileptic animals had severely impaired stability of place cell firing. This stability degraded at a similar pace to control animals indicating a significant encoding deficit rather than a deficit in the maintenance of spatial information (*i.e.*, from seizures, etc.). Decoding position across days we found significantly more error in the epileptic animals that reached chance levels by 7 days. Together, these data indicate that epileptic mice have immediate deficits in the stability of spatial representations which decay at a rate similar to control animals.

To probe interneuron dysfunction in the hippocampal circuit of epileptic mice, we trained head-fixed mice to run through a virtual linear track and performed acute extracellular electrophysiology with silicon probes. Epileptic mice had reduced power of theta and gamma oscillations as well reduced coherence of these oscillations between CA1 and dentate gyrus. We then examined the firing patterns of individual interneurons and found a desynchronization of interneurons in the epileptic mice. Epileptic mice had reduced phase locking of CA1 interneurons and an altered preferred phase of firing in dentate gyrus interneurons. Together, these changes produced a desynchronized interneuron population where CA1 and dentate gyrus interneurons were not firing simultaneously. This desynchronization is likely to disrupt processing through this circuit. Finally, we unilaterally transplanted interneuron precursors into the hippocampus of epileptic mice (which can stop seizures and rescue cognitive deficits in epileptic mice) and recorded bilateral LFPs. We found a significant rescue of theta oscillations in the lacunosum moleculare on the transplanted side. While only a partial rescue, this experiment demonstrated that interneuron transplantation can alter synchronization processes which may contribute to the rescue of cognitive deficits in these animals.

LARGE SCALE INFORMATION PROCESSING DURING SPONTANEOUS BRAIN ACTIVITY REVEALED BY CROSS-FREQUENCY COUPLING

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Cross-frequency coupling (CFC), the interaction between different frequency bands, has received increasing attention in recent years. Because neuronal generators of high-frequency activity are more topologically localized than low-frequency rhythms, CFC is a possible mechanism for integrating information across different spatial and temporal scales. However, the specific mechanims by which this is accomplished are still under investigation. Although CFC can involve any possible combination of frequencies, phases, and amplitudes of brain rhythms, most experimental works have focused on three types of CFC: amplitude-amplitude coupling (AAC), phase-phase coupling (PPC), and phase-amplitude coupling (PAC). Interactions within the same frequency band (or same-frequency coupling, SFC) are also possible. SFC-based and CFC-based magnetoencelographic (MEG) connectivity matrices offer a wide dynamical and spectral resolution range, which is unavailable in connectivity matrices obtained from functional magnetic resonance imaging (fMRI). However, there are key challenges associated with SFC and CFC estimation from MEG data, such as source reconstruction, a low signal-to-noise ratio, and lack of a gold-standard mathematical method for the computation (mainly in the case of PAC) and statistical testing. As a result, resting-state networks based on CFC are not as reliable as the fMRI-based ones, which has limited progress in the field.

In this work, we use a unique methodology based on the empirical mode decomposition (EMD) method to estimate CFC-based and SFC-based MEG connectivity matrices. We show that although specific PAC interactions are highly variable across subjects, the global topological properties of the PAC networks are consistent. In contrast, PPC and AAC are consistent at both the local and global scales. When considering direct and indirect connections, we found that most indirect connections are negatively correlated with the strength of the underlying anatomical connection and the value of topological measures such as efficiency and betweenness centrality of the areas involved, whereas direct connections present mostly positive correlations. Our analysis suggests that large-scale high-frequency interactions are related to the integration of information and are mediated by PPC, whereas large-scale low-frequency interactions are related to the segregation of information and are mediated by AAC. PAC combinations are clustered into three groups depending on their spatial complexity (and integration), and these groups determine the correlation of PAC with AAC and PPC, with higher group complexity meaning stronger average correlation. Thus, we suggest that PAC, the phenomenon that links phases of low frequencies with amplitudes of high frequencies, and presents a high spatial integration, couples the two parallel information streams associated with PPC and AAC.

Acknowledgments

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PROCESSING VARIOUS MOTION FEATURES AND MEASURING RGCs PAIRWISE CORRELATIONS WITH A 2D RETINAL MODEL

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Most models of the early visual system (V1–V2), while quite elaborated, consider simple and unrealistic retino-thalamic entries. The retina is however able to perform complex processing tasks. For instance, the visual system uses motion anticipation to compensate for delays in retino-cortical transmission, which starts in the retina [1].

There exist simplified models of retina anticipation, based on gain control at the level of retinal ganglion cells (RGCs) and bipolar cells, able to reproduce other motion features such as alert response to motion onset [1]. However, these models consider 1D receptive field kernels, and thus does not take into account the anisotropy of RGCs. Furthermore, they only simulate isolated RGCs whereas these cells are indirectly connected via amacrine cells [2] and connectivity is presumably essential in reproducing responses to complex motion. This raises the question of which part of the motion processing and anticipation are performed by the retina and which part is processed by the visual cortex.

In this work, we propose a 2D retina model, which allows us to reproduce not only responses to motion features introduced earlier, but also sensitivity to orientation. We then develop a probabilistic model of connectivity, based on biophysical measurements which allows us to reproduce RGC responses to stimuli with long range spatial correlations. We also measure pairwise correlations between the simulated RGCs. Finally, we present our work using our retina model as an entry to a primary visual cortex model.

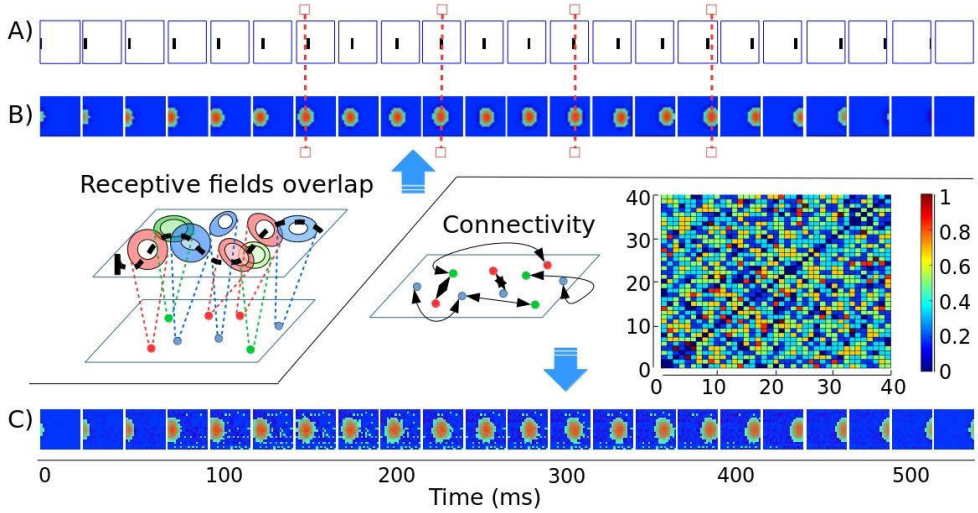

Figure 1. Retinal response to a moving bar. **(A)** The moving bar stimulus. **(B)** Retinal response using a generalized 2D gain control model shows anticipation. **(C)** Retinal response using connectivity model shows activation of distant cells.

Acknowledgments

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LOCAL AND GLOBAL NEURAL CORRELATES OF TASK VARIABLES IN THE MOUSE BRAIN

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Behavior arises from neuronal activity patterns, but whether the relevant activity is concentrated in a small number of brain regions or distributed across many regions remains unknown.

We studied mice performing a visually-guided perceptual decision task [1]. Mice were trained to give one of three responses (choose left, right, or neither) depending on the relative contrast of two simultaneously presented visual stimuli. Widefield imaging of dorsal cortex revealed that after stimulus presentation, activity progressed from primary visual cortex to secondary visual areas, secondary motor cortex, and finally primary motor cortex. Using scanning optogenetic inactivation, we determined that visual cortex and secondary motor cortex inactivation impaired performance, in distinct ways and in sequentially offset time periods of the task. However, we did not find any performance deficits when inactivating primary motor cortex.

To explore the additional roles of subcortical structures, we recorded the activity of over 20,000 neurons during task performance using multiple acutely-inserted Neuropixels probes [2]. These arrays span about 4 mm of tissue and thus record simultaneously across diverse brain regions, including: sensory, parietal, frontal, and motor isocortex; thalamic nuclei; hippocampus; striatum; superior colliculus; and multiple midbrain structures.

Neuron responding to visual stimuli or predicting decisions were localized to specific brain regions, but neurons with correlates of ongoing movement or recent reward were widespread. Visually responsive neurons were found in superficial superior colliculus, visual cortex, and striatum. Neurons that predicted the animal's choice substantially prior to movement (about 100 ms) were found in deep superior colliculus and the mesencephalic reticular formation. However, activity concurrent with action execution and following reward delivery were observed in nearly every region we recorded.

We suggest that when animals perform this task, visual information flows through visual and secondary motor cortices and striatum, to the midbrain where a behavioral choice is selected. By contrast, corollary information about ongoing movements and rewards is represented globally including in primary motor cortex, but this activity is not required for task execution.

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SOCIAL MEMORY IN CA2 HIPPOCAMPAL AREA THROUGH THE EYES OF COMPUTATIONAL MODELLING

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Memory is one of the greatest biological and philosophical puzzles of all time. Hippocampus, one of the basic components of the limbic system, is an area of the brain involved in memory formation, storage and consolidation. Damage to the hippocampus has been associated with neurodegenerative diseases such as Alzheimer's disease, autism and schizophrenia. Furthermore, homeostasis of the Central Nervous System as well as neurodegeneration have been correlated with autophagy. Autophagy is an essential intracellular, highly regulated mechanism which orchestrates the recycling of cytosolic components and organelles. However, its participation in memory formation is yet to be unraveled.

Here, we study CA2 area, a subregion of the hippocampus, which is widely hypothesized to play an essential role in social memory [1]. Social memory is the ability of an animal to recognize (remember) a previously seen animal, compared to a newly encountered one. Towards this goal, we have developed a computational model of CA2 network which consists of biophysical models of various neuronal types incorporating both morphological and electrophysiological properties [2–4]. The network is composed of 90 excitatory pyramidal cells and 10 inhibitory interneurons from three different classes: Basket (4), Bistratified (3) and SP-SR (3) cells. Pyramidal cells receive input from the Dentate Gyrus (DG), Entorhinal Cortex (EC) and CA3 and have a high level of recurrency. All neuron models as well as the network connectivity are validated against experimental data to ensure biological relevance.

Social memory in the CA2 network is implemented via strengthening the connection weights between neurons that respond to the presentation of a familiar animal but not a novel animal. In order to computationally elucidate the role of CA2 on social memory, we will study the network properties for novel *versus* familiar inputs, such as neuronal sparsity, firing rates and input selectivity. To assess the role of autophagy in CA2, we will perform the aforementioned simulations after incorporating the effects of autophagy ablation in the CA2 network. The goal is to predict which alterations have the largest effect on social memory encoding.

Acknowledgments

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DECODING SOCIAL INFORMATION FROM POPULATION CODES IN THE PREFRONTAL CORTEX OF BEHAVING MICE

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The medial prefrontal cortex (mPFC) plays a prominent role in regulating diverse cognitive functions in the mammalian brain. Functional and morphological deficits in this region are associated with several neuropsychiatric disorders, specifically ones involving social deficits. Yet, little is known about how the mPFC encodes social information, and how changes in these representations might relate to impaired social functions.

To address these questions, we utilized a novel behavioral setup to simultaneously record the activity of 10–30 single units from the mPFC of behaving mice, presented with precisely-timed social and nonsocial olfactory stimuli. To explore these representations in social dysfunction, we studied both wild type (WT) mice and *Cntnap2*$^{-/-}$ mice, an established genetic model of autism.

We compared the encoding of different stimuli using pairwise maximum entropy models of the population responses to each stimulus. We found that male and female odors evoked similar encoding distributions, which were markedly different from those evoked by the nonsocial cues, regardless of odor identity or valence. These models also allowed us to accurately decode single trial data and determine whether a given stimulus was social or not. Interestingly, the spatio-temporal responses to social and nonsocial signals became more distinct from one recording session to the next, reflecting experience-dependent refinement of social representations. In the *Cntnap2*$^{-/-}$ mice, population-level distinction of social and nonsocial cues was significantly weakened and showed only small changes with repeated exposure, suggesting impaired circuit-level plasticity processes in these mice.

Since autism-associated phenotypes have been linked to excitation/inhibition imbalance and elevated cortical noise, we quantified the fluctuations of the ongoing (baseline) activity of the population as a measure for network noise. We found that *Cntnap2*$^{-/-}$ mice show significant elevation in baseline neuronal noise compared to WT littermates. Importantly, baseline noise levels showed strong negative correlation with the distinguishability of responses to social and nonsocial stimuli.

Taken together, our results identify unique and dynamic representations of social information in the mouse mPFC, and suggest new insights into possible deficits in information processing that might underlie social dysfunction in autism.

DISTINCT ACTIVITY PATTERNS IN NEUROMODULATORY CENTERS ARE ASSOCIATED WITH DIFFERENTIAL MODULATION OF CORTICAL LOW AND HIGH GAMMA OSCILLATIONS

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Neuromodulatory systems are thought to gate cortical neuronal excitability — a generalized state consisting of high frequency (20–200 Hz) local field potential (LFP) oscillations. Stimulating neuromodulatory centers evokes a non-specific response across all components of the excited cortical state (beta and gamma band LFP oscillations). The non-specificity of neuromodulation is at odds with the fact that neuromodulators regulate distinct cognitive functions that are affiliated with different cortical LFP oscillations. For example, various dopamine and norepinephrine-dependent cognitive functions (*e.g.*, working memory, spatial navigation, and top-down attention) are each accompanied by power increases within different LFP frequency bands. How can neuromodulators contribute to cognitive processes associated with different LFP frequency bands if they non-specifically modulate cortical LFP?

Here, rather than perturbing neuromodulatory systems with stimulation, we recorded spontaneous unit activity from two primary sources of cortical neuromodulators (the noradrenergic locus coeruleus, LC, and dopaminergic ventral tegmental area, VTA) and correlated it with LFP power fluctuations in the prefrontal, visual, and somatosensory cortex of urethane-anesthetized rats. We found that neuromodulatory population spike rate rhythmically fluctuates at 1–2 Hz (delta band) in both LC and VTA. But, in the LC, an additional 5–7 Hz (theta band) fluctuation of spike rate occurred. While neuromodulatory delta oscillations non-specifically regulated the power of all cortical LFP oscillations over 20 Hz, theta spike rate oscillations were exclusively associated with cortical high gamma band (60–200 Hz) activity. As LC population spiking rhythmically rose and fell, two types of LC single units (characterized by narrow or wide action potentials) fired in phasic opposition, potentially providing differential cortical state regulation. Our results demonstrate that the noradrenergic system is a unique neuromodulatory center that can affect specific cortical activity patterns, rather than merely gate a generalized state of cortical excitability.

PROBABILISTIC ENCODING OF TRAJECTORIES WITH HIPPOCAMPAL PLACE CELLS

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Behavioural studies suggest that both humans and other animals are able to perform probabilistic computations. Such computations imply that the nervous system is capable of the representation and manipulation of probability distributions. However, the way encoded distributions are related to neural population activity remains hotly debated because measures that could dissociate these alternative models based on experimental data are remarkably lacking.

Here, we focus on hippocampal activity in the context of exploratory behavior to derive contrasting predictions for competing models. Place cells, selective for specific locations in the environment, become sequentially activated in a short period of time, the theta cycle, thus neurons encoding past, present, and future locations outline the trajectory of the animal. We interpret this activity pattern as the result of repeatedly performing inference about possible trajectories in a dynamical generative model. The crucial observation behind our theory is that the encoded uncertainty should increase monotonically along the trajectory, with a minimal uncertainty for past and maximal for future locations.

To investigate how the uncertainty associated with possible trajectories is represented in population activity, we consider four alternative *encoding models*. First, (i) the hippocampal population activity encodes a single, most likely trajectory without representing uncertainty at all. Alternatively, the population activity at any given time represents the entire probability distribution either by (ii) encoding its parameters (PPC) [1–2] or (iii) using a convolutional encoding [2]. Finally (iv) the distribution is represented by drawing samples [3], under the assumption that only a single trajectory is sampled during each theta cycle. To illustrate the predictions of the four alternatives we created a synthetic dataset. We simulated the activity of place cells in the rodent hippocampus during the exploration of a two dimensional open arena. The activity of 100 place cells with Gaussian place fields of 20–80 cm diameter and 15–50 Hz maximal firing rate were driven by the trajectory inferred by the rat based on sensory input. The trajectory was encoded by the population activity using one of the four possible encoding models.

While all four encoding models predict realistic hippocampal population activity dynamics including theta modulation and phase precession, they make distinct predictions regarding (i) the error between true and encoded trajectories; (ii) the evolution of encoding precision from early to late theta cycle phases; and (iii) the change in the population firing rate during the theta cycle. By decoding population activity under these four models we demonstrate that these measures are sufficient to distinguish the competing models and demonstrate that available experimental methodologies are adequate to dissociate competing models of probabilistic computations. Our analysis is an important step towards elucidating the strategies used by the brain to encode probability distributions and to understand the computational role of neuronal variability in the hippocampus.

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FUNCTIONAL COMPARISON BETWEEN ENCODING STRATEGIES OF TACTILE FEEDBACK FOR BIDIRECTIONAL HAND PROSTHESIS

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A key challenge for upper limb neuroprostheses is to provide an efficient and naturalistic sensory feedback to the patients, to increase functional performance and embodiement. Intrafascicular stimulation of peripheral nerves was found to effectively convey tactile feedback in implanted amputees, controlling the stimulus intensity by modulating either amplitude [1] or frequency [2] of the injected stimuli. However, as comparative studies are missing, an optimal way to convert pressure data into neural stimulation patterns able to elicit informative and naturalistic percepts is yet to be identified.

We defined and compared two encoding strategies: in the first one pressure variations were encoded in linear modulation of amplitude of bi-phasic pulses injected at constant frequency, in the second one pressure variations were encoded in linear modulation of frequency of bi-phasic pulses injected with constant amplitude. These two feedbacks were used to deliver tactile feedback from a prosthetic hand to two amputee subjects implanted in the nerves of the stump with transverse intrafascicular multichannel electrodes. The subjects were asked to evaluate their perceptions and to exploit the tactile feedback to perform functional tasks with the artificial hand of their upper limb neuroprosthesis.

We found that although most tactile information feature as compliance, shape or contact location are conveyed in a similar way by the two encoding strategies, linear amplitude encoding displayed some specific advantages. Amplitude modulation displayed indeed a broader sensitivity range and a lesser adaptation to sustained stimuli. In functional tests, these features led to a higher accuracy of amputee patients in performing time-varying force control when sensory feedback was provided them through amplitude modulation. In future works we will test further codes. in particular, rather than relying on linear modulation of frequency, we will define the temporal structure of the injected pulses generating precise spike sequences through the simulation of patterns of mechanoreceptor responses with the TouchSim model [3].

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LEARNING HIERARCHICAL PROBABILISTIC MODELS OF SENSORY STIMULI USING A DISTRIBUTED REPRESENTATION OF UNCERTAINTY

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There is a wide range of evidence that human observers are able to correctly handle uncertainty in perceptual tasks, and it has been suggested that they do this by learning a statistical model of the sensory environment. In this framework, the model of the environment is often formalised as a probabilistic generative model that describes how possible causes (latent variables) give rise to the corresponding sensory observations. Perception (or recognition) involves inverting this model by computing the posterior distribution over unobserved causes given the sensory information. Even though the idea of perception as Bayesian inference has been around in the neuroscience literature for some time, and a number of schemes have been suggested for how populations of neurons may code for uncertainty (*e.g.*, [1, 2]), there has been little focus on how a flexible internal model can be learned supporting rich sensory inference observed in experiments.

Here we present a novel approach, the Distributed Distributional Code (DDC) Helmholtz Machine, to learn hierarchical generative models and simultaneously learn to perform inference about the latent causes. Inference is implemented by a recognition model that maps observations to a representation of the posterior distribution over latent variables, analogous to the different stages sensory processing in the cortex. A key feature of our model is that neural activity encodes uncertainty about the latent causes implicitly. The inferred posterior distribution is represented as a set of expectations distributed across a population of neurons [1], *i.e.* in a distributed distributional code (DDC). To learn both the generative and the recognition model, we use a wake-sleep-like algorithm inspired by the Helmholtz Machine [3]. Even for hierarchal models, the learning rules remain local, making our approach biologically appealing.

We demonstrate that the DDC Helmholtz Machine can exploit its rich posterior representation to accurately learn generative models of sensory relevance, a prerequisite for accurate inference about latent causes. We use the example of olfaction and show that the DDC HM learns the statistics of receptor activations accurately, while variational methods relying on independence assumptions — as used for olfactory inference in [4] — fall short of capturing the distribution in detail. Furthermore, the recognition model computes posterior means of odorant and odour concentrations accurately for new observations.

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EMERGENT MOVEMENT-RELATED ACTIVITY IN PREMOTOR CORTEX UNDERLIES SEQUENCING OF SUBMOVEMENTS IN A REACH-TO-GRASP TASK

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Premotor (M2) and primary (M1) motor cortex are thought to operate as a functional hierarchy [1]. However, evidence from stimulation [2], cooling [2], and calcium imaging experiments [3] suggests that rodent M1 and M2 cortices play distinct, parallel roles in controlling forelimb movement. Specifically, several studies support the idea that M1 controls a wide range of forelimb muscles, while M2 specifically controls distal muscles required for grasping. In contrast, single unit recordings from these two regions are near-identical during forelimb task performance in well-trained animals [4]. To resolve this apparent contradiction, we used *in vivo* electrophysiology to record neural spiking activity and local field potential from M1 and M2 simultaneously in rats during the earliest stages of learning the reach-to-grasp task. In their natural environment, rats perform extensive forelimb reaching, but rarely perform single-handed grasping. To perform the reach-to-grasp task, rats must develop proficiency in grasping and coordinate this new submovement with the larger reaching movement.

We hypothesized that M1 and M2 neural signals differ in early learning, when the reach and grasp submovements are performed and timed variably. As shown in Figure 1, we found that M1 and M2 representations become similar only over the course of learning as animals develop coordinated control of different submovements of the reach-to-grasp task. We argue that this emergent movement-related modulation reflects online control of movement, specifically the sequencing of submovements. To confirm this experimentally, we inactivated M2 with muscimol in well-trained animals, which lead to unstructured movements with inconsistent submovement sequencing.

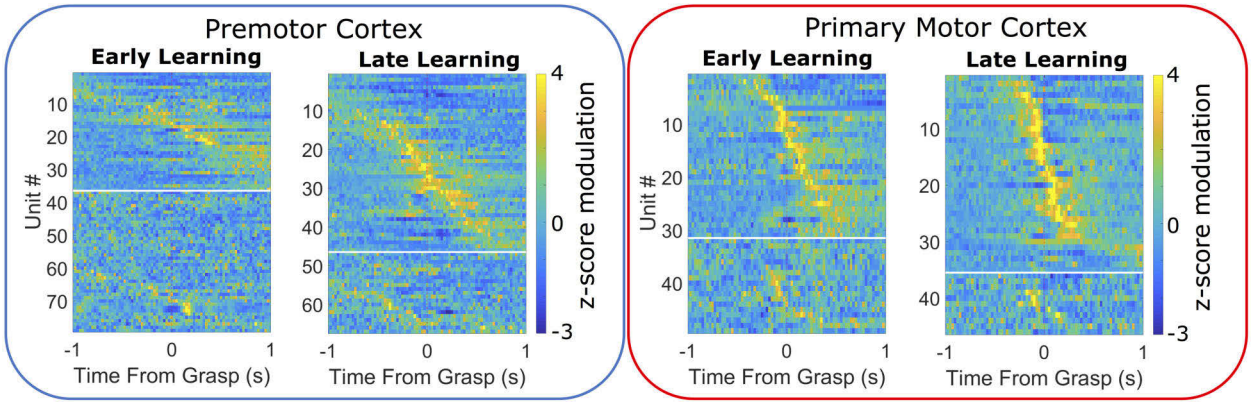

Figure 1. Peri-event time histograms. Neurons above white lines are significantly modulated.

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ENCODING SPACES ACROSS THE BEHAVIORAL REPERTOIRE OF THE COMMON MARMOSET

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From both theoretical and ethological perspectives studying the activity of neural ensembles in the cortex during complex, naturalistic behaviors will be a key step for elucidating the nature of the cortical population code [1, 2]. Evidence from multiple groups studying multiple cortical areas suggests that the activity of cortical populations has surprisingly low dimensional structure [3]. Much of this work however has been in the context of highly constrained experimental tasks. It is an open question whether or not this low dimensional structure is manifest in a less constrained, more naturalistic setting. While a recent study found evidence for low dimensional structure of neural ensemble activity in macaque motor cortex across multiple tasks [4], the structure of motor cortical encoding spaces across the broader natural behavioral repertoire remains unresolved. Consequently we are mapping the structure of the encoding spaces of sensorimotor cortical populations during unconstrained natural behavior.

To do so, we developed a surgical approach and a wireless recording setup that enabled us to implant Utah Arrays in the sensorimotor cortex of Common marmoset monkeys with a low profile mounting of the wireless headstage. This recording setup allows us to record sensorimotor cortical activity while marmosets engage in unconstrained behavior.

We describe the development of our recording approach, a summary of the unconstrained behavioral repertoire of marmosets, and our initial mapping of the encoding spaces of marmoset sensorimotor cortex across the marmosets' natural behavioral repertoire using both linear and non-linear dimensionality reduction approaches.

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IMPOSING STRUCTURE ON ODOR REPRESENTATIONS DURING LEARNING IN OFC AND BLA

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Neurons in the piriform cortex receive convergent input from random collections of olfactory glomeruli. As a consequence, odors elicit an unstructured and distributive representation of neural activity in the piriform that encodes odor identity. A restoration of order must therefore be implemented downstream to impose value on an odor representation and elicit an appropriate behavioral output. We have performed 2-photon endoscopic imaging during learning in piriform and two downstream associative areas, the basolateral amygdala (BLA) and orbitofrontal cortex (OFC). Piriform odor responses are unaffected by learning. In contrast, before learning, neurons responsive to odor in the BLA and OFC are sparse and non-specific. After learning in an operant conditioning paradigm, over 30% of OFC and BLA neurons exhibit strong responses to the rewarded CS+ odors but do not respond to unrewarded CS− odors. These responses are dependent upon context and internal state. In the BLA, CS+ responses frequently overlap with US-responses, suggesting that learning may occur through a Hebbian mechanism, whereas this was not the case in OFC. Moreover, in both BLA and OFC, the same population of neurons respond to all CS+ stimuli. These observations suggest that odor identity in the piriform is discarded in the OFC and BLA and transformed by the convergence of sensory and cognitive information to create representations of predictive value.

We have also examined the role of the BLA and OFC in associative learning tasks. We divided our task into two epochs: pre-training, during which mice learn that a single odor predicts water, and discrimination training, in which mice learn to distinguish between novel CS+ and CS− odors. Optogenetic silencing of OFC during pre-training results in a significant impairment in learning simple odor associations. Simultaneous imaging also reveal that OFC inactivation during pre-training impairs the formation of a learned representation in BLA. However, if mice have undergone pre-training with an intact OFC, silencing the OFC does not affect the learning of new associations during discrimination. Thus, distributed representations of olfactory learning emerge in multiple brain areas, and the OFC representation appears necessary for the acquisition of task structure during simple associative learning.

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NEURONAL DYNAMICS UNDERLYING STABLE POPULATION-LEVEL WORKING MEMORY REPRESENTATIONS IN PREFRONTAL CORTEX

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Neurophysiological experiments in primates have found that during the delay period of working memory tasks, a fraction of neurons in the prefrontal cortex carries information about the stimulus as sustained activity, therefore supporting a stable code during the whole delay period. However, many neurons show strong temporal dynamics, which has given rise to the dynamic coding model for working memory. This model proposes that due to the time-varying dynamics of single neurons, a stable memory representation can only be achieved at the population level through a linear combination of individual neural responses of a sufficiently large population of neurons.

Here we set out to investigate how prefrontal neurons with different delay-period dynamics contribute to population dynamics during an oculomotor delayed response task [1]. We first characterized the delay dynamics of single neurons based on their firing rate autocorrelation. Autocorrelation decays were heterogeneous, ranging from persistent neurons with slow decay to dynamic neurons with more transient delay activity autocorrelation. We extended the result of Murray and colleagues [2] by analyzing how different neurons contribute to the principal components of the pseudo-population responses and found that the persistent neurons, but not the dynamic neurons, span a stable, low-dimensional mnemonic subspace.

We then used linear decoders on single neurons and compared stimulus information during different time points throughout the whole trial period. Persistent neurons carried more information than dynamic neurons on any tested time point during the delay. Moreover, by combining single neuron recordings to pseudo-population responses we found that about 10% of neurons with the highest individual cue and delay selectivity provide a stable representation throughout the trial, as accurate as the whole population of 541 neurons.

In sum, we conclude that persistent neurons are the main drivers of memory-selective delay period dynamics in our data.

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DECISION FORMATION IN AN OLFACTORY DELAYED MATCH TO SAMPLE TASK

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In many decisions, the evidence we obtain through our senses or memory need not give rise to immediate responses. Rather, we maintain and manipulate this information in our thoughts and produce delayed, deliberate action. These decisions require not only the temporary storage of sensory information, but also the transformation of stored and incoming stimuli into meaningful actions.

In order to study these decisions, we developed an odor-guided, lick-left/lick-right delayed match to sample (DMS) task in mice. In this task, animals must remember the first sample odor during a short delay, and compare it to the second test odor to determine if it is a match or non-match, and make a choice by licking left or right, respectively. To map the neural representations of odor identity and choice, we recorded the activity of three brain areas that are thought to be involved in different stages of the task: piriform cortex (Pir), orbitofrontal cortex (OFC) and anterolateral premotor cortex (ALM). The neural representation in the three areas shows a continuum of odor identity through action planning. However, given enough neurons, the capacity to decode choice with Pir and OFC neurons can match animal's performance, suggesting sufficient information is present in the early stage of sensory processing to resolve the task, and this information may instruct ALM to plan licking.

If this is the case, a clear prediction is that ALM is only essential once test odor is delivered. Surprisingly, we found that temporally controlled photoinhibition of ALM during sample and delay epochs dramatically impairs animal's performance. Importantly, ALM silencing did not affect licking itself or control tasks that do not require sample memory. These results suggest that the sample stimulus induces a persistent change in ALM that is important for the behavior. Using 2-photon imaging, we found an enrichment of sample representation during sample and delay epochs in ALM superficial layer. It is possible that the sample memory is maintained by this group of neurons, which was revealed by imaging but not by recording due to their superficial location.

Together, our results suggest that working memory of sensory stimuli is represented in a premotor area and plays a critical role in the formation of DMS decision. Moreover, different cortical layers may perform distinct computations in an active behavior such that the superficial layer receives and maintains sensory information, whereas the deep layers are involved in action planning.

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SOURCE-SPECIFIC PROJECTIONS BETWEEN SPECIALIZED VISUAL CORTICAL AREAS

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The visual cortex is made of highly interconnected areas that encode distinct aspects of the visual scene. While the functional organization of neurons in visual areas is well characterized, the functional organization of information flow across areas remains poorly understood. We combined large-scale cellular resolution calcium imaging with retrograde and anterograde labeling to study the functional and anatomical specificity of information flow between visual cortical areas in awake mice. We characterized the functional architecture of mouse visual cortex by measuring the visual responses properties of over 40,000 neurons in primary visual cortex (V1) and six higher visual areas (LM, AL, RL, AM, PM and LI) using spectral noise stimuli varying in spatial and temporal frequency and spatial anisotropy. Distinct areas showed widely different responses encoding distinct regions of the spatiotemporal spectrum. In particular: V1 and area LM showed a broad range of response properties encompassing diverse populations; anterior areas, AL, RL and AM, preferentially responded to low spatial and high temporal frequencies, containing a large fraction of neurons tuned for visual motion speed; these contrasted with lateral areas LI and PM that preferred high spatial and low temporal frequencies. Surprisingly, cortical neurons showed distinct preferences for non-oriented and oriented stimuli. LI differed from other areas with a strong preference for non-oriented stimuli that might facilitate shape coding. Are the functional projections between these functionally distinct areas target- or source-matched? We then focused on projections between areas AL and PM that prefer distinct spatiotemporal features. Retrograde tracing and anterograde tracing showed that both projection neurons in the source area and axonal projections in the target areas presented target-like tuning properties. Altogether, these results provide a detailed functional characterization of neurons in higher visual areas and suggest specific channels conveying target-specific information between higher visual areas that might support specialized visual computations.

Acknowledgments

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NEURAL ACTIVITY SUPPRESSION IN THE MEDIODORSAL THALAMUS PRECEDES THE OCCURRENCE OF HIPPOCAMPAL RIPPLES

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Forming a persistent memory trace requires hippocampal-cortical interaction. Population bursts in the hippocampal network occurring during awake immobility or NREM sleep propagate throughout the entire hippocampal formation and generate transient dynamic interactions locally, but also between the hippocampus (HPC) and cortex. This synchronized population activity is revealed in the local field potentials as brief, high-frequency (about 200 Hz) oscillations, or ripples, which are thought to mediate the hippocampal-cortical communication underlying memory consolidation [1]. The medial prefrontal cortex (mPFC) receives direct input from the HPC and many mnemonic processes depend on these two brain regions [2]. The HPC-mPFC pathway is considered critical for consolidation of declarative memory and is currently one of the most studied memory-related pathways. A memory-supporting network is, however, not limited by the HPC and the mPFC. The thalamic mediodorsal (MD) nucleus is likely a part of an extended memory network. The MD is reciprocally connected with the mPFC and has long been implicated in different mnemonic functions [3]. Our fMRI-based mapping of the whole brain activity associated with ripples occurrence suggested that silencing of a subset of subcortical regions, including thalamus, may reduce interference for hippocampal-cortical communication [4].

We characterized neural activity in the MD around times of the hippocampal ripples in spontaneously behaving rats. Generally, the MD population activity was strongly suppressed around ripples. A substantial reduction of MD firing occurred 0.4–2.4 sec (mean: 1.1±0.1 sec) before the ripple peak and lasted for 2.1±0.2 sec. Moreover, the degree of MD activity suppression correlated with the ripple amplitude. The ripple-associated decrease of the MD firing rate was the strongest and the most consistent during awake immobility. In contrast, during NREM sleep bidirectional modulation of the MD activity was observed: the MD firing was actually enhanced around ripples that were temporally coupled with sleep spindles, while it was decreased around spindle-uncoupled ripples. Our results suggest possible competitive interaction between the hippocampal-cortical and thalamo-cortical networks supporting ‘off-line’ and ‘on-line’ information processing, respectively.

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POPULATION CODES IN V1 AND MT ARE OPTIMISED FOR THE STRUCTURE OF NATURAL IMAGES

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The middle temporal area (MT) computes motion direction based on the inputs it receives from direction-selective neurons in primary visual cortex (V1). Existing models of the hierarchical computations between these areas are among the best defined of any model of cortical processing, yet the stimulus space of visual inputs on which they have been tested remain poorly explored. While most studies explore neural responses using only gratings or dots, the natural visual world contains information at a range of spatial scales, and this information is often phase aligned. There is evidence that this structure shapes the nervous system so that natural images are encoded efficiently by single neurons. In this work, we examined how the structure of visual information impacts the way it is encoded by both single-neurons and populations, across two levels of the visual hierarchy.

To reveal how visual information is successively represented by V1 and MT, we used separate multi-electrode arrays in each area to measure neural responses simultaneously from dozens of neurons in V1 and MT of 5 anaesthetised marmosets (*Callithrix jacchus*). We recorded neural activity from overlapping receptive fields in both areas while presenting motion with different spatial structure randomly interleaved: dots, sine waves, square waves, and phase randomised square waves. These patterns evoke strong direction-tuned responses in MT, but recruit distinct V1 populations. We found that response variability in single neurons (expressed as the Fano factor), and pairwise spike count correlations between neurons were lowest during broadband, phase aligned stimulation within and between areas V1 and MT. This suggests that the network architecture in both areas is optimised to represent broadband, phase aligned contours.

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