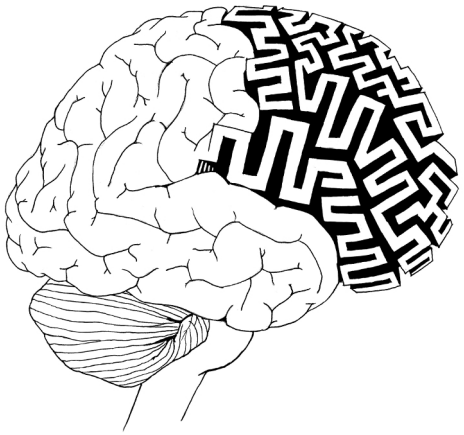
AREADNE 2014

Research in Encoding and Decoding of Neural Ensembles

Nomikos Conference Centre, Santorini, Greece

25-29 June 2014



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AREADNE 2014
Research in Encoding and Decoding of Neural Ensembles
Nomikos Conference Centre, Santorini, Greece, 25-29 June 2014
Nicholas G. Hatsopoulos and John S. Pezaris, editors

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WELCOME

Welcome

Welcome to AREADNE 2014, the fifth AREADNE Conference on Research in Encoding and Decoding of Neural Ensembles.

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 including intrinsic, voltage-sensitive dye, and two-photon imaging, high-density electroencephalography and magnetoencephalography, and multi-microelectrode array 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 project to form a systems neuroscience research institute within Greece to conduct state-of-the-art research, offer meetings and courses, and provide a center for visiting scientists from around the world to interact with Greek researchers and students.

Organizing Committee

The AREADNE 2014 conference was organized by John Pezaris (Co-Chair) and Nicholas Hatsopoulos (Co-Chair), Dora Angelaki, Yiota Poirazi, Thanos Siapas, and Andreas Tolias.

Local Organizers

Local organization effort has been provided by Nike Makris with assistance from Ariadne Pangalos and Erica Berry.

Sponsors and Support

Our conference is being sponsored with generous gifts from Dr. and Mrs. George Hatsopoulos, and Mr. Peter Pezaris, to The AREADNE Foundation, a non-profit organization that runs the

AREADNE Conferences. In addition, for 2014, the conference is being administered by the Massachusetts General Hospital, with financial or in-kind support from the the National Science Foundation (Grant number CBET-1403636), The Gatsby Charitable Foundation (Grant number GAT3291), The Wellcome Trust, and Foley & Lardner, LLC.

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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
Archipelagos	+30-22860-23673	€ € €	caldera view, Santorinian cuisine
Koukoumavlos	+30-22860-22510	€ € € €	caldera view, nouvelle cuisine
Mama Thira	+30-22860-22189	€ €	caldera view, taverna
Nikolas	+30-22860-24550	€	traditional Greek cuisine, near Murphy's Bar
Poldo	+30-22860-24004	€	souvlaki stand, near the National Bank
Sphinx	+30-22860-23823	€ € € €	caldera view, Greek cuisine
The Greeks	+30-22860-22989	€ €	taverna, near the cable car
Mama Thira	+30-22860-22189	€ € €	caldera view, taverna
Kapari	+30-22860-27086	€ €	taverna, set back from main road

Restaurants in Oia

Iliovassilema	+30-22860-71614	€ €	fresh fish
Thalami	+30-22860-71009	€ €	ouzo bar
1800	+30-22860-71485	€ € € €	nouvelle cuisine

Restaurants in Perivolos-Vlychada

Vlychada	+30-22860-82819	€ €	Greek taverna by the beach
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 08.30–15.00 (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 and 18.00–20.00, 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

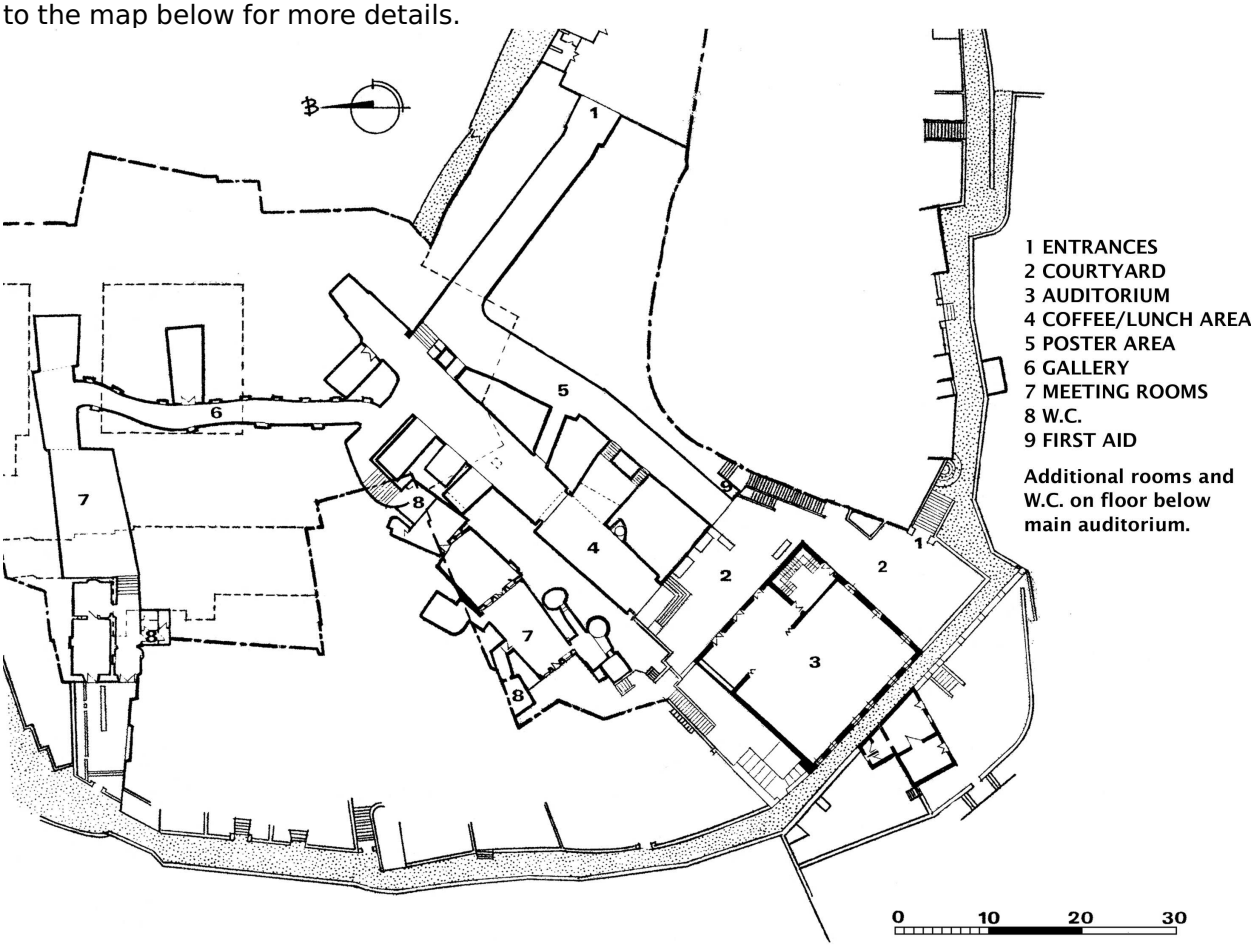
Monastery of Profitis Ilias
in Pyrgos, at the mountain peak; has a nice ecclesiastic museum; modest dress required

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
20:00–22:00 welcome reception and registration

Thursday
09:00–09:30 registration
09:30–12:30 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, 25 JUNE 2014

20:00–22:00 welcome reception at Nomikos Centre

THURSDAY, 26 JUNE 2014

09:00–09:30 registration

09:30–09:45 opening remarks

MORNING SESSION Nicho Hatsopoulos, moderator

09:45–10:30 **Gilles Laurent** (Max Planck Institute for Brain Research) *Explorations of a three-layered visual cortex*, 28

10:30–11:00 coffee break

11:00–11:45 **Tom Mrsic-Flogel** (University of Basel) *Functional organization of connection strength in mouse visual cortex*, 32

11:45–12:30 **Andreas Tolias** (Baylor College of Medicine) *The structure and function of cortical microcircuits*, 41

12:30–14:00 lunch

AFTERNOON SESSION Irini Skaliora, moderator

17:00–17:45 **Carl Petersen** (École Polytechnique Fédérale de Lausanne) *Synaptic mechanisms of sensory perception*, 34

17:45–18:15 coffee and light snacks

18:15–19:00 **Wulfram Gerstner** (École Polytechnique Fédérale de Lausanne) *Modeling neuronal dynamics across different time scales*, 25

19:00–19:20 **Desmond Patterson** (University of Texas, Austin) *Carbon-14 dating the Minoan eurption of Thera (Santorini)*, 33

19:20–19:40 **Andronike Makris** (Hellenic Education and Research Center) *The prehistoric settlement of Akrotiri and the ancient Greek city state of Ancient Thera: What is so great about them?*

20:00–21:30 posters, presenting author

Des Patterson (University of Texas, Austin) *Carbon-14 dating the minoan eruption of Thera (Santorini)*, 33

Dimitris Pinotsis (University College London) *Extracting novel information from neuroimaging data using neural fields*, 98

Maria Psarrou (IMBB-FORTH) *A simulation study on the effects of dendritic morphology on layer v PFC pyramical cell firing behavior*, 101

Pavlos Rigas (BRFAA) *Effect of early life seizures on cortical excitability and epileptogenesis*, 104

Panos Sapountzis (FORTH) *Decoding covert attention from simultaneous recordings in prefrontal and visual cortex*, 107

Charalambos Sigalas (BRFAA) *Spatiotemporal propagation patterns of cortical synchronised activity in vitro*, 110

Yann Sweeney (University of Edinburgh) *Diffusive neurotransmission as a new homeostatic mechanism*, 113

Alejandro Tabas (Bournemouth University) *Hierarchical processing of auditory asymmetry*, 115

Lyuba Zehl (Jülich Research Centre) *Metadata management for complex neurophysiological experiments*, 119

Johannes Zirkelbach (LMU Munich) *Decoding-accuracy versus integration-time for dynamic stimuli*, 122

FRIDAY, 27 JUNE 2014

MORNING SESSION Barry Richmond, moderator

09:00–09:45 **Susumu Tonegawa** (MIT) *Engrams for genuine and false memories*, 42

09:45–10:30 **Ole Paulsen** (Oxford University) *Left-right dissociation of hippocampal memory processes in mice*, 36

10:30–11:00 coffee break

11:00–11:45 **Loren Frank** (University of California, San Francisco) *Activation and reactivation of hippocampal–cortical networks*, 23

11:45–12:30 **Jennifer Raymond** (Stanford University) *Understanding both enhanced and impaired learning with enhanced plasticity: A saturation hypothesis*, 37

12:30–14:00 lunch

FRIDAY AFTERNOON SESSION Stelios Smirnakis, moderator

17:00–17:45 **Ken Britten** (University of California, Davis) *Cortical representation of cues used in visually guided steering*, 20

17:45–18:15 coffee and light snacks

18:15–19:00 **Gabriel Kreiman** (Harvard Medical School) *Visual object completion in the human brain*, 27

19:00–19:45 **Brian Wandell** (Stanford University) *Measuring activity, connections and tissue properties in the living human brain*, 43

20:00–21:30 posters, presenting author

Costas Anastassiou (Allen Inst. Brain Science) *Ephaptic coupling in cortical neurons*, 47

Ryan Ash (Baylor College of Medicine) *Cortical circuit physiology in an autistic savant mouse model*, 50

Philipp Berens (BCCN and Univ Tübingen) *What the mouse eye tells the mouse brain: A semi-supervised clustering approach for fingerprinting the retinal ganglion cell types of the mouse retina*, 53

Romain Brasselet (SISSA) *Isometric mapping between environment and temporal neural activity*, 56

Daniel Chicharro (Ist. Italiano di Tecnologia) *Modulation of correlation by activity levels: From synaptic currents to single neurons and population activity*, 59

Michael Denker (Research Centre Jülich) *Characterizing spatially organized LFP beta oscillations in the macaque motor cortex*, 62

Rainer Engelken (MPI Dynamics and Self-Org) *Supression of chaos by input spike trains in balanced neural networks*, 65

Felix Franke (ETH Zurich) *High-resolution coding with correlated neurons: Theory and application to direction-selective retinal ganglion cells*, 68

Attila Gulyas (Hungarian Acad Sciences) *Tuning excitability and synaptic efficacy switches among network dynamics and processing modes*, 71

Mike Hemberger (MPI Brain Research) *Neural circuits of three-layered cortex*, 74

Naama Kadmon-Harpaz (Weizmann Institute) *Scale invariant movement encoding*, 77

SATURDAY, 28 JUNE 2014

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

AFTERNOON SESSION Leslie Osborne, moderator

17:00–17:45 **EJ Chichilnisky** (Stanford University) *Functional circuitry of the primate retina at cellular resolution*, 21

17:45–18:15 coffee and light snacks

18:15–19:00 **Tatyana Sharpee** (Salk Institute for Biological Studies) *Coordinated encoding between cell types in the retina: Insights from the theory of phase transitions*, 40

19:00–19:45 **John Pezaris** (Harvard Medical School) *Classical and extra-classical characteristics in macaque LGN*, 35

20:00–21:30 posters, presenting author

Evan Archer (MPI Biological Cybernetics) *Low-d dynamical models of neural populations with common input*, 48

Frederico Azevedo (MPI Biological Cybernetics) *Dynamics changes of BOLD functional connectivity during natural viewing in the amake macaque brain*, 51

Matthew Best (University of Chicago) *Encoding of reach to grasp trajectories in premotor cortex*, 54

Diego Bravo (University of Cambridge) *On hippocampal basket cells showing both biphasic and monophasic phase-resetting curves, and its functional effect in gamma oscillations*, 57

James Cotton (Baylor College of Medicine) *Scaling of information in large sensory neuronal populations*, 60

Stéphane Deny (Institut de la Vision) *Surprise decoding in the retinal activity*, 63

Oxana Eschenko (MPI Biological Cybernetics) *Ripple-triggered stimulation of the locus coeruleus during post-learning sleep impairs memory consolidation*, 66

Emmanouil Froudarakis (Baylor College of Medicine) *Population code in mouse V1 facilitates read-out of natural scenes through increased sparseness*, 69

Rafi Haddad (Bar-Ilan University) *Transformation from a temporal code to a rate code*, 72

SUNDAY, 29 JUNE 2014

MORNING SESSION Yifat Prut, moderator

09:00–09:45 **Eve Marder** (Brandeis University) *Parallel pathways, multiple solutions, degenerate neuromodulation, and robustness of circuit performance*, 30

09:45–10:30 **Dan Margoliash** (University of Chicago) *Neurodynamics in bird song motor production*, 31

10:30–11:00 coffee break

11:00–11:45 **Mark Churchland** (Columbia University Medical Center) *Many movements, one trigger?*, 22

11:45–12:30 **Terence Sanger** (University of Southern California) *Risk-aware control*, 39

12:30–14:00 lunch

AFTERNOON SESSION Kenneth Blum, moderator

17:00–17:45 **Surya Ganguli** (Stanford University) *A theory of neural dimensionality, dynamics and measurement*, 24

17:45–18:15 coffee and light snacks

18:15–19:00 **Sonja Grün** (Jülich Research Centre) *Statistical methods for detection of assembly activity in massively parallel spike data*, 26

19:00–19:45 **Philip Sabes** (University of California, San Francisco) *Unsupervised learning in parietal cortex: from theory to a novel brain-machine interface*, 38

19:45–20:00 closing remarks

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

SPEAKER ABSTRACTS
(in alphabetical order by speaker)

CORTICAL REPRESENTATION OF CUES USED IN VISUALLY GUIDED STEERING

Kenneth H. Britten[*], *Seth W. Egger, Xuezhu Li*

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Optic flow is the term given to the pattern of motion that results from our motion through the environment. Most of the study of the processing of this kind of information has been done using conventional two-alternative, forced-choice tasks. This approach has been productive, uncovering a network of areas that contribute to such perception, and elucidating a number of their properties in some detail. However, the perceptual tasks used in these studies differ in significant ways from normal locomotion: the stimuli are usually briefly presented and the behavior is open-loop. Locomotion, however, unfolds over time and is closed-loop. We have developed a behavioral task where monkeys steer through a virtual environment in pursuit of a distant target, being guided by continuous dynamic feedback from optic flow. Behavior in this task is reliable and well described by simple control-system models. While the animals are performing this task, we recorded from the dorsal subdivision of the medial superior temporal area (MSTd), one of the cortical areas known to be involved in optic flow processing. Neuronal responses to both of the behaviorally relevant cues (the motion of the distant target and the optic flow) are robust. One surprise is the strength of the responses to the motion of a small target; MSTd neurons are thought to not respond very well to such stimuli. Also, the responses to the two cues also interact: optic flow responses depend on the location of the target and vice versa. This reveals a hitherto un-suspected complexity of MST motion responses. We have also analyzed both behavioral and neuronal responses for their fidelity of representation of a time-varying stimulus, using a stimulus-reconstruction approach. We find that neurons in MSTd are, on average, relatively poor at representing the stimulus, relative to behavioral fidelity. However, a few neurons approach the precision of the behavior. This suggests that relatively simple population readout would allow the signals in MST to support active steering behavior.

FUNCTIONAL CIRCUITRY OF THE PRIMATE RETINA AT CELLULAR RESOLUTION

E.J. Chichilnisky

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A major challenge in neuroscience is to decipher the functional connectivity of neural circuits. We approached this challenge in the primate retina by mapping the flow of signals between the input and output layers at cellular resolution, and using these maps along with closed-loop experiments and computational methods to infer interneuron connectivity. Large-scale multi-electrode recordings were used to examine the activity of complete populations of the retinal ganglion cell types which collectively mediate high-resolution vision (midget, parasol, small bistratified). Fine-grained white noise visual stimulation was used to separately identify the location and spectral type of each cone photoreceptor providing input to each ganglion cell. This provided functional connectivity maps at cellular resolution between complete populations of input and output neurons. Subsequent targeted stimulation of individual cones and pairs of cones was then used to identify linear and nonlinear combination of signals. These, in conjunction with computational inference of linear and nonlinear interactions between all cones identified, revealed interactions consistent with pooling of signals by intermediate bipolar cells. The spatial scale of interactions was consistent with expectations from anatomical data. Together, these approaches begin to reveal a fuller picture of the functional connectivity of the retina, from input to output via the interneuron layer, at cellular resolution.

MANY MOVEMENTS, ONE TRIGGER?

Matthew T. Kaufman[1], *Jeffrey Seely*[4], *Stephen I. Ryu*[1,3], *Krishna V. Shenoy*[1], *Mark M. Churchland*[4,*]

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To execute a voluntary movement, your brain must choose both which movement to make and when to make it. The delayed reach task separates these two components: the movement is known during the preparatory period but must not be triggered until a go cue is given. Neurons in premotor and motor cortex begin responding during preparation. Following the go cue, preparatory activity provides the initial state that seeds a complex pattern of movement-related activity. The transition from preparatory to movement-related activity can be modeled as a sudden change in the dynamics of the system. An open question is: what causes this sudden change, and in doing so triggers the movement? Here, we report that, amid the complexity of movement-period activity, there is a large component of the population neural response that is both simple and highly similar for all movements (*i.e.*, it is *condition independent*). This condition-independent component, identified using a recent technique (dPCA) was strongly predictive of movement onset on a trial-by-trial basis. Furthermore, the timing of the condition-independent signal was compatible with the onset and offset of strong local dynamics. The condition independent component dominated the cortical response, but was essentially absent in the response of the muscles. Thus, the largest response component in motor and premotor cortex reflects not which movement will be made, nor directly reflects muscle activity, but instead reflects the moment when movement will be initiated. We suggest that this component may reflect a largely untuned *trigger signal* entering M1 and PMd, and that may activate the dynamics necessary to generate movement.

ACTIVATION AND REACTIVATION OF HIPPOCAMPAL–CORTICAL NETWORKS

Loren M. Frank[*], *Shantanu P. Jadhav, Gideon Rothschild, Demetris K. Roumis*

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Interactions between the hippocampus and prefrontal cortex are thought to be critical for learning and memory processes, but the physiological mechanisms underlying these interactions remain unclear. We have previously demonstrated that awake sharp wave ripple (SWR) events, during which hippocampal memory reactivation occurs, are critical for spatial learning and memory-guided decision-making. We have also shown that hippocampal replay events can reactivate patterns of brain activity from a previous experience in awake animals and that disrupting these events interferes with learning and memory-guided decision-making. Further, we have found that the intensity of replay activity is predictive of whether an upcoming choice will be correct or incorrect. These findings suggest that hippocampal activity associated with awake SWRs should drive processing in cortical networks, but whether and how these events co-occur with specific cortical activity patterns remains unexplored. Here I will present results showing that there is coordinated reactivation of hippocampal-prefrontal neurons during awake SWRs, These patterns of coordinated reactivation recapitulate activity patterns seen during behavior and reveal highly specific functional networks of hippocampal-prefrontal neurons. This reactivation is well suited to play an important role in memory storage, memory retrieval and memory-guided decision-making.

A THEORY OF NEURAL DIMENSIONALITY, DYNAMICS AND MEASUREMENT

Peiran Gao, Eric Trautmann, Byron Yu, Gopal Santhanam, Stephen Ryu, Krishna Shenoy, Surya Ganguli *

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In many experiments, neuroscientists tightly control behavior, record many trials, and obtain trial-averaged firing rates from hundreds of neurons in circuits containing millions of behaviorally relevant neurons. Dimensionality reduction has often shown that such datasets are strikingly simple; they can be described using a much smaller number of dimensions (principal components (PCs)) than the number of recorded neurons, and the resulting projections onto these components yield a remarkably insightful dynamical portrait of circuit computation.

This ubiquitous simplicity raises several profound and timely conceptual questions. What is the origin of this simplicity and its implications for the complexity of brain dynamics? Would neuronal datasets become more complex if we recorded more neurons? How and when can we trust dynamical portraits obtained from only hundreds of neurons in circuits containing millions of neurons? We present a theory that answers these questions, and test it using data from reaching monkeys.

First, we derive a theoretical upper bound on the dimensionality of data. Our bound takes into account both the complexity of the task and the smoothness of neural dynamics, and therefore has a natural interpretation as a quantitative measure of neuronal task complexity. Interestingly, the dimensionality of motor cortical data is close to this bound, indicating neural activity is as complex as possible, given task constraints and smoothness. Our theory provides a general analytic framework to ascertain whether neural dimensionality is constrained by task complexity or intrinsic brain dynamics, furthering our ability to interpret large-scale datasets.

We also describe sufficient conditions on PCs underlying neural activity so that low dimensional dynamical portraits remain unchanged as we record more neurons, and show that they are satisfied by motor cortical data. Moreover, we show, through the theory of random projections, that the number of neurons we need to record to accurately recover dynamical portraits need only grow logarithmically with the neuronal task complexity.

Overall, this theory yields a picture of the neural measurement process as a random projection of neural dynamics, conceptual insights into how we can reliably recover dynamical portraits in such under-sampled measurement regimes, and quantitative guidelines for the design of future experiments.

MODELING NEURONAL DYNAMICS ACROSS DIFFERENT TIME SCALES

Wulfram Gerstner[*], *Richard Naud, Christian Pozzorini, Skander Mensi*

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Neuronal activity evolves on the time scales of spikes which last a few milliseconds, but leave a spike-aftereffect for several seconds. This talk addresses the following questions: (*i*) How can we extract parameters of neuron models directly from data? (*ii*) How do neurons encode a stimulus: can we predict neuronal spikes? And (*iii*), can we decode the input to a single neuron from the spikes, if we know the neuronal parameters?

Related Work

1. Pozzorini, Naud, Mensi, Gerstner, 2013, *Nat. Neurosci* 16:942–948.
2. Naud, Gerstner, 2012, *PLoS Comput.* 8:e100271.
3. Mensi, Naud, Pozzorini, Vermann, Petersen, Gerstner, 2012, *J. Neurophysiol.*, 107:1756-1775, 2012.

STATISTICAL METHODS FOR DETECTION OF ASSEMBLY ACTIVITY IN MASSIVELY PARALLEL SPIKE DATA

Sonja Grün

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We seek to understand cortical network processing during performance of natural behavior. Such insight requires (i) recordings from a large number of neurons during complex behavior, (ii) development of statistical methods for the analysis of neuronal interaction in a trial-by-trial and time resolved manner, (iii) analysis of data in relation to behavior (see poster by Zehl, *et al.*), and (iv) reproducible workflows and related necessary software to realize collaborations within and across labs (see posters by Riehle, *et al.*, and, Denker, *et al.*). This talk will concentrate on statistical methods designed to detect network interactions by identifying spatio-temporal correlations in the activities of the neurons in massively parallel data.

Earlier we developed the Unitary Events (UE) analysis (Grün, 2009, *J. Neurophysiol.* 101:1126–1140) to identify excess spike synchrony and found dynamic occurrences of UEs at specific points in time relevant for the behavior of the animal (e.g., Kilavik, *et al.*, 2009, *J. Neurosci.*, 29(40):12653–12663). However, the UE analysis does not scale for the analysis of large numbers of neurons (say $N = 100$, or more) since the method evaluates each individual spike pattern across the neurons which would require the estimation of $2N$ parameters. Therefore we started to develop new statistical methods that enable to detect higher-order correlated (HOC) spiking events in massively parallel data.

HOCs are not identifiable by pairwise correlation analyses, and are not obviously visible in multiple-unit single-trial raster displays. In population histograms which measure spike counts across neurons in small time bins, HOCs exhibit peaks that are larger than the counts resulting from independent firing. Count distributions of correlated data do not exhibit obvious heavy tails by HOCs, thus the detection of HOCs (Grün, *et al.*, 2008, *LNCS*, 5286:96–114; Louis, *et al.*, 2010, *Neural Networks*, 23:705–712) or inference of their correlation order (Staude, *et al.*, 2010, *J. Comput. Neurosci.*, 29(1–2):327–350) requires statistical approaches that include specific model assumptions.

In order to identify the neurons that are involved in such correlated events, we make use of frequent itemset mining (FIM) for fast and efficient detection of spike patterns (Picado-Muiño, *et al.*, 2013, *Front. Neuroinfor.*, 7:9). To avoid the massive multiple testing problem, patterns are pooled according to their size and occurrence count. The pattern significance is evaluated by comparison to surrogate data that realize independence (Torre, *et al.*, 2013, *Front. Comput. Neurosci.*, 7:132). False positives due to chance coincidence with background spikes are excluded by additional filtering. Sequences of synchronized patterns, as occur in synfire chains, are reliably detected by the matrix intersection method (Schrader. *et al.*, 2008, *J. Neurophysiol.*, 100(4):2165–2176). First results from these methods on data recorded by Utah arrays in behaving monkey (Riehle, *et al.*, 2013, *Front. Neural Circuits*, 7:48) will be presented.

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VISUAL OBJECT COMPLETION IN THE HUMAN BRAIN

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Recognition from partial information is a central computation across animal species and sensory modalities. Natural vision often involves recognizing objects from partial information due to occlusion, irregular illumination patterns or unusual viewpoints. Recognition of objects from partial information represents a significant challenge for theories of vision because it requires spatial integration and extrapolation from prior knowledge. In this talk, I will discuss behavioral, physiological and computational investigations to further our understanding of object completion. Consistent with previous investigations, psychophysics data showed that subjects have a remarkable ability to recognize objects from minimal information. Recognition of partial objects was delayed with respect to recognition of whole objects, perhaps suggesting that object completion involves additional computational steps. To get insights about the neural circuits underlying object completion, we recorded intracranial field potentials from 1,699 electrodes in 18 subjects to measure the location and timing of selective neurophysiological responses along the human visual cortex during recognition from partial information. Signals from the ventral visual stream, particularly the Inferior Occipital and Fusiform Gyri, remained visually selective despite strong occlusion (10–25% visibility). However, these visually selective signals emerged 100 ms later for occluded versus whole objects. These processing delays were particularly pronounced in higher compared to lower visual areas. This latency difference persisted when controlling for changes in contrast, signal amplitude, and the strength of selectivity. I will also discuss two computational models that aim to shed light on a possible explanation for the behavioral and physiological data. The computational models suggest that a purely bottom-up model can describe recognition of whole objects but seems insufficient to explain recognition of partial objects. Adding recurrent/feedback connections endows the model with the capacity to perform object completion. These results argue against a purely feed-forward explanation of recognition from partial information, and provide spatiotemporal constraints on theories of object recognition that involve recurrent processing.

EXPLORATIONS OF A THREE-LAYERED VISUAL CORTEX

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We are interested in the general issue of cortical computation and approach it exploiting the advantages of a simpler experimental system. Our studies are focused on reptilian visual cortex, a three-layered cortical structure similar to mammalian archi- and paleo-cortices (hippocampus and piriform, respectively), and probably close to the common ancestral layered structure from which all cortices arose. GL will present the experimental approaches developed in our lab and results concerning organization, connectivity, receptive field properties and population dynamics.

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

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Santorini possesses two very important archaeological sites: The Bronze Age (possibly Minoan) site of Akrotiri that dates to the 2nd Millenium B.C., and 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 types of Ancient society and show in what way each one of them is of relevance to Modern Western Civilization. How exotic is the first one since we understand little about it, and how familiar we are with the second since its values constitute to a great extend fundamental values of Modern Western type democracies. Yet we are fascinated by the Bronze Age Civilizations (Minoan and Mycenean). Why is that so?

In the case of the Greek city states it is easy to understand the relevance: The Greek 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 to a greater or lesser extend political freedom. It is in this socio-political context that, apart from philosophy, geometry, athletics etc., also democratic practices and values emerged with the seminal example of the Ancient Athenian Democracy.

PARALLEL PATHWAYS, MULTIPLE SOLUTIONS, DEGENERATE NEUROMODULATION, AND ROBUSTNESS OF CIRCUIT PERFORMANCE

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The crustacean stomatogastric ganglion (STG) is a small circuit of about 30 neurons that produces two major motor patterns that differ significantly in period. Nonetheless, there are neurons that switch back between these two patterns, and several that fire in phase with both. The connectivity among these neurons is known, and the large number of electrical synapses create numerous parallel pathways that allow neurons to interact both monsynaptically and polysynaptically. Understanding how the rich STG dynamics arise from the intrinsic properties and the known synaptic connectivity is complicated by the fact that there are more than fifty substances, including amines, amino acids, and neuropeptides, that reach the STG either as neurohormones or from the terminals of descending fibers. To what extent does this rich neuromodulation confer behavioral flexibility, and to what extent does overlapping and or degenerate neuromodulatory function ensure network robustness under disparate environmental conditions? Insights into state-dependent actions of neuromodulators come from both experimental and computational approaches.

NEURODYNAMICS IN BIRD SONG MOTOR PRODUCTION

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The neural control of bird song production is roughly divided into two streams, a vocal-respiratory direct motor control pathway, and a learning/biasing pathway involving the basal ganglia. Principle issues in understanding control of song production include pattern generation, the distribution of timing including feedback that mediates learning throughout the system, and hierarchical organization.

Progress in understanding singing behavior and its neural control has been limited by reliance on song spectrographs (spectral analysis techniques), which provide useful graphical representations of the acoustics but give little insight into the actual muscular control of song production. Working with Gabriel Mindlin (University of Buenos Aries), we are developing a new view linking biomechanics and neurophysiology to explore motor control of zebra finch singing in a non-linear dynamical systems framework. Singing is described in terms of the physical mechanics of syringeal membrane motion, coupled to resonances of the trachea and upper vocal tract. Temporal dynamics in song emerge as a sequence of elemental vocal *gestures*, with each gesture being a coordinated change over time in subsyringeal pressure and syringeal membrane tension, typically residing near bifurcations in the parameter space. This represents enormous dimensionality reduction and mechanistic insight compared to spectrographic representations of the acoustics.

The forebrain nucleus HVC is prominent in birdsong motor control research and understand HVC functional organization is a central issue. Using the gesture model we have demonstrated that HVC neurons encode significant moments in motor movements. Recording neurons in singing birds or during fictive singing achieved by song playback during sleep, we observed that sparsely firing projection neurons burst, and tonically active interneurons were suppressed, at the times of gesture trajectory extrema (the start or end of trajectories, or the unique maxima of pressure or tension). Because of the technical difficulty of conducting those experiments, only small samples of neurons were observed. We have now confirmed several predictions of the gesture model using multisite recordings from large populations of neurons, and are presently further analyzing those data. To date, these results have nearly fully falsified the fundamental underlying conjecture of the prominent clock model of HVC activity.

A noteworthy feature of HVC activity is that it occurs with near-zero delay relative to the muscle movements it is encoding. To explore this, in conjunction with Franz Goller (University of Utah) we are making simultaneous recordings from HVC and syringeal muscles during fictive singing.

In our emerging new view of bird song motor control, pattern generators at multiple levels become entrained in preparation for singing. There is functional specialization at the different levels but the nature of hierarchical organization, if any, remains uncertain. Feedback from brainstem activity contributes to entrainment. There is near zero delay across the motor pathway. These are not (yet) established facts, but a working hypothesis that describes bird song production in terms of nonlinear dynamical systems behavior of populations of coupled oscillators.

FUNCTIONAL ORGANIZATION OF CONNECTION STRENGTH IN MOUSE VISUAL CORTEX

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How do the properties of local synaptic connections influence information processing in cortical microcircuits? Connection strength is a fundamental determinant of how neurons influence each other's firing. Connection amplitudes between pyramidal cells in the neocortex vary over two order orders of magnitude, such that there are very few strong connections among many weaker ones. How connections of widely different strengths relate to neuronal response properties and how they contribute to information processing in local microcircuits remains unknown. Here we used multiple whole-cell recordings to assay connectivity between L2/3 pyramidal cells in mouse primary visual cortex, whose visual feature preference was determined by detailed receptive field (RF) mapping *in vivo*. We found that only a small fraction of neurons had RFs encoding matched visual features, and although strong connections were infrequent, they occurred between neurons with similar spatial RFs. In contrast, the majority of excitatory inputs onto a neuron from the local network was weak and stemmed from neurons with dissimilar RFs. Thus, feature-specific information is provided by a small subset of connections that are sufficiently powerful to influence the stimulus selectivity of neuronal responses.

CARBON-14 DATING THE MINOAN EURPTION OF THERA (SANTORINI)

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The cataclysmic Minoan eruption of Thera in the Late Bronze Age ranks among the 6 largest of the last 10,000 years globally, producing over 100 Km^3 of ejecta. The Minoan ash provides an important stratigraphic marker across much of the eastern Mediterranean and can be used to constrain the ages of archeological sites and Late Bronze Age events. In this context, determining a reliable date for the Minoan eruption becomes critical — more so because of a long standing disagreement between archaeology and geochronology. Specifically, conventional archeological estimates of the age of the Minoan ash based on pottery styles and linked to the well established chronology of Egyptian pharaohs indicate a date of about 1500 to 1520 B.C. In contrast, ^{14}C geochronology places the eruption as pre-1600 B.C., earlier by at least a full century. This discrepancy becomes especially important in debates about the causal links between the eruption of Thera and the collapse of the Bronze Age Minoan civilization of Crete.

Early attempts (pre-2000) to use ^{14}C dating of material from the Minoan eruption on Santorini indicated dates in excess of 1600 B.C., but where hampered by poor precision arising from the fact that the ^{14}C calibration curve (that links ^{14}C years to calendar years and corrects for variations in ^{14}C production in the upper atmosphere over time) available at the time had a plateau in the critical time period. In 2004 the determination of a more precise ^{14}C calibration curve (IntCal04) allowed Manning and colleagues [1] to give age range for the eruption of 1683–1611 B.C. based on 28 samples of seeds (fava beans and lentils) recovered from the Bronze Age ruins at Akrotiri on Santorini.

The problem of the ^{14}C calibration curve plateau was further circumvented by the discovery of a one meter section of a branch from an olive tree by Ph.D. student Tom Pfeiffer in 2002. The branch was buried in life-position at the base of the Minoan pumice in an inaccessible section of the caldera wall and was associated with olive leaves, indicating it was indeed a casualty of the eruption. Significant was the ability to identify 72 growth rings within the branch. ^{14}C dating of four sections of the branch provided internally consistent inter-correlated ages that can be matched with great confidence to the ^{14}C calibration curve using a technique known as *wriggle matching*. This yielded a date for the Minoan eruption of 1626 to 1600 B.C. [2].

Although the ^{14}C data are considered to reliably date the Minoan eruption to about 1610 B.C. (or at the very least to pre-1600 B.C.), the discordance with archeological estimates of about 1500 B.C. remain problematic, and the links between the eruption and the demise of the Bronze Age Minoan civilization unclear.

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SYNAPTIC MECHANISMS OF SENSORY PERCEPTION

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A key goal of modern neuroscience is to understand the neural circuits and synaptic mechanisms underlying sensory perception. Here, I will discuss our efforts to characterize sensory processing in the mouse barrel cortex, a brain region known to process tactile information relating to the whiskers on the snout. Each whisker is individually represented in the primary somatosensory neocortex by an anatomical unit termed a *barrel*. The barrels are arranged in a stereotypical map, which allows recordings and manipulations to be targeted with remarkable precision. In this cortical region it may therefore be feasible to gain a quantitative understanding of neocortical function. We have begun experiments towards this goal using whole-cell recordings, voltage-sensitive dye imaging, viral manipulations, optogenetics and two-photon microscopy. Through combining these techniques with behavioral training, our experiments provide new insight into sensory perception at the level of individual neurons and their synaptic connections.

Classical and extra-classical characteristics in macaque LGN

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Mapping neuronal responses in the lateral geniculate nucleus (LGN) is key to understanding how visual information is processed in the brain. This presentation focuses on our current knowledge of the dynamics the receptive field (RF) as broken down into the classical receptive field (CRF) and the extra-classical receptive field (ECRF) in primate LGN. CRFs in the LGN are known to be similar to those in the retinal ganglion cell layer in terms of both spatial and temporal characteristics, leading to the standard interpretation of the LGN as a relay center from retina to primary visual cortex. ECRFs have generally been found to be large and inhibitory, with some differences in magnitude between the magno-, parvo-, and koniocellular pathways. The specific contributions of the retina, thalamus, and visual cortex to LGN ECRF properties are presently unknown. Some reports suggest a retinal origin for extra-classical suppression based on latency arguments and other reports have suggested a thalamic origin for extra-classical suppression. The issue is complicated by the use of anesthetized animals, where cortical activity is likely to be altered, suggesting further study of LGN ECRFs is warranted to reconcile these discrepancies. In particular, because naturalistic stimuli generate a wider range of responses than white noise, RF properties of LGN neurons might be produced more easily, or in more detail, by employing stimuli with non-white spatiotemporal characteristics. Although there has been significant work in cats with natural scene stimuli and noise that statistically imitates natural scenes, we highlight a need for similar data from primates. Obtaining these data may be aided by recent advancements in experimental and analytical techniques that permit the efficient study of nonlinear RF characteristics in addition to traditional linear factors.

LEFT-RIGHT DISSOCIATION OF HIPPOCAMPAL MEMORY PROCESSES IN MICE

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Optogenetics allows spatially-restricted cell-type-specific stimulation and silencing of neurons. Using optogenetic stimulation of afferent input in mice, we previously found that hippocampal synaptic plasticity shows left-right asymmetry, such that input from the left CA3 shows spike timing-dependent potentiation, whereas input from the right CA3 does not (Kohl et al., 2011). This talk will present recent data indicating that this left-right asymmetry extends to high-frequency stimulation-induced long-term potentiation. Moreover, using optogenetic silencing of either the left or right CA3, we found that unilateral CA3 silencing of either the left or right CA3 was sufficient to impair short-term memory. However, a striking asymmetry emerged in long-term memory, wherein only left CA3 silencing impaired performance on an associative spatial long-term memory task, whilst right CA3 silencing had no effect. These results suggest a unique requirement of the left CA3 for long-term hippocampus-dependent spatial memory and that spatial memory in mice is routed via distinct left-right hippocampal pathways.

UNDERSTANDING BOTH ENHANCED AND IMPAIRED LEARNING WITH ENHANCED PLASTICITY: A SATURATION HYPOTHESIS

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Transgenic mice with enhanced long-term potentiation (LTP) or long-term depression (LTD) sometimes exhibit enhanced learning, but, paradoxically, often exhibit impaired learning. Here, we show that mice deficient in the Class-I major histocompatibility molecules (MHCI) H2-Kb and H2-Db ($KbDb^{-/-}$), which have enhanced cerebellar LTD at the parallel fiber-Purkinje cell synapses (pf-Pk LTD), can exhibit specific enhancements or deficits in oculomotor learning, depending on the recent history of experience. Our results indicate that a delicate balance between the enhanced plasticity rate versus an opposing, saturation effect determines the learning outcome. We hypothesized that the lower threshold for LTD in $KbDb^{-/-}$ mice allows spontaneous activity in the circuit to induce LTD, driving it towards saturation and reducing its availability to support new learning. Consistent with saturation, a biochemical marker of pf-Pk LTD indicated abnormally elevated levels of LTD in naive $KbDb^{-/-}$ mice, which exhibit a learning impairment. Moreover, optogenetic stimulation of cerebellar climbing fibers to induce pf-Pk LTD saturation in wild type mice created the same specific motor learning deficit as in $KbDb^{-/-}$ mice. In the $KbDb^{-/-}$ mice, behavioral pre-training designed to reverse the pf-Pk LTD saturation not only reversed the learning impairment, but also unmasked enhanced learning. Purkinje cell-specific rescue of MHCI H2-Db reversed both the impaired and the enhanced learning phenotypes in the $KbDb^{-/-}$ mice. Computational analysis identified synaptic properties that allow the same enhanced plasticity mechanism to yield either enhanced or impaired learning — a strong saturation bias, and stubborn, difficult to reverse states. Our results indicate that the recent history of activity in a circuit is critical in determining whether an enhanced plasticity rate or saturation dominates the capacity of a circuit for new learning.

UNSUPERVISED LEARNING IN PARIETAL CORTEX: FROM THEORY TO A NOVEL BRAIN-MACHINE INTERFACE

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The planning and control of even simple movements, such a reaching for an object, relies on information from multiple sensory modalities. In particular, the computations that underlie the early stages of reach planning appear to be composed of a small set of multisensory computational elements. We have shown how a simple network model can learn to perform these computations in a statistically optimal fashion, driven only by the common statistics of its inputs, *e.g.*, by spatiotemporal correlations between sensory modalities. We have also demonstrated experimentally that correlated inputs do drive *de novo* multisensory learning. Animals were trained to perform a reaching task under the guidance of visual feedback. They were then exposed to a novel, artificial feedback signal in the form of a non-biomimetic pattern of multielectrode intracortical microstimulation (ICMS). After training with correlated visual and ICMS feedback, the animals were able to perform precise movements with the artificial signal alone. Furthermore, they combine the ICMS signal with vision in a statistically optimal fashion, as would be done for two natural stimuli. This result suggests a new route to studying multisensory processing in the brain and also serves as a proof-of-concept for a learning-based approach to artificial feedback with brain-machine interfaces.

RISK-AWARE CONTROL

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Encoding and decoding of neuronal populations involved in motor function is usually performed as if movement is purely about generating muscular force. But almost all movement-related neurons have some degree of sensory tuning, for if they did not then movement would occur independently of sensory state leading to frequently inappropriate behaviors. Thus to encode and decode movement we require a mathematical theory that incorporates state-dependent effects of neuronal activity. But if the effect of neuronal firing depends on state, then for a constant firing pattern the output force depends on state, which means that tunable reflexes are a natural consequence. Furthermore, the effect of firing and its dependence on state are uncertain and can be affected by unobserved or uncontrollable processes, so a movement-related neuronal population controls a stochastic dynamical system. The optimal choice of control strategy for a stochastic system depends on the uncertainty and the cost of errors, so this predicts that control will be risk-aware in the sense that control will be exerted in a way that combines information about probability of error and cost of error. Thus our mathematical theory must permit population-based control of stochastic reflex-based dynamical systems that can be optimized to reduce overall risk.

To do this, I have developed the theory of Stochastic Dynamic Operators (SDOs). This theory describes the effect of individual neurons on whole-body dynamics, and SDOs permit stable control and adaptation of nonlinear stochastic systems in uncertain environments. Because SDOs describe uncertainty, they automatically implement risk-aware control. The response to risk can be selected based on task constraints. An emergent feature of SDOs is the direct implementation of task-dependent reflexes, since perturbations will be resisted only in the direction of high-cost errors. I will describe the use of SDOs to simulate human risk-aware behavior in robots, and I show that they can be used to describe the relation between neurological injury and components of abnormal movement in children.

COORDINATED ENCODING BETWEEN CELL TYPES IN THE RETINA: INSIGHTS FROM THE THEORY OF PHASE TRANSITIONS

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Computation in the brain involves multiple types of neurons, yet the reason for such diversity remains unclear. I will describe how a physical theory of transitions between different phases of matter can account for conditions when it becomes optimal to split neural populations into subtypes. Specifically, the maximally informative solution undergoes a sharp transition from one to two populations when noise decreases below a critical value, with neural noise playing the role of temperature in the classic theory of phase transitions. The results accounted for properties of two recently discovered types of salamander OFF retinal ganglion cells and the absence of multiple types of ON cells. We further show that, across contrasts, retinal circuits continued to operate near the critical point well described by an Ising model. Notably, retinal populations were positioned near the so-called spinodal line that delineates regions with fast and slow dynamics near a critical point. By operating in this regime, neural circuits provided over 97% of the maximal information possible for a given statistics of input signals while retaining the ability to quickly adapt to a new environment.

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THE STRUCTURE AND FUNCTION OF CORTICAL MICROCIRCUITS

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Our aim is to understand the rules by which different types of neurons in the neocortex connect to each other and work together to process information. We want to determine what constitutes the elementary computational circuit motifs in the neocortex with the ultimate goal to characterize their structure and the computations that these modules implement. We combine electrophysiological, imaging, and molecular tools with behavioral and computational approaches to dissect the functional architecture of inhibitory and excitatory microcircuits in the visual system of mice and monkeys. I will describe our ongoing work towards those goals from two perspectives. First, from an anatomical perspective where we are mapping out the detailed wiring diagram of the cortical microcircuit using high-throughput multi-cell patch clamp recording. Second, using electrophysiological and imaging methods we characterize the activity structure of large populations of neurons to understand the nature of the neural code. To this end, developed an *in vivo* 3D high-speed, random-access two-photon microscope that is capable of simultaneous 3D motion tracking. This enables us to record the activity of nearly all of the hundreds of cells (up to 500 neurons) in small volumes of the cortex to characterize the structure of microcircuit population activity during visual processing. We are particularly interested to understand how the dynamics of internally generated brain activity interact with visual input to process information.

ENGRAMS FOR GENUINE AND FALSE MEMORIES

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A fundamental question in neuroscience is how a distinct memory is formed and how it is retrieved for recall. Central to this question is whether Richard Semon's engram theory of memory is valid [1]. A direct test of memory engram theory would require specifically labeling only the neurons involved in memory formation and then subsequently re-instating memory recall by reactivating these neurons [2]. A recent study conducted by applying channel rhodopsin-mediated optogenetics to contextual fear memory of mice validated the engram theory [3].

Memory is usually a good guide for appropriate behavior but it can be grossly unreliable; under certain conditions, humans are known to form distinct false memories—memories of episodes they never experienced. In order to understand how false memories could be formed, we made a mouse model of false contextual fear memory [4]. Finally, we are investigating how memory valence is imposed on the neutral contextual memory engram in the dentate gyrus of the hippocampus.

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MEASURING ACTIVITY, CONNECTIONS AND TISSUE PROPERTIES IN THE LIVING HUMAN BRAIN

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There has been extraordinary progress in our ability to measure tissue, structure, and function in the living human brain. I will explain several magnetic resonance imaging methods that quantify properties of the living human brain — both cortex and white matter — in individual subjects. The ability to make these measures in individual subjects and patients significantly enhances the value of these techniques for clinical applications.

First, I will discuss how functional magnetic resonance is used to measure the size, position, and stimulus selectivity of cortical maps in individual subjects. I will discuss the relationship between the signals measured using BOLD and signals from electrodes implanted in the human brain. Next, I will describe how diffusion-weighted imaging is used to identify the major white matter tracts. The tissue properties within certain pathways are predictive of specific cognitive skills, including reading, demonstrating the importance of white matter tissue development for cognitive function. Finally, I will describe quantitative measurements of key MR parameters, including proton density and T1. Quantification of these parameters, coupled with biophysical models, enables us to measure new properties of tissue density and chemistry that clarify changes across the lifespan and in neurodegenerative disease.

POSTER ABSTRACTS

(in alphabetical order by first author)

A NON-PARAMETRIC PROTOTYPING SCHEME FOR LFP DYNAMICS AND ITS APPLICATION TO DETECT CHANGES IN SPONTANEOUS UP STATES DUE TO CORTICAL MATURATION AND AGING

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Spontaneous network activity in the form of Up and Down states plays an important role in the function of neural circuits and reflects intrinsic connectivity. Such cortical dynamics are shaped by genes, experience and intrinsic cellular properties and form the substrate upon which external stimuli and neuromodulation will impinge to determine cortical responses. The scope of this work was to build a methodological framework for assessing developmental changes in intrinsic cortical activity patterns obtained from LFP recordings of spontaneously active mouse brain slices.

To overcome the complexity seen in the recorded signals, which are characterized by a high variability in Up-state waveforms, we resorted to a representation that preserves the dynamic invariants of the underlying network and built a pattern-analytic scheme that includes three pipelined stages.

In the first stage, upstate waveforms are represented as dynamical trajectories and similarities are quantified by means of a non-parametric multivariate statistical test. Subsequently, for each LFP recording a prototype is extracted among all the available Up-state traces based on an algorithm that selects the most typical event in the space of trajectories. In the second stage, all the available prototypical trajectories are brought to a common space and compared against each other. Using the associated labels reflecting the age of the animal, we mine the representative trajectories with morphological characteristics specific for each age group. In the third stage, the Up-state waveforms corresponding to the representative trajectories are presented in an orderly fashion that reflects the spectrum of variations related with ageing.

The adopted scheme underlined the utility of *in vitro* Up states as an index of normal cortical development and maturation and potentially as a neurophysiological biomarker (endophenotype) of neurodevelopmental disorders, paving the path for a better understanding of their underlying cellular mechanisms.

EPHAPTIC COUPLING IN CORTICAL NEURONS

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The electrochemical processes that underlie neural function manifest themselves in ceaseless spatial and temporal fluctuations in the extracellular electric field. The local field potential (LFP), used to study neural interactions during various brain states, is regarded as an epiphenomenon of coordinated neural activity. Yet the extracellular field activity feeds back onto the electrical potential across the neuronal membrane via ephaptic coupling [1]. The extent to which such ephaptic coupling alters the functioning of individual neurons and neural assemblies under physiological conditions has remained largely speculative despite recent advances [2–4].

To address this question we use a 12-pipette setup that allows independent positioning of each pipette under visual control with µm accuracy, with the flexibility of using an arbitrary number of these as patching, extracellularly stimulating or extracellular recording pipettes only a few µm away from the cell body of patched neurons [5]. We stimulated in rat somatosensory cortical slices a variety of layer 5 neural types and recorded inside and outside their cell bodies while pharmacologically silencing synaptic transmission.

Pyramidal cells couple to the extracellular field distinctly different from interneurons. Ephaptic coupling strength depends both on the field strength (as measured at the neuron soma) as well as the spike-history of neurons. In particular, we find that ephaptic coupling strength depends both on the field strength (as measured at the cell body) as well as the spike-history of neurons. How do such effects manifest themselves *in vivo*? We address this question through detailed large-scale simulations from thousands of biophysically realistic and interconnected neurons [6] emulating circuit activity. The simulations allow us to examine ephaptic coupling and dissociate between the feedforward (from membrane currents to LFP) and feedback (from LFPs to membrane voltage via ephapic coupling) effect in unprecedented detail. Our results support the notion that ephaptic coupling to endogenous electric fields in the brain may crucially impact neural communication. We hypothesize the functional role of such coupling in various brain states, for example, during visual processing [7].

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LOW-D DYNAMICAL MODELS OF NEURAL POPULATIONS WITH COMMON INPUT

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Modern experimental technologies enable simultaneous recording of large neural populations. These high-dimensional data present a challenge for analysis. Recent work has focused on extracting low-dimensional dynamical trajectories that may underlie such responses. Such methods enable visualization and may also provide insight into neural compuations. Previous work focuses on modeling a population's dynamics without conditioning on external stimuli.

Our proposed technique integrates linear dimensionality reduction with a latent dynamical system model of neural activity. Under our model, population response is governed by a low-dimensional dynamical system with quadratic input. In this framework the number of parameters in grows linearly with population (size given fixed latent dimensionality). Hence it is computationally fast for large populations, unlike fully-connected models.

Our method captures both noise correlations and low-dimensional stimulus selectivity through the simultaneous modeling of dynamics and stimulus dependence. This approach is particularly well-suited for studying the population activity of sensory cortices, where neurons often have substantial receptive field overlap.

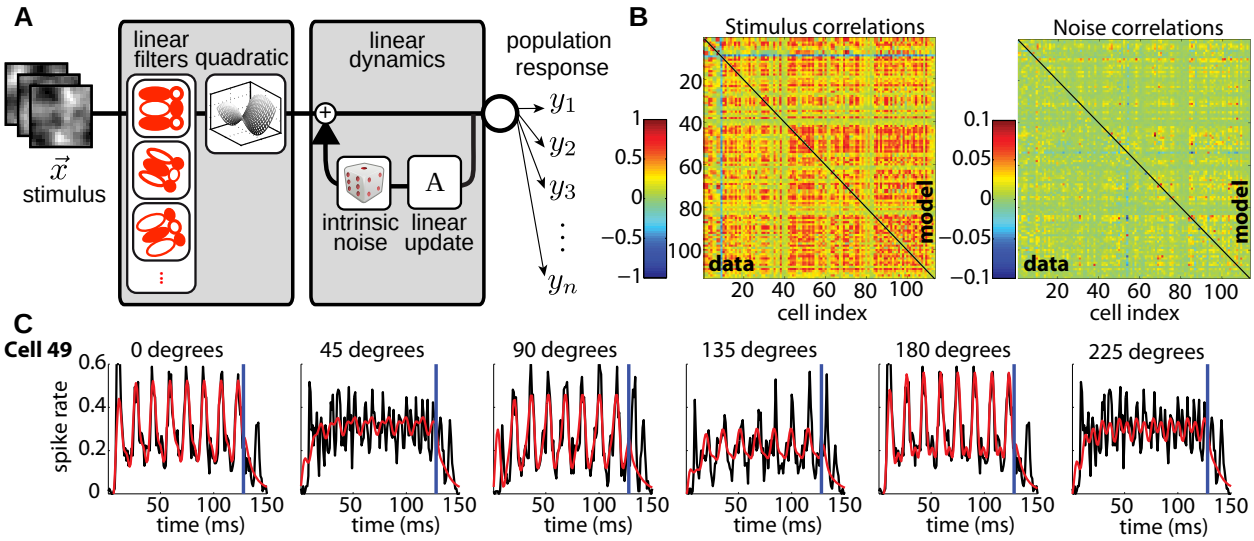

Figure 1. **A**: *Model schematic*. Stimulus is projected onto multiple linear filters, passed through quadratic function, and fed into linear dynamical system. Neural responses y_i are linear projections of dynamical state. **B, C**: *V1 population recordings (Graf, et al., 2011, Nature Neurosci.); 113 cells responding to drifting grating stimulus, 10 ms bins.* B, Stimulus and noise correlations from data (lower triangle) and model (upper triangle). C, PSTH predictions for one cell, for a selection of stimulus directions. Black lines: data, averages across 45 trials. Red lines: posterior means under single QLDS model. Vertical blue lines indicate stimulus off time, 128 ms.

DUAL RECORDINGS FROM CEREBELLAR INTERNEURONS AND PURKINJE CELLS *IN VIVO*

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In order to understand the computations performed by neural circuits, it is essential to identify the contribution of each circuit element to information processing and how the elements interact *in vivo*. In the cerebellar cortex, Purkinje cell (PC) axons provide the sole output of the network, and their spiking activity is under the control of synaptic inhibition delivered by molecular layer interneurons (MLIs). *In vitro*, single MLIs have been shown to delay simple spikes in nearby PCs, but the correlations of MLI and PC activity in the intact cerebellar circuit remain unknown. MLIs are known to be coupled via gap junctions, but also to inhibit each other chemically. Investigating the resulting interactions between MLIs *in vivo* is necessary to understand how PC activity is shaped by inhibition. To address this issue, we performed targeted simultaneous patch-clamp recordings from MLI-PC pairs as well as from MLI-MLI pairs using two-photon imaging of Parvalbumin-GFP mice under isoflurane anaesthesia. Consistent with previous results, loose-patch and cell-attached recordings demonstrated that both interneurons and Purkinje cells exhibit spontaneous firing at high rates (7.7 ± 7.5 and 29.7 ± 19.8 Hz, respectively). Crosscorrelograms from spike trains of MLI-MLI pairs exhibited inhibitory interactions as well as millisecond synchrony between MLIs. Crosscorrelograms from spike trains of nearby PC-MLI pairs showed that single spontaneous MLI spikes are associated with a decrease of PC simple spiking. Triggering single spikes by direct stimulation of MLIs caused a decrease in PC simple spiking, demonstrating that single interneurons can inhibit their targets. Crosscorrelations of PC complex spikes and MLI spikes furthermore showed that climbing fiber activity modulates MLI spiking. We are currently examining how these interactions shape sensory-evoked responses.

CORTICAL CIRCUIT PHYSIOLOGY IN AN AUTISTIC SAVANT MOUSE MODEL

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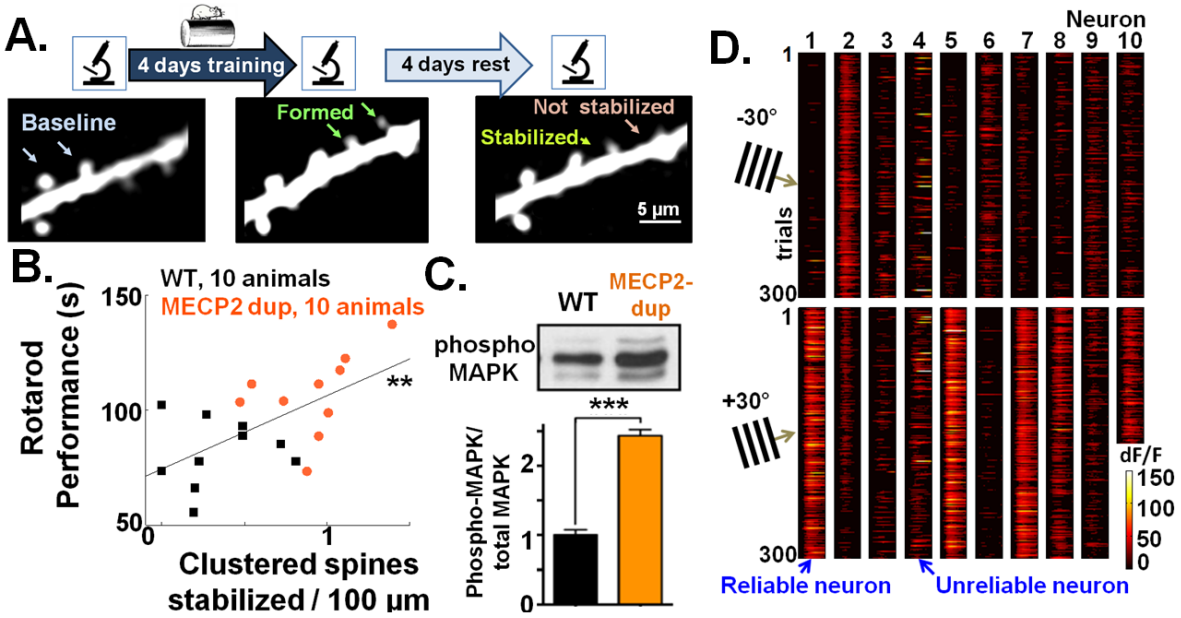
That both prominent behavioral inflexibility and exceptional learning abilities are seen occasionally in autistic patients is a mystery. We hypothesize that these altered patterns of learning and memory can arise from a pathological imbalance between the stability and plasticity of internal neural representations. We are evaluating this hypothesis in the mouse model of MECP2 duplication syndrome, which demonstrates enhanced motor learning, stereotyped behaviors, and social avoidance. In the first study, learning-associated structural plasticity was measured in the motor cortex of MECP2 duplication mice by 2-photon imaging (Fig. 1A). An increased stabilization rate of learning-associated dendritic spines was observed in mutants, and an analysis of the spatial distribution of stabilized spines revealed that the mutant's increased spine stabilization was due to a specific increase in the stability of spines jointly formed in 9-micron clusters. Clustered spine stabilization but not isolated spine stabilization predicted enhanced motor performance in MECP2 duplication mice ($p < 0.01$, Fig. 1B). Biochemical assays of Ras-MAPK and mTOR pathway activation demonstrated a profound hyper-phosphorylation of MAPK in the motor cortex of MECP2 duplication mice after motor training ($p < 0.001$, Fig. 1C), suggesting that the pathological bias towards increased stability of learning-associated dendritic spine clusters in MECP2 duplication syndrome is driven by hyperactive Ras-MAPK signaling. This aberrant form of plasticity may contribute to the neurobehavioral phenotypes seen in this form of syndromic autism.

In the second study, we aim to measure the stability of visual-evoked neuronal ensemble responses in the visual cortex of MECP2 duplication mice with GCaMP6s. Responses of the same group of cells to hundreds of stimulus repetitions are measured as in Fig. 1D. Some neurons reliably report a single orientation throughout the entire experiment (*e.g.*, neuron 1), while others fire unreliably (neuron 4). These experiments will enable us to determine if autistic behavioral inflexibility is recapitulated at the level of neuronal ensemble activity.



DYNAMICS CHANGES OF BOLD FUNCTIONAL CONNECTIVITY DURING NATURAL VIEWING IN THE AMAKE MACAQUE BRAIN

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The primate brain is a dynamic system interconnected by temporally correlated functional networks. The structure of this correlated activity depends on the brain's internal state and on stimulus input. In the absence of external stimulation, functional networks of spontaneous activity, *i.e.* the salience network, the executive control network and the default mode network, can be observed. Their origin and function are not well understood, but they could reflect neural noise within anatomically connected areas or active mechanisms related to perception and awareness. On the other hand, when the brain is being stimulated, a different pattern of activity emerges. Exactly how this spatiotemporal transition happens is still unclear.

The objective of this study is to characterize the dynamic changes of BOLD based functional connectivity between resting-state and natural-stimuli-driven networks in the awake monkey brain. Due to its high spatial resolution, BOLD-fMRI is a powerful tool to study large-scale correlated brain network activity. We used a paradigm containing sequences of movie-clips with different contexts including natural and artificial environments as well as periods devoid of any visual stimulation (resting) in order to identify the global activation patterns reflecting the interplay between different populations of neurons under these conditions.

For our experiments, two macaque monkeys (*Macaca mulatta*) were trained in a mock scanner to remain headposted and motionless in a custom-made fMRI chair while a MRI-compatible periscope presented a movie clip, a gray background (FOV 30° x 23°, 60 Hz, eff. res. 530×400 fibers) or nothing. After the behavioral training was completed, the monkeys were scanned under the same conditions in a Bruker 4.7 T vertical MRI scanner with a custom-designed whole-head coil (single-shot GE-EPI, TR 1000 ms, TE 18 ms, $128 \times 64 \times 18$ voxels, $1 \times 1 \times 2$ mm). Each run lasted 10 min (600 volumes). We collected 30 functional runs of resting state activity (without any visual stimulation) and 30 functional runs of stimulus driven activity (1 min of a natural movie presentation alternated with 1 min of gray background) for each monkey. All the volumes containing artifacts were pre-selected and excluded from the data analysis. For the visual stimulation condition, we selected the scans with strong visual activation based on a generalized linear model (GLM).

Functional connectivity data analysis (group-level ICA with 20 components) of the scans devoid of stimulation revealed resting-state networks consistent with previous reports in humans and monkeys (Mantini *et al.*, 2013, *J. Neurosci.*). Furthermore, preliminary analysis of the scans with visual stimulation revealed components reflecting visually driven networks. Currently, we are employing the eigenvector centrality mapping (ECM), which is a parameter-free effective connectivity method (Lohmann *et al.*, 2010, *PLoS ONE*) as well as models based dynamic causal modeling (DCM) (Friston *et al.*, 2003, *Neuroimage*) to delineate differences across stimulation with different contexts and to characterize the physiological mechanisms behind the transition of brain states.

BRAIN STATE DEPENDENCY IN THE AUDITORY THALAMOCORTICAL SYSTEM: MUTUAL INFORMATION AND BAYESIAN DECODING

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The brain is never silent; throughout the thalamocortical system, spontaneous firing activity occurs in different patterns that reflect ongoing behavioural state. For example, during deep sleep and wakefulness, the thalamocortical system operates in the *inactivated* state in which neurons collectively aternate slowly between periods of high and near-zero firing activity, respectively referred to as *up* and *down* phases. During wakefulness and REM sleep, however, neuromodulatory mechanisms lead to the suppression of this slow oscillation, and neurons fire in a desynchronised manner in what is known as the *activated* state. Sensory evoked activity also is affected by brain state, and brain states may be the signatures of different modes of processing. Indeed, subtle and/or local changes in ongoing spontaneous are thought to be involved in attention. However the full implications of the effects of brain state on sensory processing remain unknown.

Here we investigate the brain state dependency of sensory processing in the auditory thalamocortical system of the rat, quantifying the amount of information about stimuli carried in the post-stimulus spike counts in individual neurons, and comparing between brain states. Recordings used were taken simultaneously in medial geniculate body (MGB) and down a cortical column of the primary auditory cortex (A1), and auditory stimuli were presented in both the inactivated state (natural under the anaesthesia) and the activated state (induced through electrical stimulation of the basal forebrain). Quantification of stimulus information was performed through the use of the information theoretic measure of *mutual information* and a Bayesian decoding method known as *maximum likelihood decoding*.

Stimulus encoding strategies using spike counts were diverse even among cell-types and locations, as was the effect of brain state on these encoding strategies. However, information theoretic and decoding analysis revealed a shift in the amount of information carried in spike counts, with the least informative neurons tending to *increase* their information content in the inactivated state, and the most informative neurons tending to *decrease* their information content in the inactivated state. Considering a range of window sizes and locations after stimulus presentation, a shift is also observed in the timing of when neurons were most informative.

Summarising, the quantification of stimulus information carried in spike counts allows for the brain state dependency of sensory processing to be seen at this earliest stage of cortical sensory processing, with changes observed in both the amount and timing of information conveyed.

WHAT THE MOUSE EYE TELLS THE MOUSE BRAIN: A SEMI-SUPERVISED CLUSTERING APPROACH FOR FINGERPRINTING THE RETINAL GANGLION CELL TYPES OF THE MOUSE RETINA

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In the retina, the stream of incoming visual information is split into multiple parallel channels, formed by different kinds of photoreceptors (PRs), bipolar cells (BCs) and ganglion cells (RGCs). These cells form complex circuits with additional interneurons tuning the channels to distinct sets of visual features. The RGCs relay the output of each channel to the brain — understanding how the visual scenery is encoded by the outputs of the approximately 20 RGC types will thus yield a complete picture of the representation of the visual scene available to the brain.

To identify a functional fingerprint for each RGC type in the mouse retina, we use 2P imaging to measure Ca^{++} activity in RGCs evoked by a set of stimuli, including frequency/contrast modulated full-field and white noise stimuli. So far our database contains recordings of over 10,000 cells from the RGC layer. In addition, we obtained recordings from transgenic PV1 mice, in which 8 morphologically distinct RGC types are fluorescently labeled and can be identified based on their anatomy. Moreover, we performed single-cell recordings from a few dozen RGCs to relate their spiking responses to the somatic calcium signals and to compare their morphologies with published RGC catalogues.

We implemented a probabilistic clustering framework for separating RGCs into functional types based on features extracted from their responses to the different visual stimuli using PCA. We used a semi-supervised mixture of Gaussians Clustering algorithm, which allowed us to incorporate the uncertain label information provided by the recordings from the PV1 mice into the clustering. For our data, we obtain 25–29 functional clusters, which separate into 17–21 RGC clusters and 8 displaced amacrine cell (dAC) clusters, as verified using glutamate-decarboxylase (GAD) immunostaining. These numbers match well the number of RGC and dAC types expected in mouse retina. The RGC types include many known cell types (*off* and *on* alpha, W3, *on-off* direction-selective), as verified using our single cell data (*e.g.*, alpha RGCs) and additional information available (*e.g.*, soma size/shape and retinal tiling). In addition, they include new functional RGC types, such as a contrast-suppressed type, not readily matched to previously described ones.

Our results suggest that a functional fingerprint for each RGC in the mouse retina is within reach.

Acknowledgments

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ENCODING OF REACH TO GRASP TRAJECTORIES IN PREMOTOR CORTEX

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Coordinated reaching to grasp, or prehension, is a fundamental primate skill, yet the contribution of premotor cortex to this behavior remains unresolved. Classically, dorsal premotor cortex (PMd) has been implicated with reaching, while ventral premotor cortex (PMv) has been studied primarily in the context of grasping. Recently, however, PMd has been shown to covary with properties of grasping, thus, suggesting that reaching and grasping may not be processed in completely discrete regions of premotor cortex. In this study, we sought to elucidate the contribution of PMd and PMv to coordinated prehension by quantifying which kinematic features best predict neural responses in these two areas.

To this end, we recorded unit spiking and local field potentials from 96 channel electrode arrays implanted in the PMd and PMv of a rhesus macaque while he performed a reach to grasp task. We measured the 3-dimensional position of reflective markers affixed to the dorsolateral aspect of the animal's upper limb, and, from those data, reconstructed the angle of 15 joints in the arm and hand.

We developed encoding models to predict the spiking responses of every neuron in our sample based on intrinsic and extrinsic features. Intrinsic features included the spiking history of a given neuron at various timescales, as well as the spiking history of other neurons. Extrinsic features were joint angles and their derivatives at various lead/lag relationships to the spiking. Mathematically, we used a generalized linear model (GLM) with a log link function to infer the conditional intensity function of each neuron based on the input features. To prevent overfitting, we partitioned the data into separate training and test sets. We quantified the performance of our model on test data by computing the area under the receiver operating characteristic curve (AUC).

We found that the input features we used better predicted the responses of neurons in PMd because, on average, AUC values were higher for PMd neurons. AUC values describe the goodness of fit, however, they do not inform us about which features are important. Specifically, we wanted to compare reaching kinematics and grasping kinematics to see which set better predicted neural responses. To facilitate this comparison, we fit two additional models, one containing only reaching kinematics, and another containing only grasping kinematics. We then computed the difference of deviances between each of these two nested models, and the full model, containing both reaching and grasping kinematics. For a given neuron, if the difference in deviance is large, then the missing terms are highly predictive of spiking. We classified cells into one of two categories, reaching or grasping based on their difference of deviances. We found that in PMd, reach and grasp were represented in roughly equal proportions. In PMv, however, the majority of cells were grasp cells. These preliminary results reject the classical view of a strict dichotomy between reach- and grasp-related activity in PMd and PMv, respectively.

REMOD: A COMPUTATIONAL TOOL FOR REMODELING NEURONAL DENDRITES

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In recent years, several modeling studies have indicated that dendritic morphology is a key determinant of how individual neurons acquire a unique signal processing profile. The highly branched dendritic structure that originates from the cell body, explores the surrounding 3D space in a fractal-like manner, until it reaches a certain amount of complexity. Its shape undergoes significant alterations not only in various neuropathological conditions, but in physiological, too. Yet, despite the profound effect that these alterations can have on neuronal function, the causal relationship between structure and function remains largely elusive. The lack of a systematic approach for remodeling neuronal cells and their dendritic trees is a key limitation that contributes to this problem.

In this context, we developed a computational tool that allows the remodeling of any type of neurons, given a set of exemplar morphologies. The tool is written in Python and provides a simple GUI that guides the user through various options to manipulate selected neuronal morphologies. It provides the ability to load one or more morphology files (.swc or .hoc) and choose specific dendrites to operate one of the following actions: shrink, remove, extend or branch (as shown in Fig. 1). The user retains complete control over the extent of each alteration and if a chosen action is not possible due to pre-existing structural constraints, appropriate warnings are produced. Importantly, the tool can also be used to extract morphology statistics for one or multiple morphologies, including features such as the total dendritic length, path length to the root, branch order, diameter tapering, etc. Finally, an experimental utility enables the user to remodel entire dendritic trees based on preloaded statistics from a database of cell-type specific neuronal morphologies.

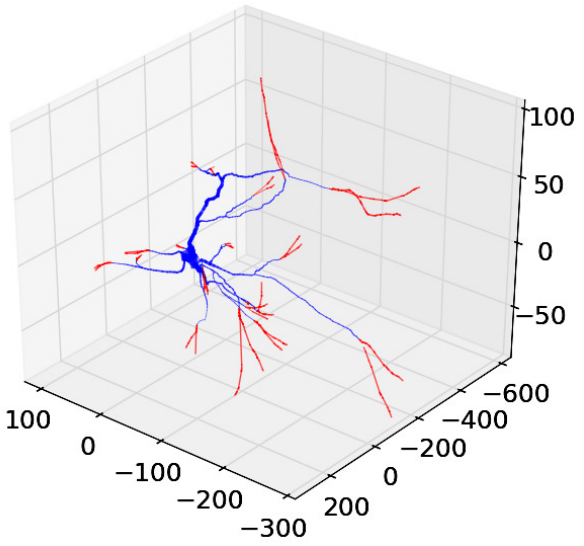

Figure 1. All terminal dendrites are branched and extended by 70% of their initial length.

To our knowledge, this is the first tool that allows (a) the remodeling of existing—as opposed to the *de novo* generation of—neuronal morphologies both ad hoc and based on predefined statistics and (b) the extraction of morphological feature statistics. Thus, REMOD allows the implementation of a systematic approach for altering neuronal morphologies that will promote further research into understanding the hidden associations between critical morphology parameters and the distinct electrophysiological patterns that individual neurons exhibit.

Acknowledgment

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ISOMETRIC MAPPING BETWEEN ENVIRONMENT AND TEMPORAL NEURAL ACTIVITY

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Sensory neural activity mediates all perceptions and must thus provide an efficient representation of the environment. In particular, the firing dynamics of population of neurons has to be such that the central nervous system can recognize the stimulation that elicited it. It has been rightfully argued that one crucial feature of the code is that it must be unambiguous, meaning that two different stimulations should not elicit the same pattern of activity. Such a property indeed allows a recognition of the stimulation provided templates exist. However, given the richness and complexity of the environment, there is in addition a need for a capacity to recognize a continuum of stimulations. It still remains unclear how the decoding task can be carried to the level of an infinite number of such possible stimulations.

Here, using data from human tactile microneurography, we show that, if read out in an efficient way, peripheral activity is unambiguous at the utmost point. We show that properly tuned decoders can capture some geometrical regularities of the input space encoded by primary afferent spiking signals. More precisely, we used a layer of second-order neurons that receive the primary afferent spiking signals as input. We define a neural distance between the outputs of these second-order neurons. Then we run an *ad-hoc* synaptic plasticity algorithm on the synapses between first and second-order neurons with the objective of matching the neural distances with the physical distances between stimuli. We assess this matching with Pearson correlations and manage to obtain values above 0.995, suggesting a very close to isometric mapping between neural activity and the environment.

In addition, we show that by training the second-order neurons with only a subset of the stimulations, they are able to generalize by classifying a previously unseen stimulation accurately. This provides strong evidence that the neural activity can be endowed with a geometry that mimics that of the tactile stimulations and enables the brain to decode features of previously never encountered stimulations. We thus argue here that such a faithful geometric organization may be crucial in order to understand human cognitive abilities such as learning and generalizing, since it shows that a subset of stimulations is sufficient to create a geometric representation of the environment.

Our results also suggest that while first-spike latencies are enough to guarantee maximum information transmission of tactile stimuli, entire primary spike trains constitute a necessary condition to encode isometric input-output mappings, a likely basis for generalization in sensory coding. Thus, spikes gradually shape the representation of the stimulation until a faithful one is attained.

ON HIPPOCAMPAL BASKET CELLS SHOWING BOTH BIPHASIC AND MONOPHASIC PHASE-RESETTING CURVES, AND ITS FUNCTIONAL EFFECT IN GAMMA OSCILLATIONS

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Gamma oscillations are a central feature of hippocampal neural activity. They strongly depend on the activity of fast-spiking inhibitory interneurons: IPSPs are important in controlling the timing and probability of action potential in pyramidal cells. Soma-targeting fast-spiking Basket Cells (BC) play the foremost role in the generation and maintenance of gamma activity.

The study of their Phase-Resetting Curves (PRC) is a fundamental tool for understanding BCs role in network dynamical effects like entrainment to periodical input, phase-locking, coherent oscillations and synchronization. They are obtained by perturbing a spiking neuron with a small depolarizing pulse at different times of its cycle and observing whether the next spike is advanced or delayed as a result. PRCs can be monophasic (the phase is always advanced by the perturbing pulse) or biphasic (allowing for delay or advancement of phase depending on the arrival phase of the perturbation). Since BCs show Hodgkin-Huxley type II excitability, it is generally assumed they would generate PRCs with biphasic shape.

We performed electrophysiological experiments in acute slices of wild type mice and PV-Cre-Tomato mice, a genetically modified variety that allows for the visual identification of cells producing Parvalbumin (intimately associated with the fast-spiking phenotype). Our whole-cell patch clamp recordings in hippocampal CA1 and CA3 regions clearly show that some neurons have monophasic PRCs (14 neurons in wild-type mice, 13 neurons in PV-Cre-Tomato mice) while others show the expected biphasic PRCs (13 neurons in wild-type mice, 11 in PV-Cre-Tomato mice).

We compare both groups in reference to passive and acting membrane (resting membrane potential, input resistance, membrane time constant, spiking threshold, spike width, after-hyperpolarization amplitude and decay time) and spiking pattern features (Frequency-Input current curves, accommodation, jitter). In order to understand the functional implications of the existence of both varieties of BCs, we have developed a computational model of hippocampal networks where we study the synchronic entrainment, maintenance and transmission of gamma oscillations as a result of the PRC characteristics of the interneurons.

INDEPENDENT PHASE CODING GENERATES POPULATION TRAVELING WAVES AND ACCOUNTS FOR CA1 THETA SEQUENCES

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Populations of hippocampal place cells encode an animal's past, current and future position through sequences of action potentials generated within each cycle of the network theta rhythm. These sequential representations have been suggested to result from temporally coordinated synaptic interactions within and between cell assemblies. In contrast, we show that a model based on rate and phase coding in independent neurons, without any requirement for further coordination, is sufficient to explain the organization of CA1 population activity during theta states. CA1 population activity in our model behaves as an evolving traveling wave that exhibits phase coding, rate coding, spike sequences and generates an emergent population theta rhythm. We identify measures of global remapping and intracellular theta dynamics as critical for distinguishing mechanisms for pacemaking and coordination of sequential population activity. We suggest that during theta activity the primary role of CA1 is to generate decorrelated representations of location. During active navigation, these representations provide a highly readable code for downstream cortical areas in spatial memory tasks. Moreover, such representations provide a format for the storage of experienced episodes which are later consolidated into flexible cognitive maps during offline states.

MODULATION OF CORRELATION BY ACTIVITY LEVELS: FROM SYNAPTIC CURRENTS TO SINGLE NEURONS AND POPULATION ACTIVITY

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The analysis of correlations between neural signals is of high importance to study sensory coding as well as information flow in the brain. At the mesoscopic scale, stimulus-dependent firing rate correlations have been proposed to contribute to neural encoding. At a macroscopic scale, the correlation between rhythmic activity in different brain regions is often used to characterize communication and functional connectivity among areas.

However, it remains an open question how changes in correlation between two neural populations reflect purely changes in the functional interactions between these populations, or whether they are mostly determined by changes in the individual properties of the signals. Recently, de la Rocha and colleagues (de la Rocha *et al.*, 2007, *Nature*) showed that, for pairs of neurons receiving common synaptic input, nonlinearities in their transfer function produce a modulation of the spike train output correlation by the firing rates, such that higher correlations occur at higher rates. This correlation-activity modulation determines an intrinsic relation between neural codes based on rates or correlations, and suggests that also at the population scale changes in connectivity are expected to covary with activity.

We here extend these previous results considering other sources of correlation-activity modulation, and examining how this modulation propagates from synaptic inputs to single-neurons rate responses, and to massed neural signals such as local field potentials (LFPs). We show that, already at the level of the synaptic inputs, the single trial variability in currents with a fixed degree of correlation originates a correlation-current strength modulation. We then examine how this correlation-activity modulation is transferred from currents to spike trains in combination with the modulation introduced by the firing nonlinearities. Furthermore, we use a recurrent network of integrate-and-fire neurons that models the connectivity between two brain areas to study how the correlation-activity modulation propagates to population activity. We consider how this modulation is reflected in particular rhythms, evaluating the correlation in a given frequency band and more specifically the degree of phase coherence. We also analyze the correlation-activity modulation for LFPs and multiunit activity recorded from the monkey visual cortex V1 during stimulation with natural movies (Belitski *et al.*, 2008, *J. Neurosci.*).

Our results provide a unified description of different sources of correlation-activity modulation and how this modulation is transferred from synaptic currents to single neurons and to population activity. Furthermore, the characterization of this modulation in terms of the phase coherence at specific rhythms provides an alternative view on the origin of the modulation of power correlation by phase differences, which has been proposed as a mechanism for flexible routing of neural communication (Fries, 2009, *Trends Cogn. Sci.*).

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SCALING OF INFORMATION IN LARGE SENSORY NEURONAL POPULATIONS

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Although we know a lot about how individual neurons in the brain represent the sensory environment, we are far from understanding how neural populations represent sensory information. Because individual neurons are noisy, pooling the activity of many neurons with similar response properties seems necessary to obtain an accurate representation of the sensory environment. However, it is widely believed that shared noise (or, *noise correlations*) in the activity of nearby neurons renders such pooling ineffective, profoundly limiting the accuracy of any population code and, ultimately, behavior. This belief is based on model-based extrapolations from correlations measured in individual pairs of neurons, as it has been impossible to record simultaneously from complete neuronal populations. Here, we use 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 and directly measure the amount of information encoded by these local populations. In contrast to previous predictions, we find that the information in a sensory population increases approximately linearly with population size and does not saturate even for several hundred neurons. Moreover, even a decoder ignoring correlations between neurons can decode 80% of the information in the population. Our results suggest that sensory neural populations represent information in a truly distributed manner and pooling of neural activity within local circuits is much more effective than previously anticipated. Thus, the representation in early sensory areas does not appear to be impaired substantially by shared sensory noise and limitations in behavioral performance in psychophysical tasks may need to be attributed to processes downstream of the sensory population.

COMPETITIVE NEURONAL TURNOVER REDUCES THE DIMENSIONALITY OF THE DENTATE GYRUS POPULATION CODE TO ENHANCE PATTERN SEPARATION

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Numerous studies have revealed a role for neurogenesis in the adult hippocampal dentate gyrus (DG) in behavioral discrimination between similar contexts or objects, referred to as pattern separation. Most adult-born cells die, and many studies demonstrate synaptic competition, suggesting that these cells compete for survival. The DG is also notoriously sparse in its activity. Yet, the computational implications of extreme sparseness, co-localized with neurogenesis has not received significant attention. We therefore evaluate pattern separation in networks with competitive neuronal turnover across varying degrees of sparseness. Our network consists of an input layer (Entorhinal cortex, EC), hidden layer (Dentate Gyrus, DG) and readout (CA3). The readout weights are trained with a pseudoinverse rule to separate two sets of patterns, each set representing two distinct contexts. The input weights are fixed, and drawn at random from a normal distribution. As synaptic competition, DG units with small readout weights are replaced with new units. At each iteration we test the network's performance by introducing noise onto the inputs and determining the generalization error of the readout. Since there are only two contexts, all errors represent failure of separation between the contexts. Our simple turnover rule greatly reduces the generalization error as a function of iterations in a manner that depends upon the fraction of active units (coding level) chosen for the DG. Furthermore, as turnover proceeds, the optimal coding level becomes sparser such that around 4% of units active is the optimal case after sufficient turnover.

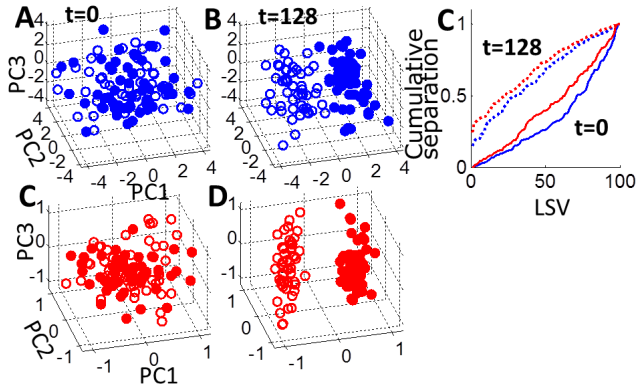

Figure 1. **A-D**: 50% coding in blue, 4% in red. **C**: 50% coding in blue, 4% in red, $t = 0$ solid, $t = 128$ dotted.

We present data demonstrating the optimal rate of neural turnover as it depends upon sparseness and the dynamics of the contexts to be separated. We demonstrate that the signal-to-noise ratio increases with turnover for both dense and sparse cases, but the sparse DG performs better partly because of a resistance to noise that is determined by the greater inherent selectivity of individual DG units. The DG population code is also reorganized in both cases such that clusters emerge and patterns of the same context are grouped together, while those of opposite contexts become separated. The sparse DG more efficiently generates clusters, as can be seen by projections onto the PCs in Fig. 1. At $t = 0$ the two contexts (open and closed circles) are mixed together, but separated after neuronal turnover, $t = 128$. Since the weight vector is a linear sum of the left singular vectors (LSVs) of the DG matrix, we observe the cumulative sum of their coefficients as as a measure of separation explained. In both dense and sparse cases, after neuronal turnover the cumulative separation curve grows more quickly as a function of the most highly weighted LSVs, thus separation is accomplished with a lower dimensional representation. The sparse case (red) is of yet a lower dimensionality. Therefore the superior performance of the sparse DG with neural turnover is a function of inherent selectivity as well as a more efficient reduction in dimensionality of the DG population code.

CHARACTERIZING SPATIALLY ORGANIZED LFP BETA OSCILLATIONS IN THE MACAQUE MOTOR CORTEX

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During states of increased arousal, motor preparation, and postural maintenance, the local field potential (LFP) in primary motor (M1) and premotor (PM) cortex typically exhibits oscillations in the beta (12–40 Hz) range (Kilavik, *et al.*, 2012, *Cereb. Cortex* 22:2148). Even for inter-electrode distances up to several millimeters, beta oscillations recorded on separate electrodes are often highly correlated, but exhibit a non-zero temporal shift. These shifts were shown to find expression as spatial patterns in the form of planar wave propagation along preferred directions across the cortical surface during an instructed-delay reaching task (Rubino, *et al.*, 2006, *Nat. Neurosci.* 9:1549). The average coherence of phase gradients across electrodes, a signature of planar wave propagation, was increased during the early delay, suggesting a behavioral modulation of the probability of observing such wave dynamics. However, in general little has been reported about the spatial patterns of beta oscillations outside epochs that exhibit a clear planar wave. Here, we demonstrate that a variety of additional spatial patterns of LFP beta activity may be distinguished in monkey motor cortex. We recorded massively parallel neuronal activity using a 10-by-10 electrode array (Blackrock Microsystems), which was chronically implanted in M1 and dorsal PM. The monkey was trained in a delayed reach-to-grasp task (Riehle, *et al.*, 2013, *Front. Neural Circuits* 7:48).

In a first step, we identify the beta frequency band which has maximum power during the start, preparatory and holding periods, and calculate the instantaneous phase from the analytic signal of the beta-filtered LFP. To investigate the spatial patterns of the beta oscillations, we estimate the phase gradients by determining the phase shift between each electrode and its 24 nearest neighbors. Visualizing the resulting vector fields in time, we identify qualitatively different activity patterns by eye: (i) planar waves, (ii) quasi-stationary states (all electrodes appear synchronized at near-zero lag), (iii) unstructured states (no spatial structure), and (iv) more complex patterns, including apparent circular and radial propagation. Based on these observations, we introduce measures to detect which pattern (i)–(iii) occurs at each point in time. In a next step, we assess the statistical properties of the patterns, including their duration and average direction, and compare these to previous reports (*e.g.*, a primarily medio-lateral wave direction for planar waves as seen by Rubino and colleagues). Also, at each time point we relate the observed pattern to the instantaneous beta amplitude, which serves as an indicator of spindle activity. Finally, we demonstrate that the occurrence probability of individual patterns is modulated during the behavioral task.

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SURPRISE DECODING IN THE RETINAL ACTIVITY

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A fundamental task of the brain is to make predictions about the future. It has been hypothesized that the brain activity should not only represent the sensory input itself, but also code for how surprising the stimulus is. Experimentally, electroencephalogram recordings from the human brain showed a response to unexpected changes among repeated stimuli. While this signaling of surprise was first measured in the cortex, recent work has shown that the retina might already be involved in surprise detection. However, it remains unclear how the retinal output can be decoded to detect surprising events in a complex visual scene.

Our purpose was to determine whether surprise, classically defined as the log-likelihood of the stimulus, could be decoded from a large population of ganglion cells, the retinal output, while displaying a randomly moving object as a stimulus. We used a new technique based on large and dense multi-electrode arrays to record a large population (approximately 200 cells) of the output neurons of the retina.

We tested two hypotheses to decode surprise from the retinal activity. A first possibility is that the retina does not compute surprise, and the brain itself estimates how frequent the different spiking patterns are, and can then associate the rare responses with surprising events in the stimulus. To test this first hypothesis, we tried to correlate the surprise in the stimulus with the rarity of spiking patterns in the recorded retinal output. This rarity was evaluated with a new model that can easily be implemented by a neural network. However, this method gave poor predictions of the surprise ($R = 0.3$).

A second possibility is that the retina explicitly represents surprise in its activity, so it can be decoded linearly. Testing this second hypothesis, we showed that the retina predicts surprise very well with a linear decoder ($CC = 0.8$). This decoding even worked when the stimulus alternated between different types of motion statistics.

Finally, we showed that the performance of a cell to represent position is largely independent of its performance to represent surprise, suggesting that position and surprise are represented in parallel by overlapping sets of cells, rather than dedicated channels.

For the first time, we have shown that a representation of surprise can be continuously read from a biological neural network, and that this representation is maintained when the motion statistics of the stimulus changed. This early representation of surprise in the retina could be useful to trigger fast reactions to unexpected events.

STATE DEPENDENCE OF NOISE CORRELATIONS IN MACAQUE PRIMARY VISUAL CORTEX

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Shared, trial-to-trial variability in neuronal populations has a strong impact on the accuracy of information processing in the brain. Estimates of the level of such noise correlations are diverse, ranging from 0.01 to 0.4, with little consensus on which factors account for these differences. Here we addressed one important factor that varied across studies, asking how anesthesia affects the population activity structure in macaque primary visual cortex. We found that under opioid anesthesia, activity was dominated by strong coordinated fluctuations on a timescale of 1–2 Hz, which were mostly absent in awake, fixating monkeys. Accounting for these global fluctuations markedly reduced correlations under anesthesia, matching those observed during wakefulness and reconciling earlier studies conducted under anesthesia and in awake animals. Our results show that internal signals, such as brain state transitions under anesthesia, can induce noise correlations, but can also be estimated and accounted for based on neuronal population activity.

SUPRESSION OF CHAOS BY INPUT SPIKE TRAINS IN BALANCED NEURAL NETWORKS

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The prevailing explanation for the irregularity of spike sequences in the cerebral cortex is a dynamic balance of excitatory and inhibitory synaptic inputs — called the balanced state [1]. The dynamics of the balanced state depends strongly on the detailed underlying dynamics of individual neurons [2–4].

Previous studies of the dynamics of the balanced state mostly used a constant external input. We generalized the analysis of Lyapunov spectra, dynamical entropy production and attractor dimension to networks where each neuron receives independent Poissonian input spike trains. An analytical expression for the Jacobian of the flow enables us to calculate the full Lyapunov spectrum. Using a single neuron model in which action potential onset rapidness can be adjusted we solved the dynamics in numerically exact event-based simulations and calculated Lyapunov spectra, dynamical entropy production rate and attractor dimension. We examined different scenarios to study the transition from constant to stochastic input, where we varied Poisson rate and/or Poisson coupling strength, while keeping the firing rate of the driven population fixed. We find a suppression of chaos by input spike trains, extending earlier studies of chaotic rate models to spike neuron models [5–6].

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RIPPLE-TRIGGERED STIMULATION OF THE LOCUS COERULEUS DURING POST-LEARNING SLEEP IMPAIRS MEMORY CONSOLIDATION

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Hippocampal ripples, brief high-frequency (150–200 Hz) oscillations occurring during quiet wakefulness or slow wave sleep (SWS), represent simultaneous discharge of a large neuronal population that is synchronized across the entire hippocampus. Learning experience increases frequency of ripple occurrence, which is predictive of memory recall, while ripple suppression impairs hippocampal-dependent learning. Experience-induced replay of neuronal ensembles occurs predominantly during ripples. These observations support the idea that ripples provide a neurophysiological substrate for *off-line* memory consolidation by facilitating synaptic plasticity within the learning-associated neuronal network. We hypothesized that noradrenaline (NE) release during ripples in subcortical and cortical targets of the Locus Coeruleus (LC) may be beneficial for memory consolidation. Rats implanted with linear electrode arrays for extracellular recording in cortex and hippocampus and a stimulating electrode in LC were trained on a spatial memory task. Neural activity was monitored for 1 h immediately after each learning session. Ripples were detected on-line using a band-pass filtered (150–250 Hz) extracellular voltage signal recorded in the CA1 region of hippocampus by applying a threshold-crossing algorithm. Trains of biphasic electrical pulses (0.4 ms, 0.05 mA) were delivered to LC at each ripple onset. Group 1 received LC stimulation (5 pulses at 20 Hz) that did not produce detectable changes in cortical or hippocampal neural activity. Group 2 received LC stimulation (10–20 pulses at 50–100 Hz) that induced a transient (1–2 s) desynchronization of cortical EEG, during which both thalamocortical sleep spindles and hippocampal ripples were suppressed. Additional control groups included random LC stimulation, stimulation outside of LC, and sham-operated animals.

Ripple-triggered LC stimulation produced a spatial memory deficit exclusively in Group 2 rats, when LC stimulation transiently eliminated sleep spindles and ripples. The behavioral performance of none of the other groups differed from intact animals. We conclude that stimulation-induced discharge of LC neurons and concurrent NE release in the projection targets of LC caused a transient brain state change, which was not favorable for off-line hippocampal-cortical communication underlying consolidation of recent memories. The obtained results challenge the original hypothesis on the ripple-coupled NE release for promoting synaptic plasticity within reactivated neuronal assemblies. Yet, the present results further support our recent discovery of a remarkable dichotomy between ripple-associated cortical activation and deactivation of many subcortical regions including thalamus and brain stem neuromodulatory centers (Logothetis, *et al.*, 2012, *Nature* 491 547–553). Thus, hippocampal ripple events may serve as indicators of a particular brain state that provide low interference for off-line consolidation of the declarative memories. Activation of any competing network during ripples may lead to less efficient consolidation.

ROLES OF CELLULAR ADAPTATION IN MULTI-STAGE SENSORY PROCESSING

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The functional consequences of spike frequency adaptation (SFA) in multi-stage processing of sensory network is unknown. Here, we reveal that the SFA has significant role in emergence of temporal sparse and reliable codes in the higher level of sensory processing. In this study, we introduce a unified description in which a temporally sparse stimulus representation and the transient increase of response reliability emerge naturally. Our approach exploits the functional consequences of spike frequency adaptation (SFA) in sensory processing (see the complete analysis in Farkooi, *et al.*, 2013, *PLoS Comput. Bio.*). First, we show that in a generic mean-field model of the sensory pathway, SFA establishes a fundamental dynamical non-linearity in the neurons' transfer function where the response to the onset of a constant stimulus becomes progressively sparser when transmitted across successive processing stages. The mean firing rate approach is insufficient to determine the reliability of the observed transient responses; therefore, we introduce an adaptive ensemble theory to study the variability of the signal representation across network stages. By employing this population density treatment, it is formally shown that the self-regulation of SFA modulates the average inhibition in the recurrent cortical network. The resulting temporally sparse representation is accompanied by a transient reduction of the trial-by-trial spike count variability (measured by the time-resolved Fano factor), and thus by an increased response reliability. We then extend the theoretical understanding by numerical simulations of a large-scale balanced cortical network model. Finally, we develop our theory further by analyzing the highly structured finite size network model of the insect olfactory pathway. Our results indicate that SFA can explain the experimentally observed temporally sparse stimulus representation in the mushroom body Kenyon cells, independent of inhibitory mechanisms. Take together, our results reveal a generic and biophysical plausible mechanism that can explain the emergence of a reliable and sparse stimulus representation, providing mathematical insight into the principles of sensory processing.

HIGH-RESOLUTION CODING WITH CORRELATED NEURONS: THEORY AND APPLICATION TO DIRECTION-SELECTIVE RETINAL GANGLION CELLS

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While positive noise correlations in the activity of neurons are omnipresent in recordings of neural populations, these were considered in theoretical studies, until recently, as detrimental to coding, or, at best, marginally favorable. However, a few studies in the past years have proposed that correlation can, in fact, significantly enhance the coding performance of a neural population.

Here, we develop a general theory, which demonstrates how noise correlations can be used for the encoding of a continuously varying stimulus. We quantify decoding performance according to the Fisher Information of the different encoding schemes, which yields the Cramer-Rao bound, a lower bound of decoding accuracy.

Two aspects of the problem, which were not appreciated hitherto, are pivotal: first, heterogeneity at the level of the coding properties of neurons (*i.e.* the cell's tuning functions); second, the structure of the noise correlations. We find that these two aspects are not independent: while, *e.g.*, an equidistant spacing of the preferred directions of direction-selective retinal cells is optimal in the uncorrelated case, small positive noise correlations on the same order of magnitude as measured experimentally can favor solutions, where several cells share the same stimulus preference, which strongly increases decoding performance.

We apply our general framework to simultaneously recorded responses of direction-selective retinal ganglion cells (DS cells), measured by means of high-density multi-electrode arrays. DS cells are interesting with respect to stimulus encoding, since they exhibit non-trivial tuning function properties: although the population of DS cells codes for a continuous angular variable, their preferred directions are neither spaced randomly nor equidistantly, but all cells react primarily to one of the four cardinal directions. This strategy is predicted by our theory to be favorable in the presence of small positive noise correlations between cells with different preferred directions.

We compare the performance of these real cells to theoretical constructs of direction coding with small populations of neurons, and we quantify the role of noise correlations in real direction-selective cells.

POPULATION CODE IN MOUSE V1 FACILITATES READ-OUT OF NATURAL SCENES THROUGH INCREASED SPARSENESS

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The neural code is believed to have adapted to the statistical properties of the natural environment. However, the principles that govern the organization of ensemble activity in the visual cortex during natural visual input are unknown. We recorded populations of up to 500 neurons in the mouse primary visual cortex and characterized the structure of their activity, comparing responses to natural movies with those to control stimuli. We found that higher-order correlations in natural scenes induce a sparser code, in which information is encoded by reliable activation of a smaller set of neurons and can be read-out more easily. This computationally advantageous encoding for natural scenes was state-dependent and apparent only in anesthetized and active, awake animals, but not during quiet wakefulness. Our results argue for a functional benefit of sparsification that could be a general principle governing the structure of the population activity throughout cortical microcircuits.

TOWARDS NEUROIMAGING OF CORTICAL LAYERS AND CORTICAL COLUMNS IN THE HUMAN BRAIN WITH ULTRA-HIGH FIELD FMRI

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It is well known that in early sensory areas of the mammalian cortex, small functional cortical patches appear to constitute fundamental units (cortical columns) of brain function that contain thousands of neurons with a similar functional preference. Using ultra high-field (UHF) functional MRI (7 Tesla and beyond), we have now the means to unravel non-invasively such mesoscopic feature representations also in higher human brain areas that allow us to understand representations used by the brain in an unprecedented way. Consider as an example the human face area: we still do not know what features are used within this area to encode faces and how different faces are represented as distributed patterns across face features. If we would be able to unravel the feature basis set, or *alphabet*, in many brain areas, we would contribute substantially to basic neuroscience. Furthermore, the possibility of UHF fMRI to separate signals from different cortical depth levels [1] may provide an indirect approach to differentiate bottom-up and top-down influences by exploiting the generic anatomical knowledge about cortical connection patterns showing that (sensory) input arrives in layer 4 whereas feedback connections target neurons in the deep and superficial layers. I will argue that the achievable mesoscopic level of investigation offered by ultra-high field fMRI provides an important bridge to invasive animal research, especially to optical imaging and electrical neural population recordings. First progress in this direction has been achieved by revealing topographic columnar-level orientation maps in human primary visual cortex [2] and in motion-selective area hMT/V5 [3]. Recently we have also shown that conscious perceptual switches of ambiguous stimuli can be related to dynamic activation changes of specific feature codes in area hMT/V5. Furthermore, we have shown that layer-specific functional connecitivity between visual areas can be revealed by cortical-depth dependent population receptive field (pRF) modeling. Unraveling functional feature representations will, however, require many experiments to test feature candidates since — contrary to early sensory areas — we do not know what features are used in specialized mid-level (visual) human brain areas. To guide experimentation and to simulate how cognitive processes may emerge from candidate feature representations, neural network simulations will play an essential role in future research. If successful, the outlined research program will help to clarify what representational units are used in the visual cortex and how they interact with each other to create more complex cognitive functions.

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TUNING EXCITABILITY AND SYNAPTIC EFFICACY SWITCHES AMONG NETWORK DYNAMICS AND PROCESSING MODES

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Cortical networks perform multiple tasks such as the encoding of current sensory input, the storage, maintenance and retrieval of past experiences in memory. Different cortical states and micro-states, correlating with behavior — and characterized by different EEG patterns — are assumed to be the manifestation of distinct modes of cortical information processing, multiplexed by subcortical modulatory inputs. Various cortical network states, such as the slow oscillation, cortical and hippocampal theta phase-modulated gamma oscillations and hippocampal sharp wave-ripples (SWR), are characterized by recurring low and transiently high activity phases. An important question is whether different activity patterns can be considered within a common framework, and, in particular, how switching between distinct types of dynamics happens in the same anatomical network?

To address this issue, we investigated the network dynamics generated intrinsically in the CA3 region of the mouse hippocampus in an improved submerged slice preparation that allows quick control of the network state by pharmacological manipulation and parallel recording of network and cellular activities. We show that the network generates irregularly recurring sharp wave-ripples in its default state, and quickly and reversibly switches to gamma oscillation as a result of cholinergic receptor activation, that simultaneously affects both cellular excitability (increases) and synaptic transmission (decreases efficacy). We propose that the initiation of the high activity phase requires the simultaneous firing of a critical number of pyramidal neurons to initiate a buildup of activity in the recurrent excitatory network of the CA3 area. When the excitability of pyramidal cells is low, this activity threshold is reached infrequently and stochastically (SWRs); conversely, when excitability is high, the threshold is reached frequently and deterministically (governed by the decay of synaptic inhibition, gamma state). The efficiency of synaptic transmission sets the level and duration of synchrony by controlling the spread of activity in the recurrent network. Cholinergic tuning alters both the incidence and the degree of synchrony of high-activity periods and evokes state transitions. We also built a neuronal network model that reproduced the transition upon modulation of the parameters.

We propose that distinct dynamics support different information processing modes, since the initial state and the synaptic weights of the network must contribute differently to the evolution of activity in the two states. During gamma relatively large amount of initial pyramidal cells initiate buildup, but the recurrent processing phase is short (10–15 ms). During SWRs the buildup of activity is initiated from a small number of neurons, but it lasts for a long while (80–100 ms) including many cycles of recurrent processing. These match the two-stage hypothesis: during gamma the final activity at the peak of the cycle is probably more influenced by the initial active population (external inputs) and less by the recurrent processing (influenced by the imprint of the recent and long past). During SWRs the initial population might have a smaller role, because recurrent processing dominates the outcome of the computation. We plan to image the activity of pyramical cell population and understand how dynamics influences the evolution and interaction of patterns.

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TRANSFORMATION FROM A TEMPORAL CODE TO A RATE CODE

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Odor stimulation evokes complex spatiotemporal activity in the olfactory bulb, suggesting that the identity of activated neurons as well as the timing of their activity convey information about odors. However, whether and how downstream neurons decipher these temporal patterns remains debated. We addressed this question by measuring the spiking activity of downstream neurons while optogenetically stimulating two foci in the olfactory bulb with varying relative timing in mice. We found that the overall spike rates of piriform cortex neurons were sensitive to the relative timing of activation. Posterior piriform cortex neurons showed higher sensitivity to relative input times than neurons in the anterior piriform cortex. In contrast, olfactory bulb neurons rarely showed such sensitivity. Thus, the brain can transform a relative time code in the periphery into a firing-rate-based representation in central brain areas, providing evidence for the relevance of relative time-based code in the olfactory bulb.

KEY FEATURES OF NEURAL VARIABILITY EMERGE FROM SELF-ORGANIZED LEARNING AND INFERENCE

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Spontaneous activity and trial-to-trial variability in neocortical recordings have long been assumed to reflect intrinsic cortical noise. However, it has been shown that spontaneous activity is highly structured [1, 2], contributes to trial-to-trial variability of subsequent evoked sensory responses [3] and predicts subsequent perceptual decisions [4]. Furthermore, it has been demonstrated that variability in neural activity decreases with stimulus onset [5]. These properties can be accounted for by the sampling-hypothesis [6], according to which instantaneous population activity corresponds to samples from a posterior distribution over the represented variables. However, it is still unclear how this hypothesis might be implemented at the level of neural circuit dynamics.

In this study, we demonstrate that many of these phenomena can be accounted for by a self-organizing recurrent neural network model (SORN, [7]). This model combines spike-timing dependent plasticity, intrinsic plasticity and synaptic normalization in a deterministic network of balanced excitatory and inhibitory McCulloch-Pitts neurons. With these plasticity mechanisms, the network adapts to spatio-temporally varying inputs. We find that following learning, the spontaneous activity in this model is highly structured: it replays input states and sequences proportionally to their presentation frequency [1] and outlines the region of possible evoked responses [2].

Next, we train a linear decoder of the network on an inference task and test its performance on ambiguous stimuli. In this setting, we observe sampling-like network dynamics that are conservative approximations of the Bayes-optimal solution. This is due to an appropriate combination of the sensory input with prior knowledge encoded in the learnt network parameters. Within this inference task, we can predict the decisions based on previous spontaneous activity [4]. Also, we can account for trial-to-trial variability with previous spontaneous activity [3] and observe a decrease of the Fano Factor with stimulus onset [5].

In conclusion, we show that key properties of neural variability develop in our model. The simplicity of this model suggests that these correlates of the sampling theory are canonical properties of recurrent networks that learn with a combination of STDP and homeostatic plasticity mechanisms. Together with the sampling-like inference that we observe in this model, this further suggests that sampling-based learning and inference could develop through the interaction of multiple plasticity mechanisms.

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NEURAL CIRCUITS OF THREE-LAYERED CORTEX

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Cortical circuits transform sensory inputs through synaptic interactions. The nature of these transformations depends on the participating circuit elements, the inter-circuit connectivity, and the plasticity that regulate the strength of interactions over time. Yet, despite decades of research on primary sensory cortices a coherent framework of cortical circuit function remains elusive. At the moment, studying the active processing in sensory cortices is limited to the level of single neurons (using intra- and extracellular recordings) or multiple neurons drawn randomly from neural networks (using extracellular recordings or imaging methods). However, our definition of neural circuits and our understanding of how they transform sensory information will ultimately build upon their connectivity. The relatively simple architecture of the reptilian three-layered cortex (and its close evolutionary links to the common ancestor of both mammals and sauropsids) offers unique advantages to decipher basic computations of cortical circuits. That is, turtle cortex consists of only one layer of densely packed excitatory pyramidal neurons (L2), while inhibitory interneurons can be found in all 3 layers. In addition, due to resistance to anoxia, *in vitro* preparations of the turtle brain remain vital and spontaneously active for several days after tissue extraction. Here, we report preliminary results on components, connectivity and plasticity of intact circuits of the turtle visual cortex.

We combine multi-neuron patch-clamp recordings (6–8 simultaneous whole-cell recordings) with large-scale extracellular recordings from tens to hundreds of neurons simultaneously to estimate neuron-type-specific local connectivity and slab-wide functional connectivity of the intact cortical network, respectively. First, we establish that local circuits ($\leq$ 200µm) in three-layered cortex are highly interconnected. High connection probabilities (p_c) of excitatory (E) and inhibitory (I) neurons ($p_{c(EI)}$ and $p_{c(IE)}$ around 0.65) rationalize an observed abundance of disynaptic inhibitory circuits ($p_{(IE|EI)}$ = 0.42). Strong and plastic E to I synapses further endow excitatory neurons with variable control over postsynaptic spiking activity. Combined intra- and extracellular recordings from L1 interneurons and the somatic layer, respectively, confirm integration of excitatory and inhibitory inputs over large cortical areas. Furthermore, a subset of L1 interneurons exhibits activity bursts with inter-spike-intervals of around 50 ms. In future experiments we hope to shed light on the temporal correspondence of L1 interneuron activity with prominent spontaneous and sensory-evoked local field potential oscillations in the 15–25 Hz band.

SPECIALISATION IN POPULATIONS OF NEURONAL FEATURE DETECTORS

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Many neurons in sensory pathways respond selectively to a narrow class of stimuli such as faces or specific communication calls. However, neural processing is also robust to a large degree of natural variablity within such complex stimulus classes. For instance, neural circuits that underly speech processing must tolerate substantial spectral differences between female and male vocalizations. It is commonly believed that such difficult perceptual invariances are realized by populations of *expert* neurons that specialize on different substructures within a sensory object category. However, it is unclear what neural mechanisms of learning can subserve such symmetry breaking within populations of sensory neurons.

The emergence and utilization of specialized learners to improve classification performance has also challenged Machine Learning for many decades. One important state of the art ensemble method for neural populations is the Mixture-of-Experts model that induces specialization of expert units via gating neurons that weight the responses of individual experts. However, due to its reliance on complex neural interactions and internal state variables, biologically plausible implementations of this model have remained challenging.

Here we show that symmetry breaking and specialization within populations of spiking neurons can emerge through a simple instantiation of a competitive population learning rule. To mimic a sensory classification task we simulate a population of sensory neurons and require the number of responding neurons to discriminate between target and null stimuli (Fig. 1). Following error trials, our learning rule uses relative spike-timing within the population (false positives) and locally available values of depolarization (misses) to select only a subset of neurons to undergo learning while the others remain unchanged.

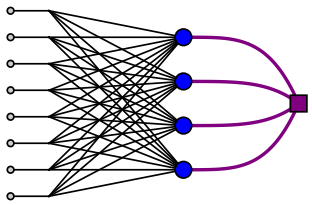

Figure 1. Network architecture; the readout neuron utilizes a number of active neurons.

We implement this algorithm within populations of integrate-and-fire neurons and demonstrate its high performance in spike pattern classification and speech recognition problems. Weak spike-timing based neural competition during learning is sufficient for neural populations to uncover structure within their input activity and induce specialisation (Fig. 2).

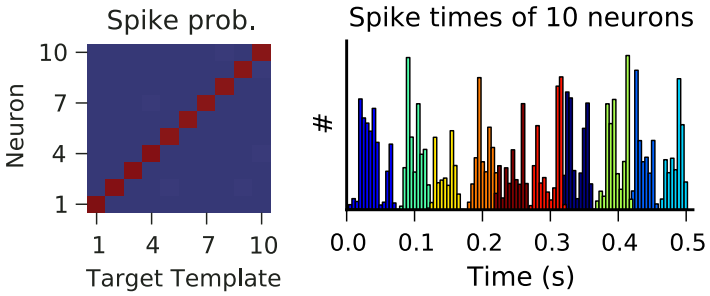

Figure 2. Discriminating a target class composed of k random latency templates from noise random latency patterns. The neuronal population assigns a sample to the target class, if at least one neuron fires. **Left**: For the same number of neurons as templates, the neurons specialize to fire for exactly one template. Shown are spike probabilities (red, $p \geq 99\%$; blue, $p \leq 0.6\%$) after training for each neuron (x-axis) and each target template (y-axis). **Right**: Training several neurons to detect one single difficult template results in specialisation based on output spike timing. Shown are histograms of 10 neurons (color coded).

THE ENCODING OF DECISION CONFIDENCE IN NEURAL POPULATIONS

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Decision confidence, the subjective probability of the correctness of a decision, is an important window on metacognitive monitoring processes. Nonetheless the neural mechanisms underlying confidence construction are still elusive. Two distinct experimental paradigms allow to measure confidence without verbal ratings: post-decision wagering and uncertain option. In the first, after the decision, subjects bet on the outcome of their choice according to their confidence. In the latter subjects are given the choice in each trial between performing a decision-making task, which could lead to a reward if the answer is correct, and selecting a sure but less valuable reward. Kepecs and colleagues [1] showed that neurons in the orbitofrontal cortex of rats encode decision confidence. In a recent report [2] we explained their data as a two stage process where a confidence signal, implicitly encoded in decision neurons is fed to a second network and biases the second confidence related decision. In that work we proposed that the confidence is encoded in the sum of firing rates of decision neurons. Latterly a notable evidence has been made available by recording neural activity in lateral intraparietal cortex of monkeys performing an uncertain option task [3]. We propose a biophysically detailed multiple choice attractor network model, where the confidence emerges from the stochastic dynamics of decision neurons, making unnecessary a separated monitoring network. The model explains the behavioral and neural data recorded in LIP as the result of the multistable dynamics of the attractors network and produces several testable predictions. We found that the confidence is encoded in a nonlinear distance measure between the activity of neural ensembles selective for different options (similar to what proposed by race/diffusion models of confidence [4]). Furthermore we make several experimental predictions, which allow to confirm (or falsify) the model with new experiments and to elucidate some aspects of confidence processing. For example we show that the model is able to trade performance for a less risky behavior and this turns into the testable prediction that confidence, reported through the uncertain option, would change if a more risk-seeking behavior is promoted. This work together with our previous model [2] suggests that decision confidence can be encoded differently by neural ensembles in different context and thereby points to reconsider the concept of confidence as an aggregate of heterogeneous processing schemes aimed at the prediction of the correctness of a decision.

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SCALE INVARIANT MOVEMENT ENCODING

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How does the motor system encode our incredibly diverse motor repertoire in an efficient manner? One possible way of efficiently encoding a variety of movements is to represent them according to their shape/trajectory and regardless of their size, using neural populations that are invariant across scale. To test this hypothesis, we asked subjects to write three different letters at two different scales without any visual feedback, while we recorded their brain activity with fMRI and their movement kinematics using a touch screen. Using multi-voxel pattern analysis, we found that writing each letter generated a letter-selective voxel-by-voxel response pattern which was similar across small and large scales, such that it was possible to accurately identify an executed letter from its corresponding response pattern regardless of its scale. This scale invariance was robustly apparent only in the primary motor cortex (M1) and in the anterior intraparietal sulcus (aIPS) across classification and correlation analyses in predefined ROIs as well as when performing an unrestricted searchlight analysis throughout the entire cortex. We interpret these results as strong evidence for the existence of distributed neural populations in M1 and aIPS that encode letter-writing movements in a scale-invariant manner. We hypothesize that these findings are not limited to handwriting movements and suggest that efficient motor control is achieved in part through the use of scale-invariant neural populations. To further test this hypothesis, we are currently studying scribbling movements of non-human primates and the corresponding recorded neuronal activation. Using machine learning classification methods we are attempting to identify whether similar movement segments are uniquely defined by the underlying neuronal activation patterns in a scale invariant manner. common problems, use this file as a template.

POSITIONAL MODULATIONS IN MOUSE PRIMARY VISUAL CORTEX

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Spatial navigation relies on the integration of different sensory inputs into a coherent neuronal representation of the environment. This process, thought to take place in the hippocampal formation, has been mostly studied bottom-up. Recent studies, however, demonstrated that neuronal responses in mouse primary visual cortex (V1) are not only driven by visual stimuli alone, but also are modulated by other nonvisual inputs [1–3].

We asked whether spatial activity in hippocampus can exert top-down control over V1 population activity. By using a well-controlled, head-fixed treadmill assay, we trained mice to run along a linear track endowed with tactile cues, and to stop for a water reward at a fixed position on the track. We then performed acute electrophysiological recordings in dorsal CA1 and V1 simultaneously and chronic 2-photon imaging of genetically encoded calcium indicators in V1 during this task.

Within 2 weeks the animals showed stereotyped locomotion behavior and ran up to 60 laps per session, allowing the delivery of 240 identical sensory stimuli per session in a position-locked manner. Consistent with previous studies, CA1 units showed stable place fields covering the entire treadmill belt [4]. As previously reported, V1 responses showed LFP and single unit activity that were strongly correlated with running. Surprisingly, however, individual V1 neurons showed specific and diverse position-related response modulations that were stable within recording sessions. Moreover, a subset of these neurons showed stable response modulations across days to weeks. This positional tuning could not be explained by locomotion, eye position, somatosensory inputs, or visual adaptation. Additionally, V1 neurons exhibited reward-suppressed modulations, which were not explained by task-relevant variables.

In conclusion, V1 population responses show specific, rich, and diverse spatial tuning, potentially reflecting top-down control from the hippocampal formation.

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ON-LINE OPTICAL OPERANT CONDITIONING OF CORTICAL ACTIVITY

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Animals can learn to modify their voluntary behavior to gain rewards in the positive reinforcement form of operant conditioning. It has been shown that animals can also learn to modify neuronal activity that is directly rewarded by using electrophysiological recordings. Electrophysiological approaches exhibit excellent temporal resolution, but do not permit recordings from the same identified neurons in dense local circuits over multiple days. Two-photon population calcium imaging makes it possible to observe the activity of the same population of identified neurons in behaving animals over long time periods. Here we introduce a platform to analyze calcium imaging data on-line and feed this neuronal activity back to behaving animals. We have used this approach to investigate how animals modify population activity during operant conditioning. We transfected neurons with adeno-associated virus encoding for the genetically encoded calcium indicator GCaMP6s. While performing calcium imaging, spiking events in multiple neurons could be inferred. Rewards were given to animals in response to inferred events. We found that single neurons in layer 2/3 of motor cortex could be trained to increase activity in a specific manner, and that this increase primes operant conditioning of the same neurons over subsequent days. By identifying the neurons that trigger operant conditioning, the approach we have introduced should be useful for localizing plastic changes and determining the parameters that lead to these plastic changes in the dynamics of neuronal populations during learning. This approach may also provide a framework for training optically based brain-machine interfaces.

ANALYSING A LARGE NEURAL POPULATION CONCURRENTLY IN SPACE AND TIME THROUGH NON-NEGATIVE MATRIX FACTORIZATION

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The foremost challenge when trying to link the neuronal activity at the single cell level to larger scale effects observed in a neuroimaging experiment is to understand how information is processed in a large neural population. Potentially, a neural population may encode information in the temporal dimension using temporal firing patterns and in the spatial dimension using interactions between neurons. Although it is currently possible to record from many hundreds of neurons in a single recording, not many methods exist to extract salient spatial and temporal patterns concurrently from a large population. We are investigating the feasibility of a space-by-time decomposition implemented using sample-based non-negative matrix tri-factorization (sNM3F) [1] for this purpose. We refer to this method as space-by-time NMF (ST-NMF). ST-NMF decomposes the full spatiotemporal dataset into three factors; a set of temporal modules containing the temporal activity patterns in the data, a set of spatial modules consisting of groups of neurons that fire together in fixed proportions and a coefficient matrix that indicates for each trial the strength of activation of each temporal activity pattern by each spatial group of neurons.

We applied ST-NMF on the spiking activity of a population of 85 neurons recorded simultaneously from the auditory cortex of an anesthetized rat to two stimuli sets; 18 tones between 2–32 KHz played at 30 dB and 60 dB sound pressure levels and 5 click sequences between 4–64 Hz. In our preliminary results, the extracted temporal modules matched the physiological activity patterns in the data. Spatial modules contained groups of neurons that had similar activation profiles across stimuli. The coefficient matrix contained a single-trial reduced dimensional representation of the spatiotemporal activity of the population. We used the coefficient matrix to decode the stimulus of each trial. By calculating the mutual information between the actual and the predicted stimuli, we found that for tones, the spatial dimension was the key contributor for encoding information in the population, while for clicks, the temporal dimension was the foremost contributor. These findings suggest that ST-NMF can effectively identify how spatial and temporal patterns of neural activity encode information, and can therefore become a crucial methodology for the study of large scale population coding.

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CODING AND DECODING FROM NEURAL POPULATIONS REPRESENTING MULTIPLE STIMULI

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Most theoretical neural decoding studies assume populations of neurons tuned to single stimuli, such as grating orientation or motion direction. For such stimuli, maximum likelihood decoding in particular has been shown to be a robust and in many cases optimal decoder. However, in reality neurons are rarely affected by a single stimulus alone, and experience a wide range of contextual effects when more complex stimuli are presented. They thus code for more than just one stimulus. Here we consider the influence of this on the maximum likelihood decoder.

First, we consider how a center and surround grating pair are encoded in a primary visual cortex population. It is well known that surround gratings strongly modulate neuronal responses to the center. Furthermore, a recent study showed that the modulation is center-dependent for many neurons, being strongest when the center and surround are co-aligned, regardless of a neuron's preferred orientation (Shushruth*et al.*, 2012). We set up two simple phenomenological population models implementing these features, one center dependent and one center independent. We then decode the center and surround orientations using a maximum likelihood decoder. Although the decoder has no bias in the absence of noise, in the presence of noise we find that (i) there is always a strong bias in the surround estimation, (ii) there is a strong bias in the center estimation for the center independent model, and (iii) there is no bias in the center estimation for the center dependent model.

Secondly, we study how to decode the orientations of two superimposed gratings. Although not fully understood, the responses to two superimposed stimuli do not seem to combine additively. Rather, the response to simultaneous presentation of both stimuli equals either the maximum of the two individual stimulus responses (*e.g.*, in V1, Lampl *et al.*, 2004), or a mean response (*e.g.*, two motion directions in MT, Van Wezel *et al.*, 1996). We again set up two simple phenomenological models implementing these features, and tried to decode both presented orientations. When the neurons respond up to a maximum, the decoder is mostly unbiased. However, for the mean response the decoder is not able to accurately estimate either stimulus, experiencing a bias dependent on the orientation difference.

In conclusion, we show that in the presence of noise a maximum likelihood decoder portrays significant biases for both center-surround and plaid stimuli. Thus decoding slightly more complicated stimuli from even relatively simple models is non-trivial. In the case of V1 coding, center dependent surround modulation allows for unbiased decoding of the center stimulus, which suggests a functional reason for the observed surround tuning.

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LATERAL GENICULATE NUCLEUS (LGN) ENCODING OF NATURALISTIC STIMULI

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The lateral geniculate nucleus of the thalamus (LGN) is a structure along the early visual pathway that communicates visual information from the retina to the primary visual cortex. The receptive fields (RFs) of many LGN cells can be accurately described by the well-known linear difference-of-Gaussians model that subtracts stimulus activity in the surround region of the RF from the center region, combined with more recently-described nonlinear components such as adaptation to local luminance and contrast. Despite decades of investigation in the visual thalamus in a variety of preparations, however, LGN encoding in awake, behaving primates in natural contexts has gone largely unexamined (Jeffries, Killian, Pezaris, 2014, *J. Physiol. Paris* 108(1):3–10). In addition, the vast majority of recordings have been performed one cell at a time, making inter-neuronal influences difficult to elucidate.

To update our understanding of the early visual system, we aim to produce a novel functional atlas of the LGN using simultaneous recordings in awake, behaving primates. The LGN may be optimized to encode natural scene statistics (Tan and Yao, 2009), suggesting that naturalistic stimuli may be efficient for such mapping experiments. Recent work on modeling the RFs of cat LGN neurons has demonstrated that a model that includes linear RFs and fast adaptation to local luminance and contrast can predict responses to arbitrary stimuli reasonably well (Mante *et al.*, 2008). Preliminary tests of this model in our laboratory have demonstrated that natural noise stimuli are capable of driving simulated LGN neurons over a wider response range than Gaussian noise stimuli (Fig. 1). Furthermore, stimulus-driven response variance and mutual information between stimulus and response could be optimized by varying parameters of the spatial power spectra.

These results suggest that naturalistic noise will enable efficient mapping of a broad scope of properties in individual LGN neurons, and when combined with multi-electrode array recordings, will allow investigation of LGN ensemble coding including intra-LGN interactions.

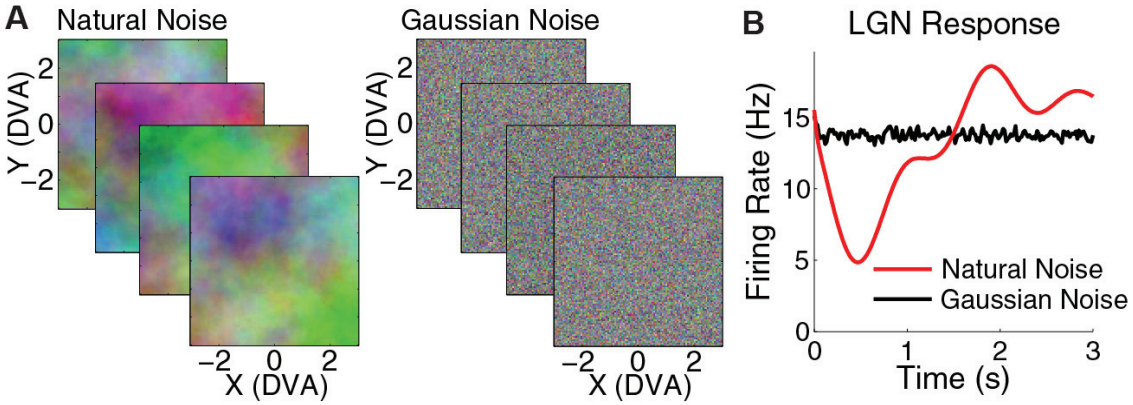

Figure 1. Modeled response of an LGN neuron to different stimuli. **A**: Four frames of a natural noise movie (left) that has the spectral power of natural scenes but lacks structured phase information, and four frames of a matched Gaussian noise movie (right). **B**: The response of a simulated LGN neuron to the same movies. Natural noise evokes responses at a wider range of firing rates than Gaussian noise, and thus may be more efficient for mapping RFs.

NEURONAL INTERACTIONS AFTER TRANSCORTICAL AND TRANSPINAL STIMULATION IN HUMANS

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Synchronized arrival of neuronal signals from the periphery and cortex has been associated with neuronal plasticity and motor learning. The main objective of this study was to establish neuronal interactions following excitation of descending motor axons from the primary motor cortex (M1) and spinal neuronal circuits. For this, we utilized transcranial magnetic stimulation (TMS) and transcutaneous electric stimulation of the spine (tsESS) in 15 healthy humans while seated semi-prone. TMS was delivered below or above the resting motor evoked potential (MEP) threshold, while tsESS was delivered at transpinal evoked potential (TEP) threshold. These stimulations were delivered either alone or in combination at different interstimulus intervals ranging from -50 to +50 ms. Experiments were conducted following institutional review approval and the written consent of all participants consistent to the procedures outlined in the Declaration of Helsinki.

The use of tsESS induced a biphasic excitability pattern of MEPs recorded from the distal ankle muscles of the right leg (contralateral to MI being stimulated). Specifically, at the negative interstimulus intervals (ranging from -20 to -4 ms), a significant depression of MEPs were noted in both ankle flexors and extensors. This was followed by a non significant effect at the interstimulus interval of 0 ms, and potentiation of MEPs at positive interstimulus intervals. These findings suggest that (i) cortical descending motor volleys can either be potentiated or depressed based on the time that cortical and spinal signals meet at the spinal cord level, and (ii) MEPs and TEPs likely share common neuronal pathways.

Direct monosynaptic corticospinal actions on spinal alpha motoneurons are absent when TMS is delivered at intensity that MEPs are not evoked. Subthreshold TMS facilitated the TEPs recorded bilaterally from thigh, knee, and ankle muscles following tsESS. This facilitation occurred mostly at negative interstimulus intervals, *i.e.*, when TMS was delivered after the tsESS. In contrast, when TMS was delivered above MEP resting threshold, facilitation was present at both negative and positive interstimulus intervals depending on the muscle and side (ipsilateral or contralateral to the M1 being activated) from which TEPs were recorded.

These findings constitute the first evidence that synchronized neuronal signals from the primary motor cortex and spine can potentiate corticospinal and spinal motor output. These findings together with the postulated suppressed spinal reflex excitability following tsESS open new avenues to induce neuromodulation and neuroplasticity in neurologically impaired patients, in whom spinal reflex excitability is increased and corticospinal drive is reduced.

INDEPENDENT REPRESENTATION OF TASK PARAMETERS IN HIGHER CORTICAL AREAS

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Modern experimental techniques allow to record the activity of hundreds or even thousands of neurons simultaneously. Despite these advances, most experimental studies still focus on single-cell responses thereby neglecting much of the distributed information encoded in the population response. This problem is particularly severe in higher order areas such as the prefrontal cortex, where single-cell responses can display a baffling heterogeneity and mixed selectivity, even if animals are carrying out rather simple tasks. The standard approach to analyzing population activity is by performing principal component analysis (PCA), but its outcome is often hard to interpret.

We developed a novel method called non-orthogonal demixed PCA (dPCA) that enhances the sensitivity of PCA in order to discover and highlight the most interesting (for the researcher) features of the data. In particular, and unlike standard PCA, dPCA takes into account labels of each data-point. In case of neural recordings, such labels are various trial conditions, *e.g.*, presented stimulus and decision of the animal. As a result, demixed principal components depend only on stimulus or only on decision, reflecting neural tuning to these parameters and making the components easy to interpret.

Here we used dPCA to analyze the population activity in four different neural datasets, comprising different animals (rats and monkeys), different higher cortical areas (prefrontal cortex, PFC, and orbitofrontal cortex, OFC) and different experimental tasks (tactile discrimination, odour discrimination, working memory task). Our analysis reveals that the population response in higher cortical areas reliably encodes behaviourally relevant task parameters (such as stimulus, decision, reward, level of confidence, or passage of time) in completely independent subspaces.

Our method presents experimentalists with a powerful and easy-to-use data analysis tool that provides a concise way of data visualization, allowing to summarize the most relevant features of the neural responses in a single plot. Indeed, in all four datasets analyzed here, we show that dPCA components *automatically* capture and visualize all the main findings that have been previously reported with these data, ranging from memory representation in PFC during delay periods to confidence coding in OFC during reward anticipation periods. Moreover, in several cases dPCA discovers some inconspicuous features of the data that remained unnoticed with more conventional analysis (*e.g.*, odour coding in the OFC during the reward anticipation period and after the reward delivery).

GENERALISABILITY OF UPPER-LIMB MUSCLE ACTIVITY DECODING USING LOCAL FIELD POTENTIALS

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The ultimate goal of brain-machine interfaces (BMIs) for motor rehabilitation is to enable patients suffering from movement impairment to interact with the world physically, for example by controlling computer and robotic interfaces, or by restoring movement of the native limb through neurally-driven functional electrical stimulation (FES) of muscles. Spiking-activity (SA) of cortical neurons has long been used as the source signal for BMIs. Recently, motor cortical local field potentials (LFPs) have been proposed as a promising alternative, due to a number of technical advantages they offer over SA (*e.g.*, higher longevity, lower sampling rates). It has been shown that LFPs can be used to decode muscle activity as well as the kinematics (*i.e.* position and velocity) of arm movement.

We implanted intracortical microelectrode arrays in the right primary (M1) and ventral premotor (PMv) cortices of a rhesus macaque, and implanted subcutaneous electrodes in 7 forearm and hand muscles of the left forelimb. We recorded LFP and electromyogram (EMG) activity under two radically different behavioural scenarios: (i) a 2D centre-out isometric wrist torque task and (ii) naturalistic reach and grasp free behaviour.

We extracted temporal and spectral information from the LFP signals in five non-overlapping frequency bands in the range 0–300 Hz. We then used a linear model, namely the Wiener filter, to decode EMG activity from LFP features. We compared within- and across-task decoding and found that, although decoding performance degraded in the latter case, it was still well above chance levels. The average decoding performance, assessed by using the coefficient of determination (R^2) between measured and reconstructed signals, was $R^2 = 0.51 \pm 0.16$ and 0.34 ± 0.16 for within- and across-task decoding, respectively.

Moving from laboratory experiments towards clinically viable solutions, would require that movement-related decoders generalise well under different behavioural conditions. Here, we demonstrate that a simple linear LFP-based muscle activity decoder can generalise reasonably well across two different behaviours. We consider the implications of our findings to be of particular importance for real-life prosthetic applications.

Acknowledgments

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TRANSSACCADIC ATTENTION SHIFTS AND REMAPPING IN AREA MT OF THE MACAQUE

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It is known that some neurons in the lateral intraparietal area (LIP), frontal eye field (FEF), superior colliculus (SC) and in the ventral stream (areas V3a, V3 and V2) respond perisaccadically as long a visual stimulus could be anticipated in their receptive fields (RFs) after the saccade: this is true even if the stimulus disappears just before the saccade so that no stimulus ever appears in their visual RF before or after the saccade. Recent psychophysical studies have led to the proposal that transsaccadic remapping represents the shift of an attentional pointer on a retinotopic map (Cavanagh *et al.*, 2010, *Trends Cogn. Sci.*. 14(4):147–153) and linked these transsaccadic shifts of attention to the perception of a stable visual world despite frequent saccades.

To explore the dynamics of transsaccadic remapping in a neuronal population, we trained a monkey to perform an attentionally demanding task on one of two moving random dot patterns (RDPs) and make a saccade when cued to do so. We recorded from neurons in area MT, an important locus in the dorsal stream that is strongly interconnected with LIP while the monkey performed this task. Either the attended or the unattended RDP appeared in the post-saccadic RF of the neurons on every trial. On half the trials, the moving patches disappeared just before the saccade so that no stimulus ever appeared in the neurons' RF: we find that the MT neuronal population showed a statistically significant postsaccadic response if the attended RDP was in the postsaccadic RF before the saccade. This *memory trace* response was 36 % larger than when the unattended RDP was in the postsaccadic RF before the saccade, which in turn was not significantly different from the control condition where the monkey only made a saccade with no RDPs present during the trial. Importantly, the effects of top-down attention manifest within 100 ms of saccade offset in the MT neuronal population we recorded from, both when the motion stimulus was brought into the neuron's RF by the saccade (the classical response) and when the motion stimulus was extinguished before the saccade (the remapped response). Motion direction had the expected strong influence on the classical response, but did not significantly influence the remapped response or its modulation by attention. Consistent with recent findings (Ong, Bisley, 2011, *J. Neurosci.* 31(29):10432–6), we did not find a response preceding the saccade (or *anticipatory remapping*) in MT.

In a second experiment, we recorded the activity of MT neurons in two monkeys during a task that required them to make a saccade while maintaining attention on one of four moving RDPs. By placing the attended RDP either in the presaccadic or postsaccadic RF (or outside both of them), we were able to investigate the time course of attention modulation on neuronal activity when the target was brought into or moved out of the neuron RF by a saccade. We find that attentional enhancement of neuronal activity emerges within about 60 ms after saccade offset when the attended stimulus enters the RF after the saccade. Similarly, attentional enhancement of neuronal activity disappears about 100 ms after saccade offset when the attended stimulus moves out of the RF due to the saccade. Taken together, the observed patterns of neuronal activity are consistent with a rapid shift of the top-down attentional locus in MT's retinotopic map across saccades and support the view that transsaccadic remapping reflects the shift of an attentional pointer across the saccade.

CHANGES IN PREFRONTAL MICROCIRCUIT ORGANIZATION INCREASE REPETITIVE NETWORK ACTIVITY IN TWO MODELS OF AUTISM

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Pathological changes in neocortical microcircuits are believed to instigate neuropsychiatric disorders including autism, but measuring such circuit-level changes remains challenging. Deficits associated with disorders such as autism often extend across multiple cognitive, behavioral, sensory, and affective modalities, suggesting that these diseases may comprise common information processing phenotypes at the level of neuronal networks. Such network-level phenotypes might be missed by studies of individual cells and instead require studies of datasets that probe patterns of network activity. Furthermore, disorders such as autism often have many causes; thus a major challenge is identifying common mechanisms that are conserved across multiple disease models and represent putative neural substrates for key behavioral and cognitive deficits.

Here, we introduce novel methods for interrogating cortical circuits and find possible microcircuit endophenotypes associated with autism. Specifically, we use single photon GCaMP imaging to measure patterns of activity generated by isolated prefrontal circuits in two etiologically distinct mouse models of autism: FMR1 knockout (KO) mice and mice exposed to valproic acid (VPA) *in utero*. In both models, we find enhanced functional interactions between prefrontal neurons in the form of increased first order and higher order correlations and an increase in repetitive patterns of network activity that could plausibly contribute to perseveration and stereotyped behavior. Notably, these changes occur despite the absence of increased network excitability. Furthermore, these changes do not occur in mice which model schizophrenia (DISC1 mutant mice), nor in mice that have undergone chronic treatment with Fluoxetine, an SSRI which may ameliorate symptoms of autism. This suggests that the changes observed in VPA-exposed and FMR1 KO mice may be specifically associated with prefrontal microcircuit dynamics in models of autism.

Finally, we addressed whether the increases in strong correlation drives the observed increase in repetitive patterns of activity. We generated surrogate datasets that maintained the temporal pattern and total amount of network activity, but selectively altered the correlation matrix. We created surrogate datasets using an iterative algorithm that reassigns the neuron associated with each epoch of activity to achieve a target correlation matrix. This can produce surrogate datasets with identical levels of activity and similar correlation distributions, but with arbitrary higher order correlations. This enables us to fit control datasets to FMR1 or VPA correlation distributions and vice versa to causally test the effects of changes in correlations. Using this method, we find that the increase in strong correlations drives the increases in repetitive patterns of network activity, and that simply scaling up pairwise correlations in the absence of higher order correlations (*e.g.*, clustering) fails to reproduce this effect. Thus, in these autism models, both the strength and the clustering of correlations drive an increase in the stereotypy of PFC network activity.

Here we show a novel approach for studying prefrontal microcircuit dynamics and a potential application to psychiatric disease. The approach outlined above may represent a powerful tool for disentangling how network structure and activity statistics each contribute to patterns of network activity. Studies of this sort could provide a foundation for understanding common phenotypes at the level of circuits and thus inform circuit-level remedies for autism and other neuropsychiatric diseases.

OVERWRITING OF MEMORIES VIA HIPPOCAMPAL RECURRENT PLASTICITY

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Fast hippocampal activity sequences have been hypothesized to underlie memory consolidation. On the cellular level, the associated re-encoding of episodic memories can either occur at the synapses between hippocampus and neocortex or within the hippocampus itself. So far, hypotheses for hippocampus-intrinsic consolidation have focused on synaptic mechanisms. We propose a mechanistic model of memory re-encoding on the circuit level whereby assemblies are reduced in size to utilize the hippocampal resources more efficiently. Sparsification of the hippocampal code may be an important intermediate step to prepare consolidation of memories in the hippocampal-neocortical loop, since generally storage capacity increases with sparseness.

Our main hypothesis is that new memories are encoded by assemblies that are not optimally sparse. During sequence replay, active cells that receive excessive synaptic input send a retrosynaptic long-term depression (LTD) signal to all presynaptic cells that were active in the previous time step. Such a learning rule allows the network to self-organize such that these assemblies move towards an optimal level of sparseness. This plasticity mechanism operates on a time scale that is slower than the fast time scale of initial imprinting.

Adding new associations increases the network connectivity, up to a point at which memories can no longer be retrieved. Retrosynaptic LTD makes it possible to integrate new associations into the network without reaching this overloaded state, and therefore provides a possible basis for online learning, *i.e.*, the ongoing storage of new memories. Our simulations show that the proposed retroaxonal spread of depression keeps the network in a robust dynamical steady state, allowing the network to operate in an online mode where old memories are gradually overwritten by new ones.

HIPPOCAMPAL PLACE CELL ENSEMBLES ENCODE TOPOLOGICAL FEATURES ROBUSTLY BY TEMPORAL PATTERNS OF COACTIVE UNITS

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The hippocampus encodes spatial information. The location-specific firing of each individual place cell is not particularly informative, however, significant spatial information can be calculated based on the firing information of an ensemble of place cells. It is often speculated that the hippocampal place cells encode a cognitive map based on geometric features of the environment, such as lengths and angles. We propose an alternative mechanism of spatial representation that depends on the topology of the environment. We consider place cells as fundamental components of a simplicial complex. A simplicial complex is a graphical representation of nodes interconnected by links. We represent each place cell as a node, or vertex. The simultaneous activity of two cells is represented by a line segment linking the two vertices. The resulting simplicial complex accurately represents the animal's environment because coactivity of place cells generally only takes place within the region of overlap of the cells' place fields. This spatial representation can be created from place cell firing data alone, without information about the animal's location during testing. This analysis also can provide information about the dynamics of spatial encoding by the place cell ensemble. This model does not require prior information about place-specific firing patterns of the place cells. It considers a dynamic representation of the environment that is constantly reiterated as more information is gathered and incorporated from exploration. In this sense, it more accurately reflects the animals situation as it is exploring and it more precisely considers the temporal dynamics of hippocampal network activity.

At each moment, a new simplicial complex is created that represents all of the single unit firing as vertices fully interconnected with links to all coactive partners. This representation is added to a growing simplicial complex by matching together common sub-simplices, meaning shared vertices or lines. This iterative computation produces a filtered simplicial complex, one that grows over time. At every moment, we determine the number of zero, one, and two dimensional topological features represented by place cell activity. To characterize the topology of the simplicial complex representation at every moment, we calculate Betti numbers, a measure of the number of holes or loops in a space. Initially, spurious features are detected due to an incomplete representation of the space, but these loops are quickly filled in by continued exploration. When the environment contains a hole, the topological feature persists once detected. The time for our model to detect the topological features of the space exclusively is called the learning time. Earlier work has shown that the learning time depends on place field parameters (number of place cells, mean maximal firing rates, mean place field size) falling within a parametric "Goldilocks zone". We show that the region of suitable place cell network parameters is constricted when connectivity detection is stochastic. We determine that place cell networks with reduced spatial specificity might be favorable when the detection of temporal activity patterns is constrained. When coincidence detection begin to fail, place cells increase the size of their place fields, decreasing their spatial specificity, to increase the amount of temporal connectivity data. Our topological theory considers the firing specificity of place cells and the degree of place field overlap as important components of information representation by the hippocampal place cell ensemble.

A MINIMAL MODEL TO REPRODUCE DYNAMICAL CRITICALITY IN THE COLLECTIVE BEHAVIOUR OF THE RETINAL NETWORK

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Modeling the dynamics of network activity is crucial to understand how a population of neurons encodes information. Several works have shown that the temporal statistics of neural network activity can exhibit a power law organization. However, it is still unclear what is the simplest model that can reproduce these experimentally observed dynamics with a minimal number of hypotheses.

Maximum entropy models are the least structured probability distributions that exactly reproduce a chosen set of statistics measured in an interacting network, and are thus ideally suited to answer this question. We describe the collective activity of a complete patch of retinal neurons with a simple dynamical maximum entropy model. Our model takes into account temporal correlations in spiking activity, but uses as a constraint only the temporal correlation present in the global population activity. Compared to previous approaches, we did not keep track of the identity of the different cells, but we modeled the dynamics of this global activity.

We fitted this model to the activity of a large population of retinal neurons (more than 100 cells) responding to a natural movie. The model reproduced well the statistics of spiking avalanches. When analyzing the thermodynamic properties of the model, we found that adding the temporal correlation as a constraint greatly enhanced the critical properties of the system. Critical dynamics are thus present in the retinal network, and can be explained with a simple model of the global population activity.

STEADY-STATE EVOKED POTENTIALS TO CHARACTERIZE THE CORTICAL ACTIVITY INDUCED BY TACTILE EXPLORATION OF TEXTURES

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When we slide our fingertip across a textured surface, complex vibrations are produced in the skin. Previous studies have suggested that the frequency content of these vibrations could contribute to the extraction of texture information. The aim of the present study was to develop a new approach to isolate and characterize the cortical activity elicited by such vibrations. Specifically, we examined whether the sustained cortical activity generated by the mechanical interaction between the finger pad and a grated texture can be captured in the form of a steady-state evoked potential (SS-EP). The electroencephalogram (EEG) was recorded using 64 channels. During the recording, passive scanning of the right index fingertip across three aluminium gratings whose spatial period (SP) was between 0.4 mm (smooth surface) and 1.6 mm (rough surface). The movement of the gratings was achieved using a robot with feedback force sensors. A constant normal force (1.5 N) and two constant exploration velocities were used (v_1 = 1.76 cm/s, v_2 = 4.80 cm/s). Depending on the SP, we expected that these dynamic stimuli would elicit SS-EPs at frequencies ranging between 11 and 120 Hz and, possibly, their harmonics. Frequency analysis of the recorded EEG signals showed that SS-EPs can be recorded in response to the sliding of the finger against the grating at a constant velocity. These results suggest that SS-EPs can be used to characterize the cortical activity induced by the tactile exploration of textures.

Acknowledgments

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COMPLEX VISUAL MOTION REPRESENTATION IN MOUSE AREA V1

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Mouse visual cortex has a hierarchical architecture similar to that of higher mammals, with primary visual cortex (area V1) providing input to a series of extra-striate areas segregated into dorsal and ventral streams. Mouse V1, having a large proportion of orientation- and direction-selective cells, is thought to perform the first stage of visual processing similarly to the V1 of higher mammals, responding to local orientation and visual motion elements rather than to complex objects or global patterns of motion. Nonetheless, notable differences in visual processing exist between mouse V1 and the V1 of higher mammals. For example, compared to cat and monkey V1, mouse V1 lacks orientation columns, has larger receptive fields and is anatomically small, allowing single cells to access information from a larger part of the visual field. This makes global motion computations in principle possible at the first stage of cortical visual processing. A different scheme of visual motion processing may then occur in mouse visual cortex, where some V1 cells act as complex motion integration units rather than as the narrow orientation and direction-of-motion filters prevalent in cat and monkey V1. To explore this possibility, we measured the response properties of mouse V1 pyramidal neurons to type I symmetric additive plaid patterns of varying cross-angle and their component gratings. Type I symmetric plaid patterns are composed of two component gratings whose directions of motion are symmetric relative to the motion of the global pattern. The angle between component gratings is the plaid's cross-angle. Cells that respond to the global drift of the intersection pattern (pattern-motion selective) have similar direction-of-motion tuning curves for both gratings and plaid stimuli. In contrast, cells selective to the motion of individual component gratings (component-motion selective) have bi-lobed tuning curves when tested with plaids, since they respond vigorously each time a component grating moves in their preferred direction.

We used 2-photon imaging with calcium-sensitive dyes (OGB) and genetically encoded calcium indicators (GCaMP-6) to monitor the grating- and plaid-evoked responses of large networks of V1 neurons located in layer 2/3 (50–200 cells per field of view). We show that on average 11.5% of direction-selective V1 pyramidal cells generate responses selective for the global direction of motion of a plaid pattern, compared to less than 0.5% in cats and primates, indicating that mouse V1 cells can integrate local motion signals to acquire global direction-of-motion selectivity — a property that, in cats and monkeys, is associated with extra-striate areas higher in the visual hierarchy. Measurement of optokinetic responses to plaid stimuli in awake mice revealed that mice demonstrate bi-stable perception, sometimes tracking individual stimulus components while, at other times, tracking the global pattern of motion. Reducing the plaid's cross-angle increases both the number of V1 neurons that generate pattern-motion selective responses and the number of optokinetic movements along the global pattern's direction of motion. This suggests that the relative fraction of pattern-motion versus component-motion selective responses of neurons in area V1 may contribute to global motion perception in the mouse.

CONTRIBUTION OF APICAL DENDRITES TO RECEPTIVE FIELD PROPERTIES IN LAYER 2/3 OF MOUSE V1

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Although slice recordings and model studies provide a lot of information about how neurons integrate their inputs to overall responses, it is still not clear how neurons in the brain integrate their synaptic inputs to derive their functional properties *in vivo*. Pyramidal neurons in layer 2/3 of mouse V1 receive input from the lateral geniculate nucleus (LGN) via layer 4 and feedback from higher visual areas. Here, we focus on the function of apical dendrites, which play an important role in communicating with higher visual areas. We ablate apical dendrites of layer 2/3 pyramidal neurons in area V1, *in vivo*, and monitor their responses to visual stimuli by two photon microscopy. We compare orientation selectivity, contrast sensitivity and other receptive field properties of layer 2/3 pyramidal neurons before and after selective apical dendritic ablation. This approach provides information on how different dendritic inputs contribute to neuronal receptive field properties of layer 2/3 pyramidal neurons in mouse V1.

DISTRIBUTION AND SPECIFICITY OF NEURONAL FIRING ASSOCIATED WITH PERCEPTUAL DECISIONS IN MACAQUE AREA V5/MT

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Modern recording techniques offer the possibility of monitoring the responses of a large sample of cortical neurons during the making of perceptual decisions. This provides the possibility of examining how the stimulus specificity of neuronal responses relates to the contribution of neurons to the perceptual decision. In this work, we examine this question from the opposite perspective: we ask whether a single neuron shows evidence of contributions to perceptual decisions about stimuli over a wide range of stimulus properties.

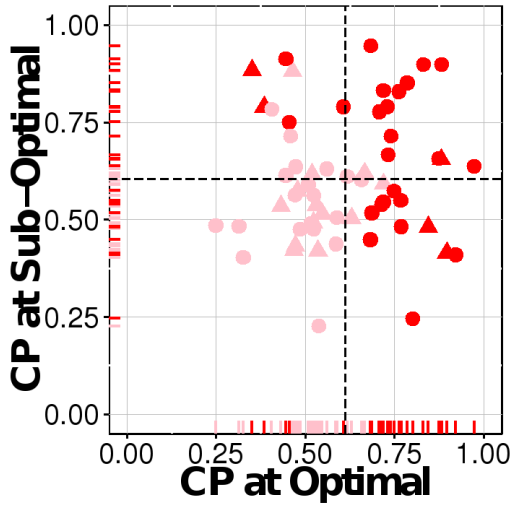

Figure 1. Choice probabilities (CP) at optimal and sub-optimal orientations. Triangles, MonkeyR; circles, MonkeyF; bold, $p < 0.05$; pale, NS; dashed lines show mean CPs.

Single cortical neurons are often able to signal discriminations between sensory stimuli with high precision. Such discriminations are typically presented as a behavioral task that requires a forced choice between two possible decisions. The signals relating to visual decisions are often apparent in the form of enhanced neuronal firing in the pool of neurons that favors the outcome that is eventually chosen. We measured the stimulus range over which this decision-related firing was present.

Macaque monkeys were trained to discriminate the direction of rotation of a cylindrical figure, by means of the binocular disparity between the moving dots that form its front and rear surfaces. The orientation of the cylinder's axis was randomly assigned to one of two values on each trial. One axis of the cylinder gave dot motion closely aligned with the motion preferences of the V5/MT neurons (optimal), whilst in the other case there was a misalignment that resulted in a significantly lower firing rate (sub-optimal). During the performance of this behavioral task, we took measures of neuronal sensitivity and choice probability by recording from single neurons in cortical area V5/MT. We find that the firing of single neurons is organized to maintain high neurometric sensitivity in the face of substantial changes in firing rate. We assessed decision-related firing by calculating measures (Fig. 1) of choice probability (CP). In this paradigm, during which the monkey must disregard the unpredictable parameter of orientation and respond only to the disparity content, the CP of neurons is not reduced for the sub-optimal orientation and its associated lower firing rates.

These measures imply that the neuronal pools that support discrimination are highly local and structured for each pair of stimulus configurations that must be discriminated. We propose a *micropool model*, in which the relevant neurons are assembled into several sets of small-sized pools. The neurons within the micropool share cortical connections, leading to measurable interneuronal correlations between the firing patterns of neurons within the micropool. Recruitment to the decision process is at the level of the micropool: that is to say, if a micropool is recruited to the decision pool, then all of the neurons within the micropool then make a weighted contribution to the decision.

STIMULATED REPLAY OF SPONTANEOUS BURSTING PATTERNS IN CULTURED CORTICAL NETWORKS

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Recent studies about the spontaneous generation and propagation of coordinated activity in cultured neuronal networks reported the existence of privileged sites that consistently fire earlier than others at the onset of synchronized bursting events (or network bursts, NBs), which have been termed major burst leaders (MBLs). At the same time, it is known that by stimulating the network from different spatial locations one can evoke variable responses, not only in size and delay but also in the activation order of the responding neurons. However, little is known about the existing relationship between spontaneous and evoked patterns, and to what extent they are determined by the corresponding ignition site.

We electrically stimulated rat cortical networks cultured on micro-electrode arrays from different locations (either leaders of the spontaneous activity or not), and we compared the evoked activation patterns to the spontaneous ones. We characterized the spiking response to electrical stimulation by measuring the area of the post-stimulus time histogram, corresponding to the average number of evoked spikes, and the delay of the first evoked spike for each recording electrode. We also compared the activation patterns of spontaneous and evoked NBs. For each pair of recorded NBs (either spontaneous or evoked), we computed the edit distance between their activation sequences. Then, we normalized all distances by using an innovative approach based on the generation of surrogate data. By averaging all normalized distances between NBs originating from the same sources, we obtained a map of distances between all sources, being either spontaneous MBLs or stimulating sites. Such color-coded maps can be ordered according to a hierarchical clustering approach, highlighting similarities/differences among patterns coming from different sites.

We found that MBLs generally respond better and more rapidly to electrical stimulation and also that electrical stimulation from MBLs evokes, on average, earlier responses than the stimulation delivered from other locations. Moreover, in all analysed cultures at least one stimulation site was able to trigger spatial activation patterns which were strongly similar to the spontaneous ones. In some cases, all stimulations caused replay of spontaneous patterns, regardless of the spatial location of the stimulating site.

To summarize, we showed that MBLs also play a special role in coordinating and driving the evoked bursts of activity. Moreover, similarity between bursting responses evoked by different stimulation sources may be attributed to the fact that the same pattern is recalled from the available dictionary of spontaneous ones.

DENTATE GYRUS CIRCUITRY IMPROVES PERFORMANCE OF THE ITERATIVE SOFT THRESHOLDING ALGORITHM

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Sparse representations are the common way of exhibiting memory oriented activity in Dentate Gyrus (DG). It has been shown that sparse neuronal populations of granule cells, the main encoding cells in DG, are concisely activated, not exceeding 2–4% of the total population. It is assumed that sparsity enhances the ability of DG to perform pattern separation, one of the most valuable contributions of DG during memory formation. Pattern separation guarantees that two separate inputs from the Entorhinal Cortex, even if they slightly differ from each other, are coded by two separate activation patterns in the downstream hippocampal area, CA3.

In this work we investigate the possibility of using DG circuitry to implement Sparse Approximation (SA), a widely used strategy in the Signal Processing field. Sparse approximation stands for the algorithmic identification of few components from a basis set (*e.g.*, a wavelet basis), that approximate a certain signal. The ability of DG to achieve pattern separation by sparsifing its representations is exploited here to augment the robustness of existing SA algorithms on such a task. Specifically, we investigate the possibility of improving already the state of the art Iterative Soft Thresholding (IST) algorithm by adding new algorithmic features inspired by the DG circuitry. Lateral inhibition of granule cells, either direct or indirect, *e.g.*, via mossy cells, is shown to enhance the performance of IST. Figs. 1 and 2 depict an example of approximation of a sparse signal x and illustrate the superiority of the proposed approach compared to the original IST algorithm. Fig. 1 shows the error (E) of the approximation in regard with the iteration of the IST (black curve) and the DG-inspired IST (green curve). In Fig. 2, red dots represent the values of signal x whereas black and green stems the approximation by the IST and the DG-inspired IST, respectively. These results highlight the ability to improve SA algorithms by using features of the DG circuitry and pave the way for further dissecting the relation between DG's circuitry and functionality.

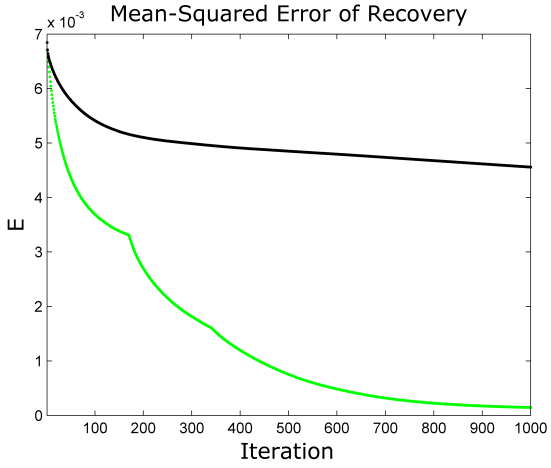

Figure 1. Error (E) of sparse approximation.

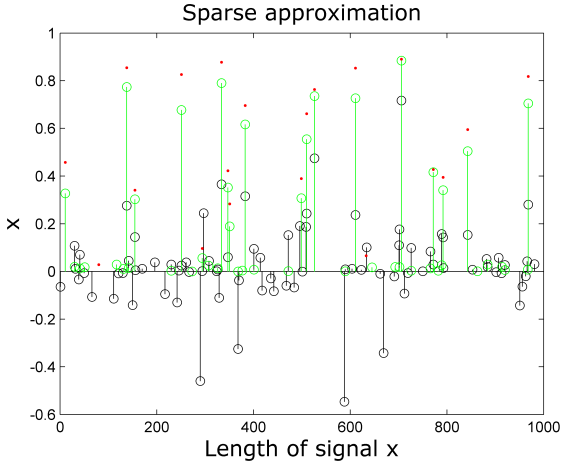

Figure 2. Approximation of signal *x*.

WHOLE-BRAIN REGION OF INTEREST DETECTION

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Recent advances in imaging technology, such as light sheet [1] and light field [2] microscopy, have made it possible to simultaneously image activity from a large fraction of the neurons in small animals such as the nematode *C. elegans* [3] and the larval zebrafish *D. rerio* [4]. The datasets created by such methods are often enormous and pose interesting challenges for practical analysis. For instance, existing algorithms developed for detecting regions of interest in imaging data [5] may not scale to very large fields of view or may not be robust to the kinds of artifacts unique to newer imaging techniques.

In this work we present an algorithm for automatic detection of cell bodies from imaging data that scales to whole brain recordings from larval zebrafish. The method applies standard morphological techniques for extracting cell bodies from static images to each frame of calcium imaging data, followed by online greedy clustering to merge regions of interest across frames. A GPU-accelerated implementation of this algorithm is able to detect regions of interest from whole-brain larval zebrafish recordings in under a day on a single machine, and distributed implementations should be much faster.

We apply this algorithm to recordings of spontaneous activity in a larval zebrafish expressing GCamp5 [4] and find thousands of active regions of interest. We show validation results comparing the number of regions of interest that are likely cell bodies, neuropil or artifacts. Future work will show direct comparisons between analyses performed directly on voxels of calcium activity and the same analyses performed on calcium activity extracted from the regions of interest, as well as more complicated analyses on the extracted calcium activity that would not be possible to scale to every voxel.

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EXTRACTING NOVEL INFORMATION FROM NEUROIMAGING DATA USING NEURAL FIELDS

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This poster presents new links between the theory of differential equations and the analysis of neuroimaging data. It focuses on a class of population models called neural fields: these are models of how the brain is wired [1]and how it responds in different experimental conditions, which embody topographic features of cortical sources. It shows how neural fields can be used to interpret brain responses measured with electrophysiology. The inversion of such models — based upon Bayesian techniques — provides estimates of biologically and functionally meaningful quantities among different experimental conditions.

We present different uses of neural fields and put forward three reasons why these models can be useful in the analysis of neuroimaging data. Each of these motivations is demonstrated by analysing a particular dataset obtained using three different modalities: electrocorticography (ECoG), magnetoencephalography (MEG) and local field potential recordings (LFPs). We will argue that neural fields allow one to: (i) compare evidences for alternative hypotheses regarding the important neurobiological determinants of stimulus-specific response variability [2]; (ii) make inferences about between subject variability in cortical function and microstructure using non-invasive data [3]; and (iii) obtain estimates of spatial parameters describing cortical sources in the absence of spatially resolved data [4].

Our analyses exploit dynamic causal modelling and include model space explorations that embody different hypotheses about the generation of observed responses in relation to model evidence — obtained using Variational Bayes. This model comparison uses a variational free-energy bound to furnish optimized models in a manner similar to fitting empirical spectra with AR and ARMA models. The advantage this approach has over other optimization criteria is that it provides an optimal balance between model fit and complexity; yielding models that are both parsimonious and accurate. The analyses presented here showcase particular instances where neural field models serve as a mathematical microscope, allowing us to extract information that is hidden in electrophysiological data.

Acknowledgments

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FAST AUTOMATIC ROI SELECTION AND SPIKE INFERENCE FROM LARGE SCALE CALCIUM IMAGING RECORDINGS

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Calcium imaging techniques have revolutionized large scale data acquisition in neuroscience, enabling the study of large neuron ensembles across many different experimental conditions. A key problem in calcium imaging data analysis is the deconvolution of the spike times from the observed fluorescence signal which has significantly slower dynamics. This is an often challenging task, since imaging data is typically acquired at a low temporal resolution and with a limited signal-to-noise ratio. Available methods for spike deconvolution typically operate on a single pixel level, or on the fluorescence trace averaged over a previously extracted ROI, a task which can also be difficult and is often performed manually.

In this abstract we extend our previous efforts on combining optimally spatial and temporal information to derive a scalable, parallelizable, automated algorithm for ROI extraction and spike deconvolution. Our algorithm divides the imaged field into a set of overlapping patches that can be processed in parallel to identify possible ROIs and then agglomerates the information obtained from the different patches. The core of the algorithm within each patch lies in the observation that the spatiotemporal fluorescence can be expressed as a product of two low rank matrices that encode the ROIs and calcium concentration of each neuron, respectively.

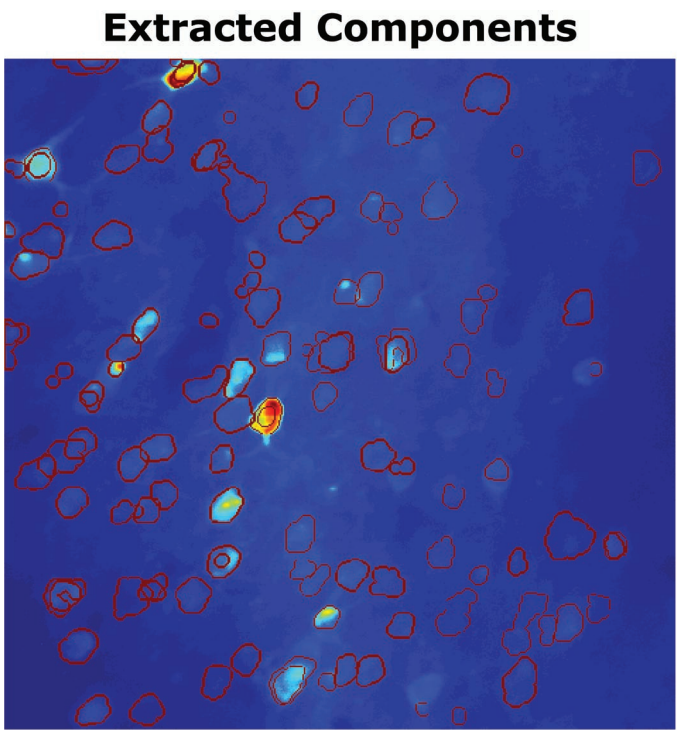

Figure 1: Automated ROI segmentation of V1 anesthetized mouse calcium imaging data (GCaMP6s). The image shows the averaged activity over time and the overlaid red circles indicate the extracted ROIs. Data courtesy of K. Poskanzer and R. Yuste, Columbia University.

To extract these components we propose a novel constrained matrix factorization method that is efficient, parallelizable and requires no hyper-parameter tuning. Since matrix factorization is a non-convex problem, proper initialization is important; we address this problem using a rank penalized convex approach. Finally we discuss several important extensions, including the estimation of drifting baseline concentration and the estimation of the spike times at an arbitrary temporal resolution using appropriate Bayesian methods. We demonstrate the performance of our algorithm on a variety of real datasets.

PLACE CELL FORMATION BY GRID CELL CONVERGENCE IN THE DENDRITES OF A CA1 MODEL NEURON

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Place cells are pyramidal neurons in CA1 and CA3 regions of hippocampus which fire selectively when the animal is located in a particular place in space. CA1 place cells receive synaptic input from CA3 via the Schaffer collateral fibers to their proximal apical and basal dendrites and from the third layer of medial entorhinal cortex to their apical tuft dendrites. Both of these input pathways encode spatial information. Grid cells, which form the entorhinal input to CA1 cells, have a spatial firing field with multiple peaks which displays a regularly spaced, triangular grid pattern that covers the entire space of a given environment. Both grid and place cells are phase-modulated by theta rhythm and this modulation may be important for their spatial properties.

Studying the formation of place cells is an important step in understanding how representation of the external environment is coded in neural networks that constitute spatial maps. It is not currently known how place fields emerge in CA1 neurons. An influential model of place cell formation predicts the convergence of various grid field inputs which combine linearly to create the place field output of CA1 cells.

In this study, we constructed a model of CA1 place cell formation through the convergence of grid field inputs to the distal dendrites of our model neuron. We created a model of grid cell activity which represents the firing of grid cells modulated be the theta rhythm. We varied the number of different grid fields used as synaptic inputs to stimulate the distal dendrites of a biophysically constrained, detailed compartmental CA1 pyramidal cell model. In addition, inhibition was placed in both the distal and proximal dendrites. These inhibitory pathways are known to be active in different phases of the theta rhythm. We used this model to study the properties of CA1 place cell formation and to assess the output of the CA1 model cell during place cell activity. Additionally, we examined the effects of local dendritic integration by altering the dendritic distribution of grid cell inputs. Finally, we examined the effect of theta modulation on the spatial extent, the coherence and the information content of CA1 place cells.

Acknowledgments

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A SIMULATION STUDY ON THE EFFECTS OF DENDRITIC MORPHOLOGY ON LAYER V PFC PYRAMICAL CELL FIRING BEHAVIOR

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The majority of neuronal cells found in the cerebral cortex are pyramidal neurons. Their function has been associated with higher cognitive and emotional functions. Pyramidal neurons have a characteristic structure, consisting of a triangular shaped soma whereon descend two extended and complex dendritic trees, and a long bifurcated axon. All the morphological components of the pyramidal neurons exhibit significant variability across different brain areas and layers. Pyramidal cells receive numerous synaptic inputs along their structure, integration of which in space and in time generates local dendritic spikes that shape their firing pattern. In addition, synaptic integration is influenced by voltage-gated and ion channels, which are expressed in a large repertoire by pyramidal neurons. Electrophysiological categories of pyramidal cells can be established, based on the action potential frequency, generated from a fixed somatic stimulus: (1) cells that fire repetitive action potentials (Regular Spiking, RS), (2) cells that fire clusters of 2–5 action potentials with short ISIs (Intrinsic Bursting, IB), and (3) cells that fire in repetitive clusters of 2–5 action potentials with short ISIs (Repetitive Oscillatory Bursts, ROB). *In vitro* and *in silico* scientific studies, correlate the firing patterns of the pyramidal neurons to their morphological features.

This study provides a quantitatively analysis via compartmental neuronal modelling of the effects of dendritic morphology and distribution and concentration of ionic mechanisms, along the basal and/or apical dendrites on the firing behavior of a 112-set of layer V rat PFC pyramidal cells. We focus on how particular morphological and passive features of the dendritic trees shape the neuronal firing patterns. Our results suggest that specific morphological parameters (such as total length, volume and branch number) can discriminate the cells as RS or IB, regardless of what is the distribution and concentration of ionic mechanisms along the dendritic trees. Moreover, varying combinations of the basal, the apical or both dendritic tree plexus produce different cell type percentages. Consequently, it appears that variations on the dendritic size and dendritic topology of the pyramidal cells influence their firing patterns and subsequently may influence the information coding that these neurons support.

DYNAMICS OF FUNCTIONAL CONNECTIVITY IN THE SENSORIMOTOR CORTEX

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Primary motor cortex and proprioceptive primary somatosensory cortical areas of primates are known to be anatomically interconnected. However, it is not well understood how these areas communicate and whether these functional connections vary across the course of a naturalistic movement. Using a statistical approach, we examined the functional topology among neurons in motor and somatosensory cortices and determined the changes in functional connectivity during a grasping behavior. A simulation of artificial neurons was used to validate the analysis.

A rhesus macaque was trained to grasp a wide variety of objects as they were presented to its hand by a robot. Although the monkey's arm was not constrained, it was trained to perform the movement while keeping its arm on an arm rest, resulting in minimal shoulder and elbow movements. We recorded neuronal activity with chronically implanted microelectrode arrays and examined the dynamic neuronal interactions between rostral motor cortex (rM1), caudal motor cortex (cM1), and primary proprioceptive areas 3a and 2. Marker positions on the arm, with a focus on the wrist, hand, and digits, were recorded using a Vicon motion-capture system. Joint angles were calculated using a customized openSim biomechanical model.

Generalized linear models (GLMs) were used to investigate the influence of neuronal signaling above that which may be predicted by kinematic parameters alone. The goodness-of-fit of a full model (using wrist and finger joint velocities, the neuron's own spike history, and a paired neuron's spike history as predictors) was compared with that of a reduced model (without the paired neuron's spike history). If the full model fitted the data significantly better than the reduced model, we assigned a directed functional connection to the neuron from the paired neuron. Furthermore, the sign of the mean coefficients of the paired neuron's spike history designated excitatory (positive) or inhibitory (negative) connections.

Simulations showed that the analytical method employed is sensitive to connections between individual neurons, even when both neurons respond to similar kinematics. Our results showed that areas that were strongly connected were likely to share bidirectional connections, and that most connections are inhibitory, suggesting the presence of inhibitory feedback loops between areas. We found that the percentage of directed connections (out of the total number of possible connections) between cortical areas did indeed change over the course of a movement. During movement onset, rM1 was the predominant source of function connections. Around maximum aperture, area 2 increased its percentage of outward directed projections. Around object grasp, cM1 increased and rM1 decreased their amounts of outward directed projections. This suggests that the dominant sources of functional connections in the network, from movement onset through to object grasp, starts from rM1, then area 2, then cM1.

VARIABILITY STATISTICS OF SPIKING ACTIVITY IN MOTOR CORTICAL NEURONS RECORDED DURING RESTING STATE AND BEHAVIOR

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Variability of neural activity is apparent throughout the central nervous system, in all types of electrophysiological signals. Understanding its nature and origin is essential for our understanding of information processing in cortical networks. To analyze variability in spiking activity we used three measures: (*i*) The coefficient of variation (CV) of inter-spike intervals (ISIs) measures the (ir)regularity of a sequence of spikes. Because it largely overestimates irregularity in case of firing rate changes, we use a local measure, the CV2 (Holt, *et al.*, 1996, Neurophysiol 75: 1806–1814), which is an average of individual measures, each calculated over two consecutive ISIs. The CV signifies intra-trial variability on a short time scale, determined by the ISI, in the range of tens of milliseconds. (*ii*) The Fano factor (FF), computed as the variance of spike counts divided by their mean, expresses the spike count variability across trials of the same experimental condition. Thus, the FF signifies inter-trial variability, on a longer time scale in the range of seconds. (*iii*) We calculate the serial rank-order correlation (SRC) between neighboring ISIs as a measure of deviation from a renewal process (Perkel, *et al.*, 1967, *Biophys. J.* 7:391–418).

We recorded the spiking activity of 80 to 160 neurons simultaneously using Utah arrays chronically implanted in monkey motor cortex. We analyzed data from two monkeys during either a wakeful resting-state *non-behavior* condition (160 neurons recorded in one 15 min session) or a delayed reach-to-grasp task *behavior* condition (1929 neurons recorded during 21 sessions evenly distributed over 6 months; Riehle, *et al.*, 2013, *Front. Neural Circuits* 7:48).

For results that do not differ in the two conditions, we found a strong negative correlation across all neurons between the averaged firing rate and the averaged CV2. However, if calculating for each neuron the correlation between rate and CV2 in sliding windows, it is not significant in 56% of the neurons, significantly negative in 34% and positive in 10% of them. Furthermore, neurons with a significant SRC show a strong negative correlation between SRC and CV2, meaning that the CV2 is lower in neurons with a positive than a negative SRC.

For results that do differ between the experimental conditions, we found that SRC is mainly positive and significant in almost all neurons (158/160) during non-behavior, compared with only 20–30% of the neurons during behavior. Note, that FF cannot be calculated during non-behavior due to the lack of a trial structure. During behavior, FF is negatively correlated with firing rate and positively with CV2, and is lower in neurons with a negative than a positive SRC. When separating behavior in periods of *wait* (during the instructed delay or object hold) and periods of *movement*, CV2 and firing rate are significantly lower and FF is significantly higher during wait than during movement. We will discuss how the various variability measures are related to behavior and the functional organization of motor cortical networks.

Acknowledgments

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EFFECT OF EARLY LIFE SEIZURES ON CORTICAL EXCITABILITY AND EPILEPTOGENESIS

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Early life seizures (ELSs) can have lasting detrimental effects on behaviour and cognition, along with a higher propensity for epilepsy. The dilemma of whether to treat early non-persistent seizures aggressively is complicated by the fact that exposure to anti-epileptic drugs at early ages can itself lead to cognitive deficits. This issue is difficult to investigate in humans because of the many contributing factors, which are difficult to control. Animal models allow the study of these factors in isolation and hence can provide insights to the underlying mechanisms. In this study we combined electrophysiological recordings and behavioural tests to assess the long-term effects of single or multiple pharmacologically-induced ELSs. Seizures were induced at two distinct developmental stages, P10–15 and P20–25, in order to identify periods of higher vulnerability. Cortical excitability was assessed by comparing (*a*) spontaneous network activity (Up/Down states) in brain slices of adult (over 4 mo) mice, and (*b*) the induction and expression of cortical epileptiform activity *in vitro*, in the 0 [Mg^{++}] model. We find that single ELSs at either developmental periods had minimal impact on cortical up states or epileptiform discharges; in contrast, the *onset* of epileptiform activity tended to occur earlier in mice with ELSs. The effects of multiple ELSs, both acutely and in adult animals, are being assessed. Current data indicate that single ELSs do not have long-term effects on basal animal behaviour, cortical excitability or the expression of epileptiform discharges, however they cause the cortex to be less resistant to the induction and propagation of seizures.

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SPONTANEOUS NETWORK ACTIVITY PATTERNS REVEAL FUNCTIONAL OPTIMIZATIONS OF NEURONAL CIRCUITS

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In the absence of stimulation, sensory brain areas remain highly active. This ongoing spontaneous neuronal activity has traditionally been considered as noise, with no functional value for brain computations. However, more recently, it was shown that spontaneous activity of large neuronal populations is coarsely structured according to the functional and anatomical neuronal circuitry, raising the possibility that it may affect brain computations. Nevertheless, the biological significance and neuronal mechanisms underlying this structure remain elusive.

We addressed these questions using two-photon calcium imaging of intact zebrafish larvae expressing GCaMP3 to simultaneously monitor the activity of hundreds of neurons representing a significant (about 15%) portion of the larva's optic tectum, a brain region involved in visual spatial detection.

Analysis of the neuron-to-neuron spatiotemporal structure of tectal spontaneous activity revealed that the latter is organised in distinct assemblies that specifically group similarly tuned neurons, globally reflecting the tectal retinotopic map. Remarkably, assembly receptive fields were particularly tuned to angular sizes and spatial positions that best triggered visually-induced prey-capture behaviour. These spontaneous assemblies seem to be internally generated by the tectal recurrent circuitry, since they were not dependent on retinal input. Moreover, we show that tectal neuronal populations support highly non-linear winner-takes-all-like dynamics that could be responsible for the emergence of the spontaneous assemblies. Interestingly, this kind of network dynamics is advantageous for visual prey detection in noisy natural environments.

Therefore, our results reveal that tectal spontaneous spatiotemporal activity patterns represent behaviourally relevant preferred network states, emerging from the intrinsic dynamics of neuronal circuits optimised for their functional role.

LINEAR AND NONLINEAR PROCESSING OF VISUAL INFORMATION IN RODENT-LIKE CORTICAL NETWORKS

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It is not yet fully clear how sensory information is being processed when it arrives in primary cortical areas. We study this general question in the context of visual information processing in the rodent-like visual cortex. We focus on the example of orientation selectivity, namely the selectivity of cortical neurons to a limited range of orientations of an elongated stimulus [1]. In large scale simulations of networks of spiking neurons and by using mathematical and computational analysis, we investigate the contribution of different mechanisms to this process. In particular, we ask which network mechanisms contribute to properties like suppression of the common mode, selective amplification of modulation, sharpening of tuning curves, invariance of tuning curves across different contrasts, and normalization. We show that a large body of experimental findings regarding the basic computations performed in early sensory processing can already be explained by linear processing in neuronal networks with realistic parameters. We then develop a theory [2] that can predict the distribution of selectivity in our networks, as well as the exact shape of output tuning curves, including all details and inhomogeneities of structure and function. A simple but essential form of nonlinearity, namely rectification of firing rates, can be further added to the model, which accounts for nonlinear phenomena appearing in networks with prominent rectification of tuning curves. We show that this type of nonlinear processing can already lead to some normalization of average tuning curves, even in networks without feature-specific connectivity. Finally we discuss the case where functional specificity in connection has emerged, a situation presumably corresponding to the mature state of rodent's visual cortex [3]. We show that, although linear amplification of selectivity can result from this scheme [4, 5], the specific connectivity can be detrimental to sensory coding, if it is not accompanied by a comparable specificity of inhibition. We discuss the relevance of our work to experimental findings, propose a general framework for explaining basic properties of sensory processing, and suggest further predications that can be experimentally tested.

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DECODING COVERT ATTENTION FROM SIMULTANEOUS RECORDINGS IN PREFRONTAL AND VISUAL CORTEX

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The use of machine learning algorithms for the decoding of neuronal signals has been rapidly increasing in neuroscience literature. Such techniques are primarily employed for the control of brain-machine interfaces (BMIs) that allow patients with mobility impairments to operate assistive equipment. Although research has mainly focused on the decoding of sensory and motor signals, the application of neuronal decoding to study cognitive, endogenous, processes could facilitate the development of more efficient BMIs and also improve our understanding of how these processes are represented in the brain. The ultimate goal of real-time decoding of cognitive states can only be achieved through simultaneous recordings of neuronal signals from multiple sites either within a single brain area or across different areas. However, it remains an open question whether recordings from different areas can improve decoding performance.

It is known that activities in the Frontal Eye Field (FEF) and area V4 are modulated by and synchronized during covert attention, with the FEF providing top-down feedback to V4. In this study, we used simultaneous recordings to examine whether signals from the two areas can be used to decode the locus of spatial attention. Recordings were carried out in two rhesus monkeys engaged in a covert attention task (Gregoriou *et al.*, 2009). In each recording session up to four microelectrodes were lowered in each area to record spikes and Local Field Potentials (LFPs). A Support Vector Machine (SVM) was used to decode activity on a trial-by-trial basis. Classification accuracy in each decoding run was calculated using a 5-fold cross-validation. Prior to decoding, a grid search procedure was used on each train set to estimate the optimal SVM hyper-parameters, using a nested 5-fold cross-validation.

Although only a small number of features was available for decoding in each session (2–4 simultaneously recorded multi-units in each area), readout performance was significantly above chance in 97% of sessions in FEF and in 88% in V4. Average performance across sessions was higher in the FEF compared to V4 in agreement with the notion that the FEF is mainly responsible for shifts of attention. Interestingly, combining signals from the two areas improved performance only slightly. Merging signals from different sessions resulted in impressively high performance (FEF 99%, V4 96%). These results provide a quantitative account of how efficiently the allocation of spatial attention can be read out on a single-trial basis from FEF and V4. Moreover, they indicate that successful decoding of covert attention using simultaneously recorded signals from a single session is possible even with a limited number of features. Thus, they could allow for real time decoding of mental states. Although combining signals from FEF and V4 did not significantly improve performance, future studies should address whether the combination of signals from other areas in the attentional network may be more informative for decoding purposes.

Acknowledgments

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HIGH-PERFORMANCE BMI ENABLED BY AN ADAPTIVE OPTIMAL FEEDBACK-CONTROLLED POINT PROCESS DECODER

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Neural representations can differ when subjects control a BMI compared to when they control their own arm. Motivated by this observation, closed-loop decoder adaptation (CLDA) methods fit the decoder parameters during closed-loop BMI operation based on the neural activity and inferred user velocity intention. This progress has resulted in the recent high-performance ReFIT Kalman filter (ReFIT-KF). Here we demonstrate proficient, robust, and generalizable spike-by-spike BMI control enabled by a novel CLDA algorithm, termed an adaptive optimal feedback-controlled (OFC) point process decoder (PPF). Adaptive OFC-PPF allows users to issue neural commands and receive feedback of the consequence of such commands at a faster rate (every 5 ms) than the KF (typically every 50–100 ms). Moreover, it updates the decoder parameters in closed-loop on a fast spike-by-spike time-scale compared to the currently used time-scale of minutes. Finally, it models the brain in closed-loop BMI operation as an infinite-horizon optimal feedback-controller to infer velocity intention during adaptation. This is in contrast to the current intention estimation methods (CursorGoal). We explore how BMI control quality changes as a result of (i) the fast spike-by-spike control and feedback rate, (ii) the OFC intention estimation, and (iii) the fast time-scale of parameter adaptation. Variability in recordings and task designs make across-study comparisons difficult, so here we compare performance across different decoders within the same subjects. Our data collected in two monkeys suggest that adaptive OFC-PPF improves BMI control. In both monkeys, OFC-PPF outperformed ReFIT-KF in a self-paced center-out movement task with 8 targets. This improvement was due to both the PPF's increased rate of control and feedback compared with the KF, and to the OFC model suggesting that the OFC better approximates the user's strategy. Also, the spike-by-spike adaptation resulted in faster convergence in decoder parameters compared to current techniques and was robust to initialization. Finally, performance improvements over ReFIT-KF also generalized to more challenging tasks beyond those used for CLDA training, including a multi-curvature obstacle avoidance task.

Multi-unit activity was recorded from the primary motor cortex of two rhesus macaques over tens of online BMI sessions. We calculate the number of successful trials per minute (TPM), the movement error, and the reach time. In Monkey J, adaptive OFC-PPF outperformed ReFIT-KF across all measures, improving TPM by 30%. This improvement was due to both the faster control and feedback rate in the PPF and to the OFC intention estimation model. In particular, TPM in OFC-PPF was 30% higher than a ReFIT-KF that used the OFC intention estimation method, demonstrating that PPF's faster control and feedback rate was essential for control improvement. Moreover, OFC-PPF improved the TPM 27% compared to a PPF trained with CursorGoal, demonstrating the advantage of the OFC intention estimation. We also found that continuous spike-by-spike adaptation of decoder parameters allowed the subject to achieve proficient control faster than SmoothBatch adaptation in which the parameters were adapted smoothly once every 90 sec. Finally OFC-PPF outperformed ReFIT-KF in a target jump task and in a multi-curvature obstacle avoidance task, reducing the path length by 25% in the latter task. In Monkey C similar improvements were observed on the center-out task in all measures. These data suggest that adaptive OFC-PPF results in higher BMI performance.

OPTOGENETIC STIMULATION OF MACAQUE MOTOR CORTEX REVEALS A LINK BETWEEN COHERENCE AND PHYSIOLOGICAL CONNECTIVITY

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Measures of connectivity and functional integration across brain areas are increasingly important as the number and density of simultaneous brain recordings increase. Typically, functional connectivity is inferred from correlations in neural activity between different sites in the brain. Correlations in neural activity may arise from a variety of causes including direct and indirect connections as well as common inputs from other sites. The role of common inputs poses a serious confound for interpreting causality from correlational measures. In order to control for the common input confound, we have performed experiments using optogenetic stimulation to manipulate neural activity in long-range circuits. We propose that recordings during stimulation allow us to measure a form of causal physiological connectivity, which can be compared with inferential measures of functional connectivity in widespread use.

We injected AAV5-hSyn-ChR2(H134R)-EYFP in motor cortex of one cynomolgus macaque. In an anesthetized preparation we stimulated optogenetically and simultaneously recorded from a single electrode in the stimulation region in motor cortex and from a 32-channel microdrive with movable electrodes over somatosensory cortex. Optogenetic stimulation was able to drive multiunit activity on four electrodes on the array. In addition, we found significant evoked LFP responses across the array at all recording depths, although only a subset of sites showed LFP responses that varied with depth (10/32 sites). Since depth-dependent changes in LFP activity are consistent with the presence of a current source, we propose that recording sites with depth-dependent LFP responses can be characterized as physiologically connected to the stimulation site. Moreover, since common input cannot explain the response of one site to stimulation at another, the correlations we observed cannot be due to common input.

We computed field-field coherence between all 33 electrodes in the baseline period prior to light stimulation and during bursts of stimulation. We found that areas that had high baseline functional connectivity with the stimulation site (coherence greater than 0.15, 40 Hz; 16/32 sites) were either physiologically connected to the stimulation site (10/16 sites) or functionally connected with areas that were physiologically connected to the stimulation site (mean coherence with physiologically connected areas greater than 0.2, 40 Hz; 6/16 sites). Importantly, areas that had low baseline functional connectivity with the stimulation site (coherence less than 0.15, 40 Hz; 16/32 sites) were not physiologically connected to the stimulation site and had lower functional connectivity with physiologically connected areas (mean coherence with physiologically connected areas less than 0.2, 40 Hz; 16/16 sites).

SPATIOTEMPORAL PROPAGATION PATTERNS OF CORTICAL SYNCHRONISED ACTIVITY IN VITRO

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During quiescent behavioural brain states, such as non-REM sleep, a spontaneous slow-rhythm synchronized activity develops in the cerebral cortex. This activity is maintained in slice preparations of isolated cortex, in the absence of sensory inputs or active neuromodulation, indicating that it is chiefly the outcome of intrinsic properties of the local neuronal networks. Hence, this type of synchronized activity seems to reflect the default activity of the cortex but the mechanisms that facilitate its manifestation and its functions are poorly understood. Moreover, little is known about the spatiotemporal dynamics of the generation and propagation of this spontaneous activity and how these are altered during pathological conditions exhibiting abnormal synchronization, such as epileptic seizures. We have developed a technique that allows simultaneous recordings of local field potentials from 60 sites forming a 6×10 matrix of electrodes spaced at 100 microns in acute cortical slices. Spontaneous activity was monitored in coronal brain slices from 4–6 week old C57BL/6 mice using a multi electrode array (MEA) in the absence or presence of the $GABA_A$-antagonist, gabazine, to induce epileptiform activity. Preliminary results show variable patterns of spatiotemporal propagation of the spontaneous synchronized activity. In contrast, epileptiform discharges were associated with more uniform spatiotemporal propagation patterns. These results reflect different modes of activity propagation during physiological and pathological network states.

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LEAST INFORMATIVE DIMENSIONS

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An important aspect of deciphering the neural code is to determine the stimulus features a population of sensory neurons is most sensitive to. Approaches to that problem include white noise analysis, in particular spike-triggered average or spike-triggered covariance, canonical correlation analysis, generalized linear models, or maximally informative dimensions (MID) [1]. While spike-triggered average is restricted to a single subspace, spike-triggered covariance and canonical correlation analysis can extract multi-dimensional subspaces. However, both are restricted to second-order statistics of the spike-triggered ensemble. MID is the only technique of the above that can extract *multiple* feature vectors *and* is sensitive to *higher-order* statistics.

Many techniques focus on characterizing the stimulus ensemble triggered by a single spike thereby ignoring the temporal correlations between spikes as well as the information carried by the silence of a neuron [2]. In order to estimate most informative features for populations or temporally correlated spike trains, every spike word needs to be taken into account. Since the number of spike patterns grows exponentially in the number of bins and neurons a straightforward generalization can quickly become a computational burden.

We propose an alternative approach to this problem that *minimizes* the information between *uninformative stimulus features*, and the combination of informative features and neural responses [3]. We avoid direct estimation of mutual information by using integral probability metrics in kernel Hilbert spaces. Since estimators of these metrics are easy to compute and exhibit good theoretical convergence properties, our method can readily be generalized to populations of neurons or spike patterns. By using a particular expansion of the mutual information, we can show that the informative features must account for the entire mutual information if we can make the uninformative features independent of the rest with respect to the integral probability metric.

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STRUCTURED CONNECTIVITY SHAPES MICROCIRCUIT FUNCTION IN THE PREFRONTAL CORTEX

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The application of new experimental techniques *in vivo* has shed light on the wiring diagram of cortical networks, revealing the highly non-random connectivity of pyramidal neurons. This structured connectivity is characterized by distance-dependent formation of neuronal clusters and over-represented structural motifs [1]. In the prefrontal cortex (PFC) in particular, pyramidal neurons were shown to form hyper-clusters, compared to other sensory regions. Yet, very little is known about the functional properties of these microcircuits and their role in Persistent Activity (PA), a well known function of the PFC. PA is the spiking activity that persists beyond the stimulus presentation and is considered to be the cellular correlate of working memory. Although, PA was traditionally assumed to emerge in large scale networks, recent *in vivo* data in the PFC suggest that small microcircuits mediate its functional output [2].

Motivated by the above findings this work probes the role of realistic connectivity constraints in shaping the functional output of PFC, through simulations of biophysically and morphologically detailed PFC circuits. Towards this goal, we used a compartmental modeling approach, whereby layer 5 PFC pyramidal neurons are modeled with detailed morphological and biophysical properties. Three different types of interneurons were also implemented; the Fast-spiking (FS), Regular-spiking (RS), and Irregular-spiking (IS). These were biophysically detailed, yet morphologically simplified. Microcircuits consisted of 75 pyramidal neurons, 13 FS, 6 RS and 6 IS. Properties (location, number, amplitude, kinetics) of both excitatory and inhibitory synapses were extensively validated against experimental data.

The network model was used to investigate the effect of connectivity on the emergence of persistent activity. Two different connectivity profiles of pyramidal cells were implemented: one highly non-random (structured) and one random. In the structured network, the connection probability was both distance-dependent and local clustering dependent, based on experimental data, whereas at the random microcircuit, each pair was connected independently with fixed probability. Both types of microcircuits exhibited the same overall connection probability. Using the same stimulation protocol, directed in a sub-region of each network, we examined the ability of each microcircuit to hold and distribute persistent activity to neighboring neurons, as well as its spiking profile. Preliminarily results suggest that structurally connected microcircuits are characterized by different activity attributes, suggesting that the wiring diagram plays a key role in the formation of functionally distinct processing clusters in the PFC.

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DIFFUSIVE NEUROTRANSMISSION AS A NEW HOMEOSTATIC MECHANISM

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Gaseous neurotransmitters such as nitric oxide (NO) provide a unique and often overlooked mechanism for neurons to communicate through diffusion within a network, regardless of synaptic connectivity. NO is known to provide homeostatic control of intrinsic excitability. Employing simulations of cortical networks and dynamical mean-field analysis, we conduct a theoretical investigation of the distinguishing roles of NO-mediated diffusive homeostasis in comparison with canonical non-diffusive homeostasis.

We find that both forms of homeostasis provide a robust mechanism for maintaining stable activity across a wide range of perturbations. However, the resulting networks differ substantially, with diffusive homeostasis enabling and maintaining substantial heterogeneity in activity levels of individual neurons, a feature which is disrupted in network with non-diffusive homeostasis. Additionally, this results in networks capable of representing changes in input more faithfully than those undergoing non-diffusive homeostasis, leading to improved separability of learned input patterns. These results suggest a plausible mechanism for maintaining heterogeneous neural activity in networks, and expose computational advantages of non-local homeostatic processes.

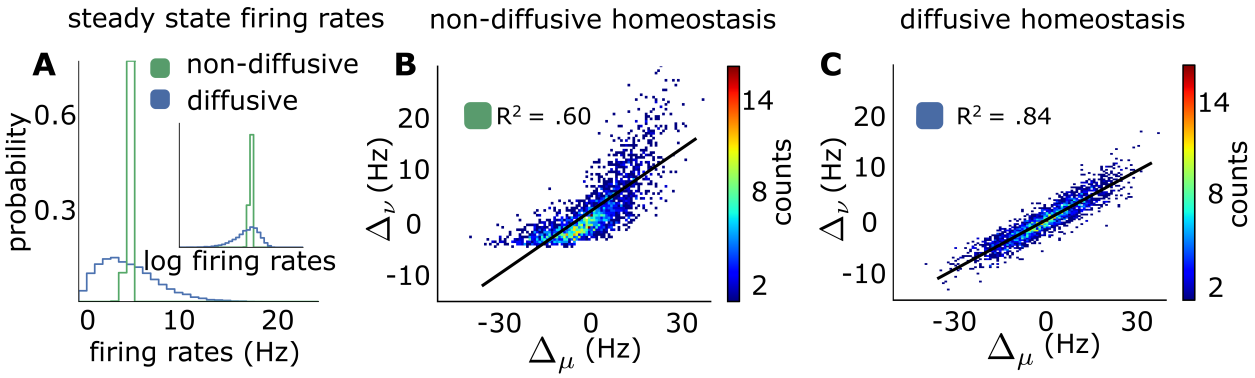

Figure 1. **A**. Distributions of firing rates after diffusive (blue) and non-diffusive (green) homeostasis, for a recurrent network of LIF neurons receiving independent Poisson inputs drawn from a Gaussian distribution. **B, C**: Population response to a change of inputs to these networks. Each count corresponds to a single neuron. We interpret the goodness of a linear fit to change in input rate Δ_μ versus change in output rate Δ_ν as a measure of how little homeostasis interferes with the ability of the network to represent fast changes brought about by novel stimuli or processes such as synaptic plasticity. Black lines shows linear fit, with corresponding R^2 values inset.

AN INTERNAL ACTION REPRESENTATION RULE THAT CAPTURES LEARNING OF OPTIMAL FEEDBACK CONTROL STRATEGIES IN OBJECT MANIPULATION TASKS

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A rapidly growing body of evidence suggests that human motor control is consistent with Optimal Feedback Control (OFC) [1]. However the representations and neural mechanisms that underlie learning optimal controllers remain elusive, particularly in complex motor tasks that involve the manipulation of objects. We propose here that the brain learns OFC for object manipulation tasks by identifying unknown parameters of both body and object dynamics. We present experiments and a novel theoretical framework that can capture in a top down fashion the temporal dynamics of motor learning on a trial-by-trial basis.

Human subjects ($N = 15$) were instructed to move a virtual object of unknown dynamics from start to target locations in an unintuitive task that translated hand velocity into control forces on the object state. While learning an optimal controller directly is a sophisticated non-linear dynamic programming problem, we test here the hypothesis that for the considered task context the brain only needs to learn the unknown task parameters, composed by arm and object dynamics, in a locally linear system identification process that in turn determines an OFC policy. Our approach describes motor learning as gradient descent steps in the space of unknown task dynamics parameters. This mechanism is driven by the error between predicted and actually produced object movements in each trial and can be implemented at the neuronal level by the modification of synaptic weights via Hebbian learning rules. The aspect of adaptation in our approach merges the update of task dynamics and that of the applied OFC strategy. It thus proposes a novel framework that expands and unifies studies which on one hand use predictive models of OFC to fit human performance, assuming that the system dynamics are already known by humans at the initiation of a task [2] and on the other hand previous work which limits the investigation of motor learning to the update of task dynamics while considering a fixed control strategy throughout the experiment [3].

Crucially, our action representation and adaptation model predicts accurately the gradual progression of human learning from trial to trial ($t_{\text{half-life}} = 3.2$ trials). Our results suggest that the brain employs simple learning rules to learn the near optimal control of complex object manipulation in a system identification fashion that updates internal composite representations of body and object dynamics. Our proposed framework provides thereby an algorithmic formalization, which can guide further experimental investigations on the neural foundation of cortical action representations and motor learning rules.

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HIERARCHICAL PROCESSING OF AUDITORY ASYMMETRY

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Communication sounds are typically asymmetric in time and human listeners are highly sensitive to this kind of short-term asymmetry. Traditional models of auditory perception, essentially based on extracting auditory nerve periodicities in a fixed time window, cannot explain these perceptual differences when the Fourier spectra of the stimuli are identical. This is the case of *ramp* and *damp* stimuli, consisting on pure tones modulated by either a raising (ramped) or a falling (damped) exponential envelope. These stimuli elicit an asymmetric perception: ramped sounds are perceived as continuous tones with the pitch of the carrier whereas the damped ones are perceived as a drumming sound without salient pitch sensation.

In this work we propose that the different perception of these stimuli can be explained by introducing a stimulus-driven adaptation of the effective temporal integration window in a hierarchical model of neural ensembles with top-down modulation (1), consistent with predictive coding principles.

In the current study, we investigated the neuromagnetic representation of the auditory perceptual asymmetry of ramp and damp stimuli at the light of this ensemble model by performing MEG recordings and psychoacoustic experiments. Specifically, we considered the perceived salience of the sound and the N100m deflection of the auditory evoked field (AEF), a well-known transient neuromagnetic response elicited around 100 ms after the tone onset, whose latency in the antero-lateral Heschl's Gyrus has been associated with the perceived pitch (2).

We found that N100m amplitudes were significantly larger in ramped sinusoids when compared to damped stimuli. Moreover, the model's responses showed a strong correlation with the N100m deflection, both in amplitude and in latency, further suggesting a hierarchical processing of pitch asymmetry in human auditory system.

In summary, in this work we provide neurophysiological evidence of the representation of perceptual asymmetry in human auditory cortex, and how this representation could be the result of a hierarchical process with multiple integration windows.

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A SIMPLE MODEL OF ENCODING ACCOUNTING FOR MULTIVARIATE NEURAL NOISE IN V1

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The activation of neurons in response to sensory inputs is highly variable and probabilistic methods are essential in decoding the information in neural populations that may be encoded in response to sensory inputs. The Poisson process is the most commonly used process to model the variability of neural spike firing [1]. For instance, Jazayeri and Movshon [2] suggest such a model and derive a decoding which is computed directly as a weighted sum of firing rates. However, Poisson processes constrain spike count variance to be equal to its mean: This is clearly not the case in many cortical areas where responses are more variable [3, 4]. This over-dispersion could be related to hidden variables. For instance, in a visual fixation task, the stimulus is never fully immobilized on the retina due to the continuous small eye jitters. This represents an additional uncertainty about the stimulus representation, and different sources of variability may exist, extrinsic (in the sensory signal) or intrinsic (for instance from lateral interactions within a cortical area, feedback).

We propose an extension of Jazayeri and Movshon's work in which we introduce an explicit model of extrinsic noise. This encoding model includes neurophysiological mechanisms transforming the raw input into spiking neural activity. This results in a compound stochastic mechanism that gives, as in Goris *et al.* [5], better fits to synthetic and a first biological dataset resulting from extracellular recordings of area V1 in macaques monkeys.

Preliminary orientation decoding results, using different methods (maximum likelihood, vector averaging, tuning function), show that, the doubly-stochastic process is as efficient as the simple-Poisson process. With better heuristics of the process parameters estimation and different datasets, we should get a better decoding. Moreover, even if there is no gain in the angle decoding, this novel doubly-stochastic decoding method allows to distinguish different sources of noise and to evaluate their effects on the neural dynamics. Finally, this approach permits a better characterization of the inter-trial variability that helps to deal with low quality recorded data with a limited number of both trials and training stimuli.

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CHARACTERIZATION OF THE EFFECTS OF TONIC AND PHASIC NOREPINEPHRINE RELEASE ON LAYER-SPECIFIC PREFRONTAL CORTEX AND PRIMARY SOMATOSENSORY CORTEX ACTIVITY

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Cortical connectivity is organized by cortical layer. Cognitive control over perception relies on connectivity between the prefrontal cortex (PFC) and sensory cortex, yet little is known about their laminar interactions. Moreover, cognition and sensory-evoked activity are modulated by norepinephrine (NE), which has a layer-specific distribution of receptors. We recorded extracellular laminar activity in rat PFC and primary somatosensory cortex (S1) under urethane anesthesia. Tonic NE release (minutes to hours) was increased by chronic administration (28 days) of the NE reuptake inhibitor Atomoxetine (0.03, 0.3, 1.0 mg/Kg or vehicle). Phasic NE release (sec) was increased by brief electrical stimulation (30 µA, 0.4 ms biphasic pulse at 50 Hz) of the locus coeruleus (LC), which releases NE in the PFC and S1. Increasing tonic NE had opposing effects on superficial and deep PFC laminar activity. Atomoxetine (ATX) reduced spiking (20 min recording) in PFC layer 2/3 (vehicle: 2.55 ± 0.77 Hz, $N = 12$ single units; 1.0 mg/Kg ATX: 1.22 ± 0.22 Hz, $N = 30$ units), while it increased spiking in layer 5 (vehicle: 0.88 ± 0.22 Hz, $N = 17$ units; 1.0 mg/Kg ATX: 3.26 ± 0.49 Hz, $N = 48$ units). Increasing phasic NE predominately evoked sustained (about 1 sec) excitation in a similar proportion of units in all PFC layers. The excitatory effect of phasic NE differed in the context of high tonic NE in that, 83% of units exhibited sustained excitation in the vehicle condition ($N = 18$ units combined across layers), whereas only 34% ($N = 65$ units) exhibited this pattern in the 1.0 mg/Kg ATX condition. Furthermore, the magnitude of firing rate change evoked by phasic NE release was significantly reduced under high tonic NE (0.3 and 1.0 mg/Kg ATX versus vehicle). Therefore, although tonic NE has a layer-specific modulatory effect on PFC neurons, phasic NE evokes excitation in a layer non-specific manner. Moreover, at high tonic levels of NE, further brief NE increases have a reduced excitatory effect. Given that NE affects population activity oscillations, ongoing analyses focus on spike timing (Fano factor and noise correlations), excitatory population response (current source density), and laminar spike-LFP relations. Additionally, we will report how NE modulates the long-range communication between local PFC and S1 circuits by measuring Granger causality between the LFP signals in individual layers of PFC and S1. We expect NE to modulate communication from PFC output layers to circuits in individual S1 layers. Indeed, this may be one mechanism by which ATX improves cognition in individuals with mental illness.

Acknowledgments

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PARTICIPATION OF NEURAL POPULATIONS IN M1 IN THE COORDINATION OF REACH-TO-GRASP

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Extensive psychophysical work has shown that during reach-to-grasp, reaching of the proximal arm (reaching or transport component) is temporally and spatially coordinated with preshaping of the hand (grasp component) (Jeannerod, 1984; Haggard, Wing, 1995). It remains unclear, however, how this coordination is orchestrated at the level of cortex. How do populations of motor cortical neurons representing the movement of proximal and distal joints of the upper limb participate in this coordination? This study looks at population level dynamics of neurons primarily related to either proximal or distal joints. The interactions between these two populations of neurons are compared and contrasted to the coordination of proximal and distal joints required for reach-to-grasp movements.

Two female rhesus macaques were trained on a reach to grasp task. Multiple single units were simultaneously recorded in primary motor cortex while macaques performed reach-to-grasp movements to four different objects presented in seven different locations by a robot. A Vicon motion capture system tracked the kinematics of a set of infrared reflective markers placed on the arm, wrist and fingers from which the kinematics of 17 joints and wrist position were reconstructed. A total of between 33 and 50 neurons were isolated using spike sorting in each data set.

*Neuron*s were classified as primarily related to either the reach component or the grasp component of movement using GLMs; neurons whose activity could be better predicted through a model using only proximal (*e.g.*, flexion or extension angle of the elbow) joint velocities were labeled as reach-related, and those through a model using only distal (*e.g.*, adduction or abduction of the index finger) joint velocities, grasp-related. Single-trial reach and grasp neural trajectories of both populations were examined in a reduced subspace using principal components analysis. Each dataset was subdivided by condition, defined by the object and location used for a given trial. Mean reach and grasp neural trajectories were computed in each condition. Single-trial reach and grasp neural trajectories were then compared to the mean trajectories to measure deviations from the mean as a function of time. These trajectories of reach and grasp neural deviations were then analyzed. Since both populations were simultaneously recorded, the differences between reach and grasp deviations directly reflect how much either lead or lag the other at any point during the trial. We found that the trajectories of neural reach and grasp deviations were coupled, and that the strength of this coupling varied over the course of the trial. Moreover, when one trajectory type started to lag the other, the trajectories appeared to compensate such that they would once again be synchronized; this compensation effect followed a proportional derivative control law—the greater the delay between the two, the greater the magnitude of compensation. The strength of this compensation varied over the course of the trial, and was consistent for each monkey. Shuffling of trial order reduced the degree of this compensation effect particularly towards the middle of movement. In addition, we used linear models to predict these reach or grasp neural deviations on a single-trial basis; the predictive power of models for the grasp neural deviation was always improved by including the reach neural deviation rather than just relying on kinematics, and vice versa.

METADATA MANAGEMENT FOR COMPLEX NEUROPHYSIOLOGICAL EXPERIMENTS

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Technological progress in neuroscience allows recording from tens to hundreds of neurons simultaneously using powerful recording techniques (*e.g.*, multi-electrode recordings) and stimulation methods (*e.g.*, optogenetics), both *in vitro* and *in vivo*. In addition, recordings can be performed in parallel from multiple brain areas, under more or less natural conditions in (almost) freely behaving animals. As a consequence, electrophysiological experiments become increasingly complex. Moreover, to disentangle the relationship between behavior and neuronal activity, it is necessary to additionally document animal training, experimental procedures, and details of the setup along with the recorded neuronal and behavioral data.

Given these various sources of complexity, the availability of information about the experiment, commonly referred to as metadata, is of extreme relevance for reproducible data analysis and correct interpretation of results. Typically, experimenters have developed their own personal procedure to document their experiment, allowing at best other members of the lab to share data and metadata. However, at the latest when it comes to data sharing across labs, details may be missed. In particular if collaborating groups have different scientific backgrounds, implicit knowledge is often not communicated. In order to perform interpretable analysis of the data, each data set should therefore clearly link to metadata annotations about experimental conditions such as the performed task, quality of the data, or relevant preprocessing (*e.g.*, spike sorting).

In order to provide metadata in an organized, easily accessible, but also machine-readable way, an XML based file format called odML (open metadata Markup Language), was proposed (Grewe, *et al.*, 2011, *Front. Neuroinform.* 5:16). Here we will demonstrate the usefulness of standardized metadata collections for handling the data and their analysis in the context of a complex behavioral (reach to grasp) experiment with neuronal recordings from a large number of electrodes (Utah array) delivering massively parallel spike and LFP data (Riehle, *et al.*, 2013, *Front. Neural Circuits* 7:48). We illustrate the conceptual design of an odML metadata structure and provide a practical introduction on how to generate an odML file. In addition, we offer odML templates to facilitate the usage of odML across different laboratories and experimental contexts. We demonstrate hands-on the advantages of using odML to screen large numbers of data sets according to selection criteria (*e.g.*, behavioral performance) relevant for subsequent analyses (see companion posters by Denker *et al.* and Riehle *et al.*). Well organized metadata management is a key component to guarantee reproducibility of experiments and to track provenance of performed analyses.

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IDENTIFICATION OF IMAGES FROM fMRI REPONSE IN VISUAL AREAS USING BERKELEY WAVELET PYRAMID BASED RECEPTIVE-FIELD MODEL

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Over the past 5 years, the identification of visual image using brain signal recording during a person viewing the image is the hot topic in visual information decoding studies. Kay's study used Gabor wavelet pyramid (GWP) to model the reception field, and identified natural images from fMRI signal (Kay, Naselaris, Prenger, Gallant, 2008, *Nature* 452(7185):352–355). However, this GWP based receptive-field model is very complicated and time consumption. Here, we proposed a novel receptive-field model based on the Berkeley wavelet pyramid (BWP) to improve its efficiency.

The receptive-field model based on BWP for a single voxel is composed with a set of Berkeley wavelet bases with four scales, four orientations, and two phases. The stimulus visual images are projected onto each individual Berkeley wavelet base, and the inner-production of stimuli and BWP is half-wave-rectified, taking the positive and negative values separately. And then rectified Berkeley projections are squared and summed, yielding a measure of contrast energy, which is named an input channel. Then we model the response of single voxel as a weighted sum of the input channels. Formally, let p be the number of the images and q the number of input channels. The voxel responses were modeled as $y = X\,h$ where y is the set of responses ($p \times 1$), X is the set of input channels ($p \times q$), and h is the kernel ($q \times 1$). The public data of Kay *et al.* was reanalyzed in this study.

To explore the contribution of different visual partitions to image identification, the voxels of V1, V2 and V3 areas are feed into the identification model respectively. The top of Fig. 1 showed that response in V2 can correctly identify more images than V1 and V3. The computation time is shown in bottom of Fig. 1 (Intel Core i7–3770 CPU@3.4GHz, Matlab 2012a), which is approximately 1/20 of that of the GWP model.

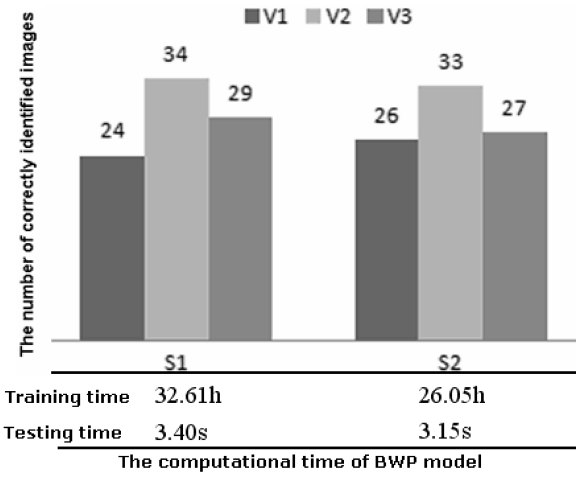

Figure 1. The identification performance of BWP model.

In this study, BWP model was used to identify the natural images from human brain activity. The BWP model form a complete, orthogonal set that minimizes the number of filters required to represent an image. This makes the BWP more computationally efficient than Gabor filter. Moreover, the identification accuracy showed that BWP is suitable for model the voxel response in V2, which is in accordance with the previous study (Willmore, Prenger, Gallant, 2010, *J. Neurosci.* 30(6):2102–2014). It demonstrated that BWP model not only imitates the response from V1 area, but also can efficiently estimate the response from V2 area.

SYNAPTIC CONSOLIDATION: FROM SYNAPSES TO BEHAVIOURAL MODELING

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The brain is subject to a continuous stream of sensory events. If it were to encode all this information, it would soon saturate. A filter is therefore needed to discriminate memories worth remembering from others. The current consensus is that memory engrams are formed by a modification in the strength of synapses involved in the relevant neural assemblies. The changes in synaptic efficacy should withstand the passage of time for extended periods.

The theory of *synaptic tagging and capture* (STC) represents a possible implementation of learning and memory at the level of cellular neurobiology. This framework proposes that memory engrams be first *encoded* in the synapses of relevant brain networks, *tagged* for future maintenance, and finally *consolidated* after their pertinence has been assessed by other brain networks. These processes are highly dependent on neuromodulation of synaptic plasticity by dopamine in the hippocampus and other neuromodulators in other brain regions.

We use theory and simulations to evaluate the hypothesis that STC underlies learning and memory. We first introduce a synapse model that includes internal variables representing the properties of the synaptic weight, the tag and the consolidation process. Along with that model we propose a learning rule exhibiting metaplasticity that can account for experimental findings. Finally we assess the consequences of such a learning rule on memory traces in neural networks.

We find that increasing the number of internal variables is necessary for the implementation of several metaplasticity phenomena observed experimentally. We also show by simulation of a neural network including our synapse model that synaptic plasticity together with tagging and capture could be an explanation to behavioural observations on live rats undergoing inhibitory avoidance training, thereby refining the link between cellular mechanisms and behaviour.

DECODING-ACCURACY VERSUS INTEGRATION-TIME FOR DYNAMIC STIMULI

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Speed and accuracy are two major demands on the neural code. For static stimuli and noisy neurons, the accuracy of stimulus reconstruction improves the longer spikes are collected. This is not true if stimuli are dynamic: in this case, accumulating information by counting spikes over long intervals leads to errors because both the stimulus and neural response change over time. On the other hand, instantaneous decoding and hence immediate stimulus reconstruction is not possible because action potentials are generated with a finite maximal rate. This leads to a trade-off between speed and accuracy, raising the question how the time available for decoding is related to decoding accuracy if the encoded variable is dynamic.

To answer this question, we study populations of independent, Poisson model neurons with Gaussian tuning curves and analyze how the average error of a maximum likelihood decoder depends on the length of the time window in which spikes are collected. As such, this setup is an abstraction of an array of neurons encoding a moving object (Fig. 1A), for instance retinal ganglion cells representing a moving light stimulus or place cells in the hippocampus encoding the position of an animal. We analyze how the properties of the neural population and the dynamical statistics of natural and artificial stimuli affect decoding speed and accuracy.

In all scenarios studied, the average squared error has exactly one minimum value at an intermediate integration time. For short decoding times, an analytic lower bound for the error is given by an exponential function whose decay constant is the population firing rate. For long decoding times, the statistics of the temporal stimulus evolution determine the error, whereas the properties of the neural population become less important. In between, namely around the minimum squared error, our analysis reveals that the part of the error caused by the stimulus dynamics is a quadratic function of the decoding time whose curvature is given by the average value of the squared stimulus speed (Fig. 1B).

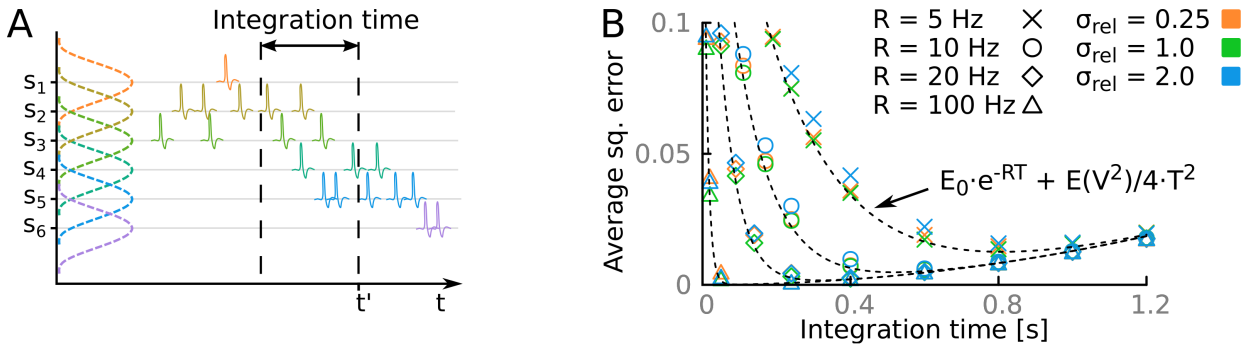

Figure 1. **A**: Spikes fired by six model neurons in response to a dynamic stimulus. **B**: Average squared error as a function of integration time for different population rates R and tuning widths σ_{rel}.

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