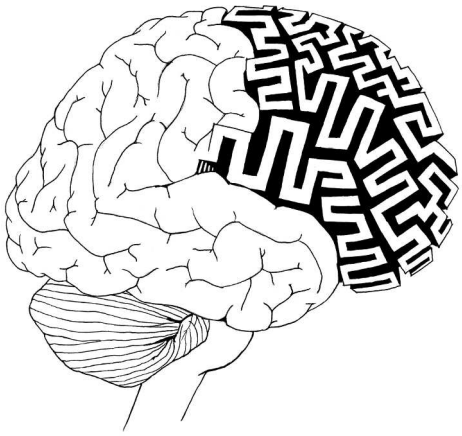
AREADNE 2012

Research in Encoding and Decoding of Neural Ensembles

Nomikos Conference Centre, Santorini, Greece

21–24 June 2012



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Research in Encoding and Decoding of Neural Ensembles
Nomikos Conference Centre, Santorini, Greece, 21–24 June 2012
J. S. Pezaris and N. G. Hatsopoulos, editors

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WELCOME

Welcome

Welcome to AREADNE 2012, the fourth 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 2012 conference was organized by Nicholas Hatsopoulos (Co-Chair) and John Pezaris (Co-Chair), Andreas Tolias, Catherine Ojakangas, Thanos Siapas, and Yiota Poirazi.

Local Organizers

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

Sponsors and Support

Our conference is being sponsored with generous gifts from Dr. and Mrs. George Hatsopoulos, and from Mr. and Mrs. Peter Pezaris to The AREADNE Foundation, a non-profit organization that runs the AREADNE Conferences. In addition, for 2012, the conference is being administered

by the Massachusetts General Hospital, with grant or in-kind support from the the National Science Foundation (Grant number CBET-1205468), The Gatsby Charitable Foundation (Grant number GAT3170), Foley & Lardner, LLC, and The Center for Integrative Neuroscience and Neuroengineering Research at the University of Chicago and the Illinois Institute of Technology.

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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 additional information, we recommend selecting one of the many guidebooks that have been written on island travel in Greece.

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 nap. 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

Ambelos	+30-22860-22544	€ €	caldera view, wine restaurant
Archipelagos	+30-22860-23673	€ € €	caldera view, Santorini cuisine
Koukoumavlos	+30-22860-22510	€ € € €	caldera view, nouvelle cuisine
Nikolas	+30-22860-24550	€	Greek cuisine, next to Town Club
Poldo	+30-22860-24004	€	souvlaki stand, near the National Bank
Saltsa	+30-22860-28018	€ € €	Greek nouvelle cuisine
Sphinx	+30-22860-23823	€ € € €	Greek cuisine, caldera view
The Greeks	+30-22860-22989	€ €	taverna, near the cable car
Mama Thira	+30-22860-22189	€ €	caldera view, taverna

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
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.

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

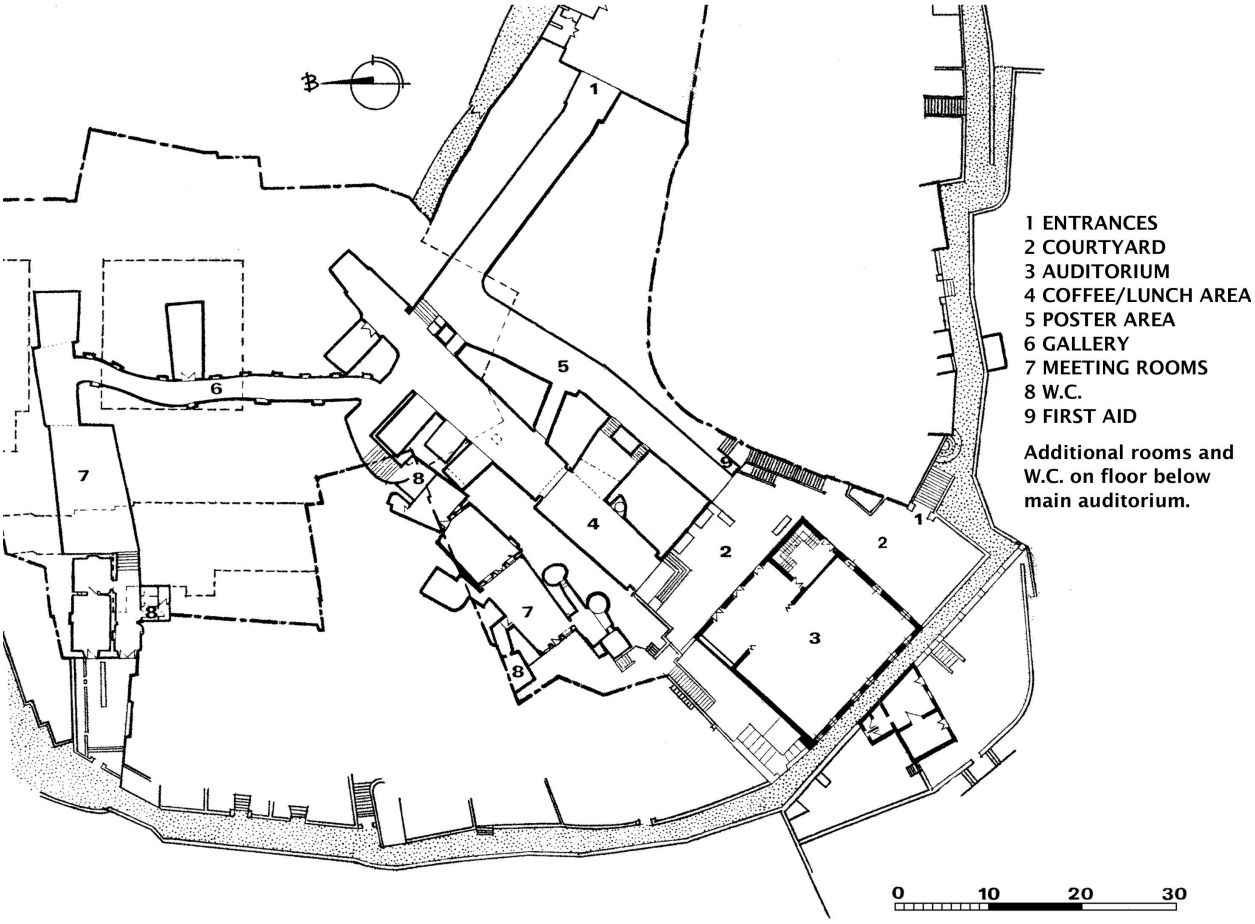
Monastery of Profitis Ilias
in Pyrgos, at the mountain peak; has a nice ecclesiastic museum

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 some care as the water gets deep very 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 held in the reception area and courtyard. Posters will be hung on the walls of the passage from the courtyard to the gallery. A first aid station will be available. Please refer to the map below for more details.



DAILY SCHEDULE AND PROGRAM

Overall Schedule

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

Wednesday
19:00–21:30 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, 20 JUNE 2012

19:00–21:30 welcome reception at Nomikos Centre

THURSDAY, 21 JUNE 2012

09:00–09:30 registration

09:30–09:45 opening remarks

MORNING SESSION John Pezaris, moderator

09:45–10:30 **Tirin Moore** (Stanford University) *Differences and similarities between neural circuits controlling visually guided saccades and visual spatial attention*, 33

10:30–11:00 coffee break

11:00–11:45 **Leslie Osborne** (University of Chicago) *Connecting cortical sensory coding to behavioral performance in smooth pursuit*, 35

11:45–12:30 **Elad Schneidman** (Weizmann Institute of Science) *A thesaurus for a neural population code*, 41

12:30–14:00 lunch

AFTERNOON SESSION Yiota Poirazi, moderator

17:00–17:45 **John O'Keefe** (University College London) *The roles of firing rate and spike timing in hippocampal spatial computations*, 34

17:45–18:15 coffee and light snacks

18:15–19:00 **Michael Hasselmo** (Boston University) *Oscillations, grid cells and encoding of spatial location*, 26

19:00–19:20 **Desmond Patterson** (Patterson Instruments) *Recent seismicity and cone inflation at Santorini: "Doctor, we have a pulse!"*, 36

19:20–19:40 **Andronike Makres** (Hellenic Education and Research Center) *The ancient Greek city states and modern western democracy*, 31

20:00–21:30 posters, presenting author

Gulcan Akgul (Stony Brook University) *Sap97 expression correlates with a physiologically distinguished subset of PV interneurons*, 46

FRIDAY, 22 JUNE 2012

MORNING SESSION Andreas Tolias, moderator

09:00–09:45 **Davi Bock** (HHMI/Janelia Farm) *Neuronal network anatomy from large-scale electron microscopy*, 23

09:45–10:30 **Shy Shoham** (Technion) *Population neuronal interfaces: New methods and results*, 42

10:30–11:00 coffee break

11:00–11:45 **Jean Livet** (INSERM) *A color code for tracking neural lineage*, 29

11:45–12:30 **Yali Amit** (University of Chicago) *A simple network model for a variety of delay match-to-sample tasks*, 20

12:30–14:00 lunch

AFTERNOON SESSION Barry Richmond, moderator

17:00–17:45 **Peter Latham** (University College London) *Olfaction as probabilistic inference*, 28

17:45–18:15 coffee and light snacks

18:15–19:00 **Sliman Bensmaia** (University of Chicago) *Temporal coding in the primate somatosensory system*, 22

19:00–19:45 **David Dickman** (Baylor College of Medicine) *Neural correlates of a magnetic sense*, 25

20:00–21:30 posters, presenting author

Stelios Anastasakis (IMBB FORTH) *Computational modeling of fear memory allocation in amygdalar neuronal populations*, 47

Ryan Canolty (UC Berkeley) *Task-dependent changes in cross-level coupling between single neurons and multi-scale network activity*, 50

R. James Cotton (Baylor College of Medicine) *Three-dimensional random access multiphoton imaging of neural populations*, 53

Alexander Ecker (University of Tübingen) *The correlation structure induced by fluctuations in attention*, 56

Makoto Fukushima (NIH) *Neuronal population dynamics of auditory cortex in stimulus-driven and undriven-resting states in the awake macaque*, 59

SATURDAY, 23 JUNE 2012

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

AFTERNOON SESSION Irini Skaliora, moderator

17:00–17:45 **Idan Segev** (Hebrew University) *Inhibition in the brain — Design principles*, 39

17:45–18:15 coffee and light snacks

18:15–19:00 **Panayiota Poirazi** (FORTH) *Coding with dendrites*, 38

19:00–19:45 **Jeff Magee** (HHMI/Janelia Farm) *Input comparison in neocortical L5 pyramidal neurons produces an object localization signal*, 30

20:00–21:30 posters, presenting author

Tassos Bezerianos (University of Patras) *Advanced techniques to model bi-directional communication of neural ensembles: Theoretical considerations and obstacles*, 48

Rodrigo Cofre (INRIA) *Role of electric synapses in spike trains statistics of linear integrate and fire neural networks*, 51

Thomas Deneux (CNRS) *The spatiotemporal structure of ongoing and evoked activity investigated using optical imaging of voltage sensitive dyes in awake monkey v4*, 54

Pierre Enel (INSERM) *Neural coding in the cortico-striatal system in a decision making task: Insights from reservoir computing*, 57

Felipe Gerhard (Ecole Polytechnique, Federale de Lausanne) *Can network structures be derived from calcium imaging data? — a simulation study*, 60

Julija Krupic (University College London) *Neural representations of location composed of spatially periodic bands*, 63

Wasim Malik (Harvard Medical School) *Inferring movement intention from wideband multiunit activity in the Braingate neural interface system*, 67

Tomislav Milekovic (Brown University) *Decoding kinetic parameters of grasping movements from single unit activity in monkey motor cortex*, 70

Simon Nougaret (CNRS) *Different encoding of reward size and motor effort in the monkey striatum and external part of the globus pallidus*, 73

Amalia Papanikolaou (MPI Biological Cybernetics) *Population receptive field mapping in human subjects after lesions of the visual pathway*, 76

Yury Petrov (Northeastern University) *CARMA: A better linear MAR causality measure*, 79

SUNDAY, 24 JUNE 2012

MORNING SESSION Stelios Smirnakis, moderator

09:00–09:45 **Dan Margoliash** (University of Chicago) *Combining biomechanics of the syrinx and HVC recordings: A new model of motor coding in the bird song system*, 32

09:45–10:30 **Hans Scherberger** (German Primate Center) *Coding and decoding of hand grasping movements in macaque parietal and premotor cortex*, 40

10:30–11:00 coffee break

11:00–11:45 **Eilon Vaadia** (Hebrew University) *Conditioning of neuronal activity in brain machine interface: Local field potential oscillations and spike synchronization*, 43

11:45–12:30 **Nicholas Hatsopouolos** (University of Chicago) *Spatio-temporal spike patterning in motor cortex*, 27

12:30–14:00 lunch

AFTERNOON SESSION Nicho Hatsopoulos, moderator

17:00–17:45 **John Pezaris** (MGH/Harvard Medical School) *Spikes, LFP, and spatiotemporal response fields*, 37

17:45–18:15 coffee and light snacks

18:15–19:00 **Anne Churchland** (Cold Spring Harbor Laboratory) *Putting the pieces together: Integrating information across time and sensory modalities for decision-making*, 24

19:00–19:45 **Dora Angelaki** (Baylor College of Medicine) *Neural correlates of multisensory integration, calibration and plasticity*, 21

19:45–20:00 closing remarks

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

SPEAKER ABSTRACTS
(in alphabetical order by speaker)

A SIMPLE NETWORK MODEL FOR A VARIETY OF DELAY MATCH-TO-SAMPLE TASKS

Yali Amit

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The electrophysiology of delay match-to-sample (DMS) experiments has inspired much of the modeling in attractor networks. In particular, these networks have attempted to model the observation of persistent activity of selective neurons in the delay periods. The basic paradigm posits that stimulation with learned patterns leads to sustained activity due to the learned recurrent connections in the network, serving as a model for the DMS tasks. In this context, several questions arise that are rarely addressed in the literature. How does the network ensure the first sample pattern stays in memory? How does the network figure out that the test pattern is active in memory? How does the network avoid distractor repetitions such as those in the ABBA paradigm of Miller and Desimone (1994)? Additional interesting phenomena have been observed in more recent experiments on repetition detection, including better performance with novel patterns than with learned patterns (Yakvolev *et al.*, 2005). I will present a parsimonious network model based on the original Amit-Fusi (1994) network and show how all these phenomena can be handled within this framework, using simple adjustments of certain global parameters such as inhibition, noise level and depression rate.

NEURAL CORRELATES OF MULTISENSORY INTEGRATION, CALIBRATION AND PLASTICITY

Dora E. Angelaki [*], *Adam Zaidel*

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A fundamental aspect of our sensory experience is that information from different modalities is often seamlessly integrated and calibrated into a unified percept. We have previously explored multisensory cue integration for self-motion (heading) perception using both visual (optic flow) and vestibular (linear acceleration) signals. We recorded from single neurons in the dorsal medial superior temporal (MSTd) and ventral intraparietal (VIP) areas of parietal cortex during a heading discrimination task where trained monkeys, like humans, behaviorally combine visual and vestibular cues to improve perception. Under bimodal stimulation, MSTd and VIP neurons with congruent heading preferences for visual and vestibular stimuli show improved sensitivity and lower neuronal thresholds under cue combination, in line with behavioral integration. These findings provide the first behavioral demonstration of statistically-optimal cue integration in non-human primates and identify a population of neurons that may form its neural basis. Accurate perception of a dynamic environment, however, also requires continuous multisensory calibration. When present, external feedback is particularly beneficial for multisensory calibration, since it serves as a "teacher". However, the principles of interaction between external feedback and relative cue-reliability, and their combined influence on multisensory calibration are currently unknown. To investigate these properties, a systematic heading discrepancy was introduced between the visual and vestibular stimuli and external feedback was congruent with either the more-reliable or less-reliable cue. When external feedback was aligned with the more-reliable cue, the less-reliable cue shifted towards the feedback, and the more-reliable cue (which was already accurate) did not shift. However, when external feedback was aligned with the less-reliable cue, a surprising form of calibration occurred: cues were yoked and shifted together in the same direction. Hence, whilst the more-reliable cue shifted to become more accurate, the less-reliable cue simultaneously shifted away from the external feedback, becoming less accurate. We propose two different mechanisms of multisensory calibration: (1) cue-specific (local) calibration, and (2) reference-frame (global) calibration. When the more-reliable cue is incongruent with external feedback, the entire reference frame (zero) is considered to be inaccurate. Hence cues are yoked and shift in conjunction. When the more-reliable cue is congruent with external feedback, the global reference frame is considered accurate and the less-reliable cue is calibrated individually/locally. These results suggest that the Bayesian-optimal cue-combination is used to assess global accuracy. Congruent MSTd and VIP neurons might provide a neural correlate of these properties.

Acknowledgement

This work was supported in part by EY019087 and EY017866.

TEMPORAL CODING IN THE PRIMATE SOMATOSENSORY SYSTEM

Sliman J. Bensmaia [*], *Michael A. Harvey, Louise R. Manfredi, Hannes P. Saal, Alison I. Weber*

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In primates, the sense of touch has traditionally been considered to be a spatial modality, drawing an analogy to the visual system. In this view, stimuli are encoded in spatial patterns of activity over the sheet of receptors embedded in the skin. We propose that the spatial processing mode is complemented by a temporal one. Specifically, the transduction and processing of complex, high-frequency skin vibrations play an important role in tactile texture perception: When we run our fingers across a textured surface, small vibrations are produced in the skin and travel the extent of the finger and beyond (Figure 1, left). Because different surfaces elicit distinct skin vibrations, textures can be accurately classified based on these vibrations.

Cutaneous afferents exhibit highly repeatable and temporally patterned responses to both simple and complex vibrations. We demonstrate that this patterning conveys stimulus information at millisecond precision and shapes the evoked vibratory percept. This temporally precise spike patterning is also observed in afferent responses to everyday textures (Figure 1, right) and conveys textural information, more so, in fact, than does the spatial pattern of activation elicited over the receptor sheet. A neural code for texture based on spike timing constitutes a significant departure from the commonly held notion that texture is represented spatially.

Finally, we show that the frequency content of both simple and complex skin vibrations is reflected in the temporal patterning in responses of neurons in primary somatosensory cortex to simple and complex skin vibrations up to 800 Hz (Figure 2). Thus, a temporal coding mechanism mediates the tactile processing of skin vibration and, by extension, texture, at the periphery and, more surprisingly, in somatosensory cortex. Having previously revealed analogies between visual and tactile processing, these results underscore a complementary model of somatosensory processing, one that draws a powerful analogy with the auditory and vibrissal systems.

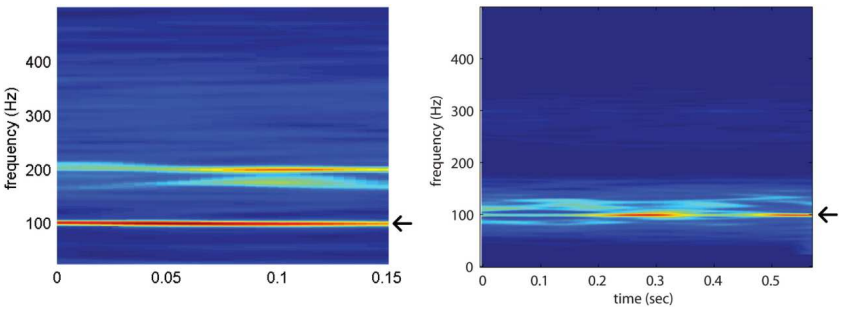

Figure 1. Left: Spectrogram of vibrations, measured using a laser Doppler vibrometer, elicited in the skin when wool gabardine is scanned across it at 80 mm/s. This fabric elicits highly periodic skin vibrations, with a dominant component at around 100 Hz. **Right:** Spectrogram of the response evoked in PC afferents by wool gabardine scanned at 80 mm/s: The dominant periodicity in the vibrations is reflected in the neural response.

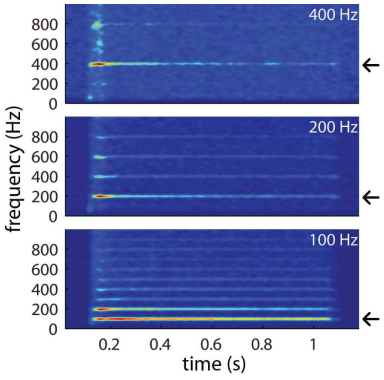

Figure 2. Spectrograms of the population response of S1 neurons to sinusoidal skin stimulation at 100, 200, and 400 Hz (**lower** to **upper**). Cortical populations exhibit entrainment up to 800 Hz.

NEURONAL NETWORK ANATOMY FROM LARGE-SCALE ELECTRON MICROSCOPY

Davi D. Bock

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In mammalian cerebral cortex, axonal and dendritic overlap alone fails to predict the connectivity of excitatory neurons. The chance that one neuron will make a synapse on its neighbor can depend on their *in vivo* tuning properties, long-distance targets, and whether they both participate in a common higher-order connectivity motif. How do these factors integrate to generate an overall pattern of cortical connectivity? And how does this overall pattern relate to the information processing capabilities of the cortex?

Large-scale electron microscopy (EM) of cortex-scale volumes may help answer these questions. In early proof-of-principle work, we have shown that *in vivo* calcium imaging and EM can be combined, allowing physiology and anatomical connectivity to be compared in reasonably large sets of cortical neurons in a single cortical layer. Currently we are scaling up the imaging capacity of our transmission electron microscope camera array (TEMCA) and designing new experiments. Additional work is underway to automate the sectioning, staining, and imaging of thousands of serial thin sections in a hands-free fashion, and to improve correlative light and EM approaches. I will summarize past work and the current effort to determine neuronal connectivity of physiologically characterized cells at the scale of cortical columns.

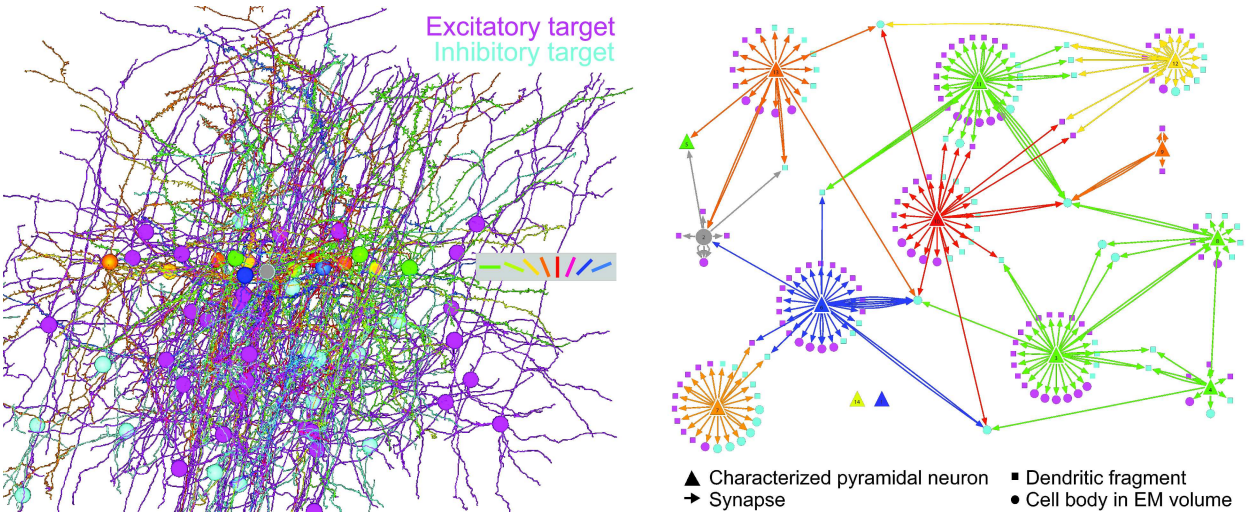

Figure 1. Adapted from Bock DD, Lee WC, Kerlin AM, Andermann ML, Hood G, Wetzel AW, Yurgenson S, Soucy ER, Kim HS, Reid RC (2011) Nature 471(7337):177–82.

PUTTING THE PIECES TOGETHER: INTEGRATING INFORMATION ACROSS TIME AND SENSORY MODALITIES FOR DECISION-MAKING

Anne Churchland [1,*], *David Raposo* [1,2], *John Sheppard* [1,3]

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Sensory stimuli can be ambiguous and uncertain. Considerable recent research has focused on how animals can generate more accurate estimates of a parameter of interest by integrating visual information across time. I will argue that the same circumstances that lead animals to integrate information across time, ambiguous and uncertain stimuli, lead them to integrate information across sensory modalities. My laboratory has developed a novel multisensory decision task that uses dynamic, time varying auditory and visual stimuli. We have collected data from both rats and humans on the task and report three main findings. First, we have found that for multisensory stimuli, both species show improvements in accuracy that are close to the statistically optimal prediction. Next, we report that subjects make use of time in a similar way for unisensory and multisensory stimuli, and for reliable and unreliable stimuli. Finally, we report that synchronous activation of auditory and visual circuitry likely does not drive the improvements in accuracy, since a comparable improvement was evident even when auditory and visual stimuli were presented asynchronously.

Taken together, these findings identify two possible strategies, integrating across time and integrating across sensory modalities, that can help animals overcome sensory uncertainty to make better decisions. Because the inherent variability of cortical neurons renders all sensory stimuli, to some degree, uncertain, these strategies are likely used in many circumstances.

NEURAL CORRELATES OF A MAGNETIC SENSE

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Many animals use the Earth's geomagnetic field for directional heading and navigation, but until now, the neural mechanisms underlying that ability remained unknown. Magnetoreception has been most well studied in birds, where at least three magnetoreceptors have been proposed, including magnetically activated photochemicals in the retina, ferrimagnetic particles in the beak, and ferrimagnetic particles in the inner ear lagena. Regardless of the transduction mechanism/s, the brain must process geomagnetic information to derive constructs representing directional heading and geosurface location. To determine how a vertebrate magnetic sense might function, we first used the c-Fos transcription factor, a marker for activated neurons, to discover where in the brain these computations occur. We found a major magnetoreception pathway that includes the vestibular nuclei, the dorsal thalamus, the hippocampus, and the dorsal hyperpallium; all neural loci known to be involved in orientation, spatial memory, and navigation. We also found, through ablation studies, that avian lagena organs are important contributors to brain regions processing geomagnetic information. We then performed neural recordings from vestibular nuclei cells in awake pigeons during artificial magnetic field manipulation. We quantified the responses of 53 magnetic sense neurons (MR cells) and observed that MR cells encode the direction, polarity, and intensity of the Earth magnetic field. An additional 276 vestibular neurons were responsive to motion, but not magnetic field stimulation, indicating that the MR cell responses were not artifactual. We also found that MR cell sensitivity was proportional to magnetic field intensity and spanned the range of the natural Earth magnetic field (20–65 μT), but saturated at levels over 100 μT. MR cells were cosine tuned with high direction discrimination index values (DDI) to magnetic field orientation, with the cell preferred directions mostly grouped in 45 degree alignments in head coordinates. Recording site identification (electrolytic lesion) verified that these neurons were located in the same vestibular nuclei regions where magnetic field activated c-fos labeled neurons were also found. Finally, we examined the inner ear receptors using high energy X-ray spectroscopy and found Fe_2O_3 ferrimagnetic particles to be located in specific regions of the lagena vestibular organ, but not other vestibular receptors. X-ray absorption near-edge spectroscopy analyses identified the Fe_2O_3 particles as 80% maghemite and 20% hematite, both being highly ferrimagnetic and capable of attraction at weak intensities equal to those of the Earth geomagnetic field. Together, we have characterized a receptor, pathway, and processor of a new magnetic sense.

Acknowledgement

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OSCILLATIONS, GRID CELLS AND ENCODING OF SPATIAL LOCATION

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Grid cells in entorhinal cortex fire when a rat visits an array of locations in the environment that fall on the vertices of tightly packed equilateral triangles (Hafting, *et al*., 2005; Moser and Moser, 2008). The spacing and size of firing fields becomes progressively larger for grid cells recorded in more ventral anatomical locations (Sargolini, *et al*., 2006). Models of grid cells using interference of oscillations predicted that this difference in spacing could arise from differences in the intrinsic oscillation frequency of entorhinal neurons (Burgess, Barry, O'Keefe, 2007).

Whole cell patch data from my laboratory shows that neurons have higher frequencies of resonance and membrane potential oscillations in dorsal compared to ventral entorhinal cortex (Giocomo, *et al*., 2007; Giocomo and Hasselmo, 2008; Heys, *et al*., 2010). This supports the prediction of the oscillatory interference model. We further tested the role of oscillations by combining the recording of grid cells with inactivation of the medial septum by infusions of muscimol (Brandon, *et al*., 2011). These infusions cause a strong reduction in theta rhythm oscillations in the entorhinal cortex and are accompanied by a clear loss of spatial periodicity of grid cell firing, while sparing the head direction selectivity of conjunctive grid-by-head direction cells and of pure head direction cells. This supports an important role of theta rhythm oscillations in generating the spatially periodic firing of gird cells, but not the head direction selectivity.

Further data shows that neurons with head direction selectivity also have a greater propensity for firing on alternate cycles of theta rhythm oscillations (Brandon, Bogaard, Schultheiss and Hasselmo, submitted) and different groups of cycle skipping cells show low cross-correlations indicating that they fire on different cycles of theta rhythm. The pattern of theta cycle skipping also varies depending upon the relative head direction preference of neurons and the location relative to grid cell firing fields.

Simulations have further explored the oscillatory interference model of grid cells. One variant of the model (Hasselmo, 2008) uses velocity modulation of neurons showing rhythmic persistent spiking in the entorhinal cortex (Fransen, *et al*., 2006; Tahvildari, *et al*., 2007; Yoshida, *et al*., 2008) and in the postsubiculum (Yoshida and Hasselmo, 2009). Newer versions of the model have overcome the problem of variance in single cell oscillations or persistent spiking (Zilli, *et al*., 2009) by enhancing reliability via network interactions between spiking neurons (Zilli and Hasselmo, 2010). Another recent model has combined oscillations with network attractor dynamics to generate the spatial periodicity of grid cells (Hasselmo and Brandon, in review).

SPATIO-TEMPORAL SPIKE PATTERNING IN MOTOR CORTEX

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Wave propagation of neural activity has been documented in a number of neocortical areas including visual, somatosensory, and motor cortices as measured by local field potential (LFP) recordings and voltage sensitive dyes. In particular, we have shown that motor cortical LFP oscillations in the beta frequency range (about 20 Hz) propagate as travelling waves across the surface of primary motor cortex along a rostral-to-caudal axis while monkeys perform a variety of visuo-motor tasks including simple reaching tasks and more complex reach-to-grasp tasks. We provide evidence here that simultaneously-recorded, motor cortical neurons coordinate their spiking activity in a sequential manner that mirrors the dominant wave propagation directions and speed of propagation. Moreover, we show that the temporal dynamics of wave propagation signal aspects of motor behavior. We suggest that these patterns of wave propagation may serve to sequentially recruit neurons representing different limb segments in a coordinated fashion.

OLFACTION AS PROBABILISTIC INFERENCE

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Inferring what odors are in the air is a hard problem, for at least two reasons: the number of odorant receptor neurons (the first neurons in the olfactory pathway) is smaller than the number of possible odors, and multiple odors can be present at once. Consequently, even if there is a simple mapping from odors to odorant receptor neurons that mapping cannot be uniquely inverted. Presumably, the brain solves this problem by computing the probability that any particular odor is present. We present an inference algorithm that does this, discuss how it maps onto olfactory circuitry, and comment on what we learn about sensory processing in general.

A COLOR CODE FOR TRACKING NEURAL LINEAGE

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Correlating the lineage relationships of individual neurons with their functional and anatomical properties will help understanding the developmental constrains that participate in shaping neural circuits. To this aim, a convenient readout of individual cells' developmental history applicable to relatively densely labeled samples and compatible with functional measurements would be useful. While several methods have been used to label and identify clonally related cells in the developing and mature brain, most of them are based on a single or a few labels, making it difficult to track multiple clones in a given sample.

I will present the steps that we undertook to establish a multiplex lineage tracing scheme applicable to the cerebral cortex, taking advantage of Brainbow transgenes expressing random combinations of fluorescent proteins (CFP, YFP and RFP) for simultaneously marking multiple precursors during development and identifying their progeny at a later stage. We express new Brainbow transgenes creating an expanded palette of markers in embryonic cortical progenitors using *in utero* electroporation and/or transgenesis. Cre recombination triggers focal yet semi-sparse multicolor labeling of the cells born at the time of electroporation, sustained into adulthood. Genome integration of Brainbow vectors using transposase-dependant vectors or transgenic mouse lines allows for maintaining color labels in dividing neural stem cells and their progeny over multiple rounds of cell divisions. With this approach, we visualize the descendants of embryonic progenitors in the neural and glial lineages. Discrete combinations of markers expressed by genome-integrated transgenes provide a readout of the labeled cells' lineage relationships. This combinatorial labeling strategy opens the possibility to explore and correlate the clonal relationships, morphologies and interactions of multiple individual cells in the developing and adult nervous system.

INPUT COMPARISON IN NEOCORTICAL L5 PYRAMIDAL NEURONS PRODUCES AN OBJECT LOCALIZATION SIGNAL

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Layer 5 pyramidal neurons are the primary output of the barrel cortex and they receive functionally distinct inputs onto separate dendritic regions. Coincident input from these segregated pathways initiates regenerative dendritic electrical events that shift the action potential output mode to burst firing. This powerful dendritic nonlinearity could mediate computations based on input correlation. To test this we recorded dendritic activity from layer 5 pyramidal neurons in the barrel cortex of awake behaving mice using *in vivo* two-photon imaging. Large amplitude, global Ca^{++} signals were observed throughout the entire apical tuft dendrites as mice performed an object detection task with their whiskers. Dendritic recordings in anesthetized mice and *in vitro* suggest these novel global signals are produced by dendritic plateau potentials that are coincident with widespread layer 1 (L1) synaptic input. Quantitative behavioral assessment indicates that the dendritic signals were evoked by whisker-object contact at particular locations. Also, learned refinements in the whisking pattern were associated with modifications in the dendritic signals. These data provide evidence of nonlinear dendritic processing during a behaviorally relevant computation.

THE ANCIENT GREEK CITY STATES AND MODERN WESTERN DEMOCRACY

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After the end of the Bronze Age palatial Minoan and Mycenean civilizations (around 1000 B.C.), followed the Dark Ages for approximately two centuries. Then in the 8th c. B.C. emerged the Greek City states which were small scale politically independent communities as opposed to the large scale imperial powers of the Near East.

The Greek states used the alphabet for the first time, spoke and wrote Greek, believed in the 12 gods, trusted the potential for excellence of simple individuals and secured for their citizens 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 which was a highly sophisticated direct Democracy. What do Modern Western type democracies owe to the Ancient Greek city state civilization and particularly to Ancient Athenian Democracy?

COMBINING BIOMECHANICS OF THE S12INX AND HVC RECORDINGS: A NEW MODEL OF MOTOR CODING IN THE BIRD SONG SYSTEM

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In principle, the organization of the motor system can be understood by reference to the biomechanics of the peripheral articulators. In practice, it has been challenging to find the proper modeling framework to capture essential features of movements in a low dimensional description. Another challenge in exploring motor systems organization has been the constraint of recording from behaving animals. Whereas the technical challenge of such recordings has often been emphasized, the larger conceptual issue is the lack of experimental control over the variance in the behaviors being analyzed.

We have developed solutions to these problems and applied these to analysis of motor organization. We used a dynamical systems model that represents subsyringeal pressure, syringeal membrane tension, and filtering by the upper respiratory tract to represent the songs of zebra finches. Using only recordings of the airborne song it was possible to produce realistic songs, that matched the original recording. The modeling resulted in significant reduction in dimensionality of singing dynamics, with songs described as as a sequence of trajectories in pressure vs. time and tension vs. time. Examining the pressure-tension space we observed that for most trajectories, birds maintained the control parameters near Hopf or saddle-node bifurcations of the model. The trajectories were often associated with individual notes of a song syllable. We call these trajectories motor vocal “gestures” — the movements a bird needs to make to produce the corresponding sounds.

Song system neurons in sleeping zebra finches selectively respond to playback of the bird’s own song (BOS), with the same or similar pattern of bursts as that neuron emits while the bird sings during the day. We took advantage of this aspect of neuronal replay in coordination with the song models to explore features of motor system organization.

We observed that premotor cortical HVC neurons responded maximally to playback of BOS synthesized in a limited range of static parameters (noise and dissipation). This demonstrated that neurons were tuned to features of song in a motor framework. We then examined the response of HVC neurons to BOS playback, and analyzed the results in relation to dynamic model parameters. Phasic HVC neurons (projection neurons) were excited at the times of gesture trajectory extrema (onset, offset, or maxima of pressure or tension paths). Tonic HVC neurons (interneurons) were suppressed at extrema, on average lagging phasic neurons by circa 5 ms. Thus one model is that sparse bursts of phasic neurons drive tonic neurons, which maintain the dynamics in HVC. Song dynamics must be created anew in the cortical motor output nucleus RA, which HVC projects to. For both phasic and tonic neurons, the time between HVC activity and the associated gesture was much shorter than the delay between HVC activity and sound production in the periphery. Preliminary data of recordings from singing birds are consistent with these observations.

We conclude that HVC activity encodes song dynamics in terms of trajectories of movements. The timing of this activity represents a “forward” model making predictions on expected behavior. These results identify the kernel of song production, and emphasize the importance of movement trajectories and non-linear temporal integration for prediction in motor organization. We are interested in exploring these predictions for speech production.

DIFFERENCES AND SIMILARITIES BETWEEN NEURAL CIRCUITS CONTROLLING VISUALLY GUIDED SACCADES AND VISUAL SPATIAL ATTENTION

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Recent work indicates that while structures involved in the control of visually guided saccadic eye movements also appear to control covert visual spatial attention, separable neural circuitry can nonetheless be demonstrated. Neurons within the frontal eye field (FEF), an area of prefrontal cortex, play a key role in the programming and triggering of saccades and also influence signals within posterior visual cortex. I will discuss neurophysiological results from a broad range of past studies, as well as very recent work, that elucidate how frontal-visual cortical networks function to both guide oculomotor behavior and to select visual information according to behavioral goals. This evidence suggests that interdependent, but separable, neural circuits underlie covert and overt visual attention.

THE ROLES OF FIRING RATE AND SPIKE TIMING IN HIPPOCAMPAL SPATIAL COMPUTATIONS

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The rodent hippocampal formation constructs a spatial representation of the local environment which can be used to identify the animal's current location, to remember events that happened there in the past, and to navigate to desirable locations in that environment. Spatial cells found in hippocampal formation represent the animal's location (place cells), its current heading direction (head direction cells), the metric of the environment (grid cells), and the animal's distance from boundaries of the environment (boundary vector cells). All of the cells use firing rate as the code for spatial representation. In addition, however place and, perhaps also, grid cells use a timing code. This timing code takes the form of the phase of spike firing relative to the ongoing theta-LFP (local field potential) wave. The sinusoidal theta rhythm is a prominent feature of the hippocampal LFP which ranges 6–11 Hz in the rat, the rate varying as a function of the animal's running speed. We have suggested that theta-LFP is an integral part of one of the mechanisms by which the hippocampus carries out spatial computations. A key idea here is that there is not one but several theta-like oscillations of differing frequencies which interact within cells and produce oscillatory interference patterns which can account for many of the properties of place and grid cell firing. I will describe these ideas and provide evidence in support of them.

CONNECTING CORTICAL SENSORY CODING TO BEHAVIORAL PERFORMANCE IN SMOOTH PURSUIT

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Performance in sensorimotor behaviors guides our understanding of many of the key computational functions of the brain: the representation of sensory information, the translation of sensory signals to commands for movement, and the production of behavior. Eye movement behaviors have become a valuable testing ground for theories of neural computation because the neural circuitry has been well characterized and eye movements can be tightly coupled to cortical activity. We use an eye movement behavior called smooth pursuit as a model for testing theories of sensory coding. Pursuit is a natural behavior in which we move our eyes along with a visual target in order to stabilize its image on the fovea, a region of the retina with high spatial acuity, so we can see it in detail. There is a performance cost for errors in pursuit, as a failure to match the eye to target movement will cause the retinal image to slip and impair visual acuity.

The visual signals that guide pursuit arise from cortical area MT. Neurons in area MT provide information about a target's movement with the first few spikes of their responses on the timescale relevant to pursuit. The precision of pursuit behavior and motion perception are quite similar over time, suggesting that pursuit provides a close lower bound on the amount of information that is decoded from MT. It is not possible to record from the entire MT subpopulation mediating pursuit initiation, but we can use experimental data to construct realistic cortical populations that preserve the diversity of rate dynamics and motion tuning observed in MT neurons. Using these data, we can estimate the size of the coding pool under different correlation models and test the efficiency of cortical codes.

RECENT SEISMICITY AND CONE INFLATION AT SANTORINI: "DOCTOR, WE HAVE A PULSE!"

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The remarkable and beautiful island of Santorini is the result of a long history of repeated volcanic activity. The geologic record indicates at least twelve major eruptive episodes over the last 400,000 years. And, over the last 200,000 years, four of these are believed to have resulted in the collapse of the central cone with subsequent caldera formation. These eruptions are related to the repetitive discharging and recharging of the shallow (4 to 8 km deep) Santorini magma chamber. The ultimate magma source being partial melting of upper mantle material beneath the Hellenic arc.

The most recent major event (the Minoan eruption ca. 1610 BC) was truly catastrophic, with the total volume of ejecta now estimated at about 100 Km^3 (equivalent to 60 Km^3 of magma). This is five to ten times larger than Krakatau (Indonesia, 1883), and a hundred times St. Helens (USA, 1980). Eruptions of this magnitude are quite rare, with only six occurring worldwide in the last 10,000 years. The Minoan eruption effectively emptied the Santorini magma chamber leading to significant foundering and deepening of the caldera floor, and the process of recharging has been likely ongoing ever since.

The Conference Volcano Field Excursion will be to the Kameni Islands in the centre of the Santorini caldera. These young (< 2000 y) islands represent the first stages of the next cycle of volcano building and are comprised of lavas geochemically distinct from the products of the 1610 BC Minoan eruption. As such they are the surface expression of an injection of new magma into the system. The last (relatively minor) eruption of Nea Kameni ended in 1950, and for the subsequent six decades Santorini has been quiescent — the only evidence of active volcanism being minor stem vents and warm springs.

This situation, however, has changed dramatically since the last AREADNE meeting of 2010. In January of 2011, Santorini awakened with a significant swarm of shallow (1 to 6 Km) earthquakes beneath the caldera and detectable deformation of the volcanic edifice. Using a dense network of GPS stations (5 permanent and 19 temporary) a predominantly Greek and American team have determined that the volcano is slowly expanding radially — in the twelve months to January 2012 the distance from Nomikos Conference Centre to the southern tip of Therasia (7.2 Km) had increased by about 140 mm, and was continuing to expand at a rate of about 180 mm/y. A best fit spherical model of the cone inflation is consistent with injection of 14 million m^3 of magma into a chamber approximately 4 Km deep located about 1 Km north of Nea Kameni (Newman et al., 2012).

Although impressive on human scales, these figures represent only 0.03% of the estimated eruptive volume of the Minoan event. Professional volcanologists are uncertain if this activity heralds an imminent eruption as other calderas have behaved similarly without erupting, but it demonstrates powerfully the dynamic nature of active volcanoes such as Santorini — "Doctor, we have a pulse!"

SPIKES, LFP, AND SPATIOTEMPORAL RESPONSE FIELDS

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Spike trains have long been used to determine the response characteristics of individual neurons through reverse-correlation mapping techniques, such as spike-triggered averaging, to create spatio-temporal response fields (STRFs). In this presentation, such standard techniques are generalized from using spike trains as the input signal to using continuous-valued recordings such as the wideband counterpart to the LFP, that we call the WFP (Wideband Field Potential). Examining signals from two separate brain areas, we find the resulting spatiotemporal response fields reflect a robust signal within the WFP that carries more information than sorted spike trains from the same recording.

We first examine primate motor (MI) and dorsal pre-motor (PMd) cortex recordings made in the Hatsopoulos laboratory at the University of Chicago during a random reach task and find stronger evidence for gesture-based tuning than for velocity or acceleration tuning. Additionally, by tuning the WFP filters to different bands, we find apparently independent information streams in different frequency channels. Continuous signal response fields tend to have higher signal-to-noise than spike-based fields, but not overwhelmingly so.

We then examine primate thalamic lateral geniculate nucleus (LGN) recordings made during a visual mapping task and again find clear evidence for strong response fields computed with WFP that have substantially higher signal-to-noise (SNR) than those from spike trains from the same recordings. Tantalizing hints were found for different response channels in different WFP frequency bands, although not as strong as for motor cortex.

If we take the relative strengths of the WFP and spike-based STRFs to be an indicator of the level of local similarity within an area, our findings suggest that there are differences in encoding locality and redundancy from one cell to the next in the two brain areas presented. Specifically, LGN carries much more encoding redundancy for information contained in the mapping task than the motor cortex does in the random reach task.

CODING WITH DENDRITES

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The goal of this presentation is to provide a set of predictions generated by biophysical and/or abstract mathematical models regarding the role of dendrites in information coding across three different brain regions: the hippocampus, the prefrontal cortex and the amygdala. Towards this goal I will present modelling studies — along with supporting experimental evidence — that investigate how dendrites may be used to facilitate the coding of both spatial and temporal information at the single cell, the microcircuit and the neuronal network level. I will first discuss how the dendrites of individual CA1 pyramidal neurons may allow a single cell to discriminate between familiar versus novel memories and propagate this information to down stream cells [1]. I will then discuss how these dendritic nonlinearities may enable stimulus specificity in individual PFC pyramidal neurons during working memory [2] and underlie the emergence of Up and Down states at the single cell and the microcircuit level [3,4]. Finally, I will present findings from our ongoing work regarding the role of dendrites in shaping the formation of fear memory engrams in the amygdala [5].

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INHIBITION IN THE BRAIN — DESIGN PRINCIPLES

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In 2012 we celebrate the “80 years of Inhibition” — a mechanism that was the focus Sir Charles Sherrington’s seminal work. In his 1932 Nobel lecture Sherrington says that, “in the working of the central nervous machinery inhibition seems as ubiquitous and as frequent as is excitation itself,” and that, “nice co-adjustment of excitation and inhibition upon each of all the individual units which cooperate in the act.” Yet, the division of labor between excitation and inhibition is not fully understood, neither is it clear why the various brain systems utilize a pleura of inhibitory cell class (chandelier, basket, Martinotti etc.). In recent years the fine connectivity pattern of inhibition is beginning to be unraveled; it became clear that in many central systems, including the hippocampus and the neocortex, individual inhibitory axons from distinct input sources targeting specific dendritic sub-domains, where each axon forms multiple (10–20) synaptic contacts. This domain-specific dendritic inhibition is expected to play a key role in controlling local nonlinear and plastic dendritic processes. However, our understanding of dendritic inhibition is currently dominated by the viewpoint that considers the impact of inhibition at the soma/axon region; we lack a theoretical framework for understanding the local impact of dendritic inhibition (a “dendro-centric” viewpoint). I will present an analytical approach that fills this gap and that provides several new and counter-intuitive insights on the operation of dendritic inhibition. It explains why some inhibitory synapses target very distal dendrites, why single inhibitory axons form multiple synaptic contacts and why in many central systems inhibition consists of about 20% of the total number of synapses. Our findings call for a revision in our understanding the computational and plastic functions of dendritic inhibition.

CODING AND DECODING OF HAND GRASPING MOVEMENTS IN MACAQUE PARIETAL AND PREMOTOR CORTEX

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Hand function plays an important role in all primate species, and its loss often leads to severe disability. Hand grasping is a complex motor behavior for which the brain integrates sensory and cognitive signals to provide meaningful actions. To achieve this computation, specialized brain areas in the parietal (anterior intraparietal area, AIP) and premotor cortex (area F5) play important roles. This presentation highlights recent experimental results to characterize how AIP and F5 generate hand grasping intentions and how grasp movements can be read out, or decoded, in real-time. Such characterizations could be useful to evaluate the suitability of these motor-planning areas for the development of neural interfaces that aim to restore hand function in paralyzed patients.

Macaque monkeys were trained to perform a delayed grasping task where they grasped a target (a handle) either with a precision grip or with a power grip, and with the handle oriented in five different orientations. Grasp trials consisted of four epochs (fixation, cue, memory, and movement), and eye position was monitored with an optical eye tracker. After training, neural activity was recorded simultaneously from AIP and F5 using either movable electrodes (Thomas Recording, Germany) or permanently implanted electrode arrays (Microprobe Inc, USA), while the animal performed this this task.

In AIP and F5, we found several types of neurons that represented in different task epochs some of the following signals: the visual stimulus, motor intention prior to the movement, or movement execution signals. These signals persisted in a choice task and there also reflected reward modulation. Variation of the spatial location of the grasp target and of the eye position revealed that AIP and F5 also represent the reach target location in addition to the grip type. Furthermore, we could successfully decode grip type and object orientation in real-time from a population of AIP and F5 neurons during the motor planning, *i.e.*, without requiring the animal to actually execute the grasp action.

These results demonstrate that neurons in AIP and F5 are actively involved in the sensorimotor transformation of sensory information into motor intention and execution signals for hand grasping. Signals are modulated by choice and the amount of reward, suggesting that they play an important role for the selection of specific grasp actions based on their behavioral relevance. Furthermore, high-level grasping signals can be used for real-time predictions of hand movements, which might be relevant for future clinical applications in neural prosthetics.

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A THESAURUS FOR A NEURAL POPULATION CODE

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Noise in neural circuits determines the capacity of the neural code and how information can be decoded. To correctly decode, we (and the brain) must understand which activity patterns are semantically rather than syntactically similar. To characterize the semantic organization of the codebook of large neural populations, we learned a population code *thesaurus*: the dissimilarity of two population patterns R_i and R_j, was given by the distance between the distributions over stimuli that may elicit them, $P(S|R_i)$ and $P(S|R_j)$. Applied to large groups of retinal ganglion cells presented with natural and artificial movies, and found that the population codebook is organized in clusters of words with similar meanings (which simple syntactic metrics like Hamming distance failed to capture). Moreover replacing each codeword with the identity of the cluster it belongs to, retained most of the information about the stimulus. The neural thesaurus further allowed us to accurately decode novel stimuli from population responses we did not observe before. Our results suggest a new framework for mapping the nature of neural population code and decoding.

POPULATION NEURONAL INTERFACES: NEW METHODS AND RESULTS

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The talk will present several recent steps in the development of tools for controlling and monitoring neuronal populations and looking at how they encode information. I will describe patterned holographic stimulation for simultaneously controlling populations of retinal ganglion cells with millisecond temporal precision and cellular resolution, and its early translation to *in vivo* conditions. I will then discuss the development of a multiphoton temporal-focusing microscope allowing to monitor activity in over 1000 neurons simultaneously in “optonet” artificial neural networks. Finally, I will present recent results on the encoding of speech features in neuronal populations recorded in human subjects, and the development of a simple and effective decoding strategy and structural inference for this data (joint work with Itzhak Fried and Ariel Tankus).

CONDITIONING OF NEURONAL ACTIVITY IN BRAIN MACHINE INTERFACE: LOCAL FIELD POTENTIAL OSCILLATIONS AND SPIKE SYNCHRONIZATION

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Frequency bands of LFP have been associated with a plethora of cognitive roles. In particular, various clinical disorders have been associated with abnormalities in the power of the lower gamma frequency (30–50 Hz), such as ADHD, Autism, Schizophrenia, Epilepsy and others. These abnormalities are thought to reflect in turn abnormalities in the degree of neural synchronization in either a local or distributed manner. Furthermore, in recent years it has been shown that a wide variety of cognitive functions incorporate changes in the power and synchronization of the lower gamma band. The precise role of these oscillations, however and the extent of their contribution to single neuron synchrony in a behavioral context remain unclear.

In this study we used a Brain-Machine Interface (BMI), to train monkeys to specifically increase the power of the 30–43 Hz band in the motor cortex. Over the course of several sessions the monkeys learned to use the BMI to move a cursor on the screen and obtain a reward. The evoked activity was oscillatory in nature, band specific and clearly apparent on a single-trial basis. This was done absent any overt activation of arm muscles or movements. The increase in the LFP band power was accompanied by a dramatic increase in the amount of neural synchrony, allowing previously uncoordinated pairs of neurons to fire together in a time-precise manner.

Our findings have a two-fold significance: On the clinical side, they stand as an important step in the development of treatments for a wide variety of conditions in which the level of neural synchrony is impaired. From a neurophysiological perspective, we have shown a causal link between LFP oscillations, neural synchrony and behavior, which hopefully leads us towards a more complete understanding of computations in the brain.

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POSTER ABSTRACTS

(in alphabetical order by first author)

SAP97 EXPRESSION CORRELATES WITH A PHYSIOLOGICALLY DISTINGUISHED SUBSET OF PV INTERNEURONS

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In the cortex, one of the most prominent interneuron subtypes that regulate the activity of local microcircuits are parvalbumin (PV) positive interneurons. PV interneurons are mainly basket cells and Chandelier cells that are fast-spiking. The fast-spiking phenotype of PV interneurons are determined with specific types of K channels and interestingly enough, K channel expression is differential in subsets of PV interneurons in the cortex (1).

SAP97 is a member of the MAGUK (membrane-associated guanylate kinase) family of proteins. It interacts with various subtypes of K channels and regulate their trafficking and clustering at the membrane (2). Additionally, it interacts with GluA1 subunit of AMPARs which is prominently expressed in PV interneurons.

SAP97 expression in cortical PV interneurons is developmentally regulated, with a subset of PV interneurons showing greatly decreased expression in adult mice (3). Given the important functional roles of SAP97 in membrane expression of ion channels and morphology of neurons, we wanted to elucidate the identity of these interneuron subsets and the functional consequences of SAP97 expression. To do so, we used whole-cell patch clamp technique to monitor physiological properties of SAP97-expressing and non-expressing PV interneurons along with single cell RT-PCR. Our results showed that SAP97-expressing PV interneurons exhibit a significantly lower input resistance, faster action potential kinetics and stuttering fast-spiking firing pattern in response to depolarizing current. Glutamatergic synaptic currents of SAP97-expressing PV interneurons have significantly increased frequency than the currents of SAP97-nonexpressing subgroup whereas the amplitudes and the rise and decay kinetics of currents are comparable. Overexpression of SAP97 in SAP97-nonexpressing PV interneurons transformed their intrinsic firing properties as well as the glutamatergic input they receive.

Our results suggest that SAP97 is involved in different mechanisms in PV interneurons including their intrinsic physiological identity and connectivity with pyramidal neurons. The detailed description of these mechanisms and their biological consequences are yet to be found.

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COMPUTATIONAL MODELING OF FEAR MEMORY ALLOCATION IN AMYGDALAR NEURONAL POPULATIONS

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The amygdala is a subcortical area with a well-known role in emotional memories, such as fear memory. In auditory fear conditioning, a well studied form of classical conditioning, fear memories are stored in the synapses formed by afferent inputs to the Lateral Nucleus of the Amygdala. The process of this associative memory formation has been shown to be affected by the regulation of the activation of the transcription factor CREB. Lateral Amygdala neurons with artificially increased CREB activation are preferentially recruited to form the fear memory trace, and ablation or reversible inactivation of these neurons disrupts the fear memory (Han, Science 2009). CREB overexpression however does not alter the neuronal size of the memory trace.

In order to investigate the formation of the fear memory trace, we create a computational model of Lateral Amygdala neurons using adaptive integrate-and-fire neurons with plastic synapses. Our model incorporates an interplay between excitatory and inhibitory connections as well as afferent inputs according to experimental information. The spatial pattern of the synaptic connectivity within the neuronal population is modeled according to electrophysiological studies (Pape and Pare, Physiol. Rev. 2010) and CREB activation is modeled via the modulation of the excitability of excitatory neurons. By modeling connectivity and the time course of CREB expression, we aim to study the process and the properties of the fear memory trace formation and its implications for memory models. Preliminary results show that the connectivity pattern can limit the size of the population encoding the memory trace.

ADVANCED TECHNIQUES TO MODEL BI-DIRECTIONAL COMMUNICATION OF NEURAL ENSEMBLES: THEORETICAL CONSIDERATIONS AND OBSTACLES

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The brain is a complex, dynamical system. It is characterized by strong recurrences (highly nonlinear) and widespread, bidirectional communication. As a consequence it is enormously difficult to distinguish local processing from interactions between structures. This is a major obstacle to the identification of a modular organization of the brain. However, complex network analysis enables the researcher to consider the whole brain directly as a network and then characterize its topology. The main goal of brain connectivity analysis is to study the "where," "when," and "how" of our brain functions.

Macroscopic models of neurons can inform us about whole brain dynamics and interactions between large-scale neural systems such as cortical regions, the thalamus and brain stem. Moreover, brain stimulation methods, such as optogenetics and transcranial magnetic stimulation (TMS), have been proposed to probe and interfere with brain functions.

To exploit all of these techniques, mathematical models are necessary in order to permit the mapping of brain networks and the subsequent investigation of their components. To date, we have implemented several techniques to identify directionality of interaction in weakly coupled oscillator systems (Cimponeriu, Bezerianos, *et al.*, 2002). Moreover, Stavrinou, Bezerianos, *et al.*, (2007) employed event related synchronization and desynchronization phenomena and phase synchronization analysis. In addition, network approaches have also been investigated through a Time-Varying Dynamic Bayesian Network (Benz, Bezerianos, *et al.*, 2011). The next step of the latter research is the investigation of time-frequency decomposition of ECoG signals, so that more degrees of freedom are included in the study.

We may say that proposed methods suffer from two fundamental limitations: Firstly, they do not take into account the "state-dependency" of the neurons. That is, neuronal activity depends not only on the external stimulus but also on the internal state of the neural microcircuit network. Secondly, the methods investigate only the unidirectional interactions between neurons, so they do not discriminate between inhibitory and excitatory activities.

In this work we are considering the brain as a complex network, and investigate the bidirectional communications between ensembles of neurons using mathematical models through the understanding of chimera states for coupled oscillators. We develop a parametric chimera state model incorporating physiological parameters of neuronal ensembles (distributed coding, multitasking, mass effect principle, plasticity, context principle) and explore possible solutions for both numerical solution of the model and applications with real neurophysiological signals.

Acknowledgment

The E.U. European Social Fund and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework, Research Funding Program: Thalis. Investing in knowledge society through the European Social Fund.

IDENTIFYING TEMPORAL CONTINUITY OF NEURAL POPULATION ACTIVITY WITH REGULARISED LATENT DYNAMICAL SYSTEMS

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With the help of modern multi-cell recording techniques, it is possible to observe at high temporal resolution the activity of up to hundreds of neurons *simultaneously*. Such high-dimensional data sets call for appropriate methods to analyse the statistical structure of the recorded population activity. Latent variable models, including Gaussian-process factor analysis and hidden linear dynamical system (LDS) models, turned out to be particularly well suited to model population dynamics in some cortical recordings (Macke *et al.*, NIPS 2011). These models can account for temporal continuity in the data, especially in the shared variability of multiple neurons, by modelling the activity as noisy observations of an unobserved low-dimensional process in time. In this work we investigated what aspects of the unobserved dynamics are important to faithfully describe multi-cell recordings, focussing especially on time constants of the dynamics.

The quality of parametric statistical models is often assessed based on their ability to generalise beyond data used for estimation of the model parameters. If the model is in accordance with the underlying process that generated the data, *e.g.* the activity of a population of cortical neurons, then it should be able to make respectable predictions for data not used during training. Generalisation is often helped by a regulariser — a term that biases parameters towards values favoured *a priori*. A common approach to regularisation penalises large parameter values. Applied to the LDS dynamics parameters this favours describing the data by latent processes with short correlation timescales *i.e.*, by dynamics with low degrees of temporal smoothness.

Here, we propose an alternative regularisation scheme for LDS dynamics which penalises deviations from constancy. This corresponds to a prior on dynamics favouring longer timescales *i.e.*, high levels of temporal continuity. We show that this approach yields a better statistical model for neural data from primate motor cortex using likelihood on test data, as well as a previously established cross-prediction measure. This finding holds for a wide range of training set sizes and latent dimensions and is quite robust with respect to exact values of the regularisation parameters. This suggests that shared variability in the neural population is indeed best described by a smooth process in time.

Furthermore, our method for estimating LDS parameters is guaranteed to yield stable systems: All parameter estimates describe processes with well-defined stationary distributions ruling out biologically-implausible high firing rates and variances when predicting neural activity with LDSs. This facilitates identifying linear latent dynamical systems from little training data. In conjunction with the proposed regularisation encouraging smoothness this yields a more robust parameter estimation method which may help overcome the difficulties posed by limited data to both scientific and prosthetic applications.

TASK-DEPENDENT CHANGES IN CROSS-LEVEL COUPLING BETWEEN SINGLE NEURONS AND MULTI-SCALE NETWORK ACTIVITY

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Understanding the principles governing the dynamic coordination of functional brain networks remains an important unmet goal within neuroscience. In particular, complex goal-directed actions require distributed ensembles of neurons to transiently coordinate their activity across a variety of spatial and temporal scales. A mechanistic account of how this is accomplished remains elusive. However, several groups have proposed that neuronal oscillations may play a key role in this process, with different brain rhythms influencing both local cortical computation and long-range communication.

To investigate this question, we recorded neural ensembles of identified single units and local field potential (LFP) activity from microelectrode arrays implanted bilaterally in macaque motor areas. Monkeys engaged in a delayed center-out reaching task using either their arm (Manual Control, MC) or changes in spike rates used as input to a brain-machine interface decoder (Brain Control, BC). Here we show that the spiking activity of individual neurons is coupled to multiple aspects of the ongoing motor beta rhythm (10-45 Hz) during both MC and BC, but that the model parameters describing this beta-to-rate mapping can change in a reversible and task-dependent way. For example, as beta power increases, a given neuron may increase spiking during MC but decrease spiking during BC, or exhibit a reversible shift in the preferred phase of firing. For both MC and BC, the instantaneous beta-to-rate mapping was given by: $R_{BETA}(a,\theta)=R_{BASELINE}+R_{AMP}(a)+w_{AMP}(a)R_{PHASE}(\theta) = p_1+p_2 \tanh((a-p_3)/(2p_4))+(p_5a+p_6a^2)p_7\cos(\theta-p_8)$, where $R_{BETA}(a,\theta)$ is the estimated firing rate for the neuron, $a>0$ is the instantaneous beta amplitude, θ is the instantaneous beta phase, $R_{BASELINE}$ is the constant baseline firing rate, $R_{AMP}(a)$ is the change in firing rate due to amplitude alone (amplitude-to-rate mapping), $R_{PHASE}(\theta)$ is the change in firing rate due to phase alone (phase-to-rate mapping), $w_{AMP}(a)$ is a weighting factor, and $[p_1,\ldots,p_8]$ are model parameters. The within-task stability of model parameters, combined with the reversible cross-task changes in parameter values, suggests that task-dependent changes in the beta-to-rate mapping plays a role in the transient functional reorganization of neural ensembles.

In addition to these within-neuron, cross-task changes, there was a wide diversity of responses across neurons during a single task. For example, 49.4% (31.8%) of neurons increased (decreased) their firing rate as beta amplitude increased. We consider the influence this amplitude-to-rate mapping, paired with a fluctuating instantaneous beta amplitude, may have on sequential winner-take-all competitions. Furthermore, the distribution of preferred beta phases (covering ~10 ms) imposes a (probabilistic) sequential ordering of neurons by regulating relative spike timing. We characterize the range of task-dependent changes in the mapping from beta amplitude, phase, spatial patterning, and inter-hemispheric phase coupling to the spike rates of an ensemble of simultaneously-recorded neurons, and discuss the implications that dynamic remapping of cross-level coupling has for different neuronal models of computation and communication in distributed functional brain networks.

ROLE OF ELECTRIC SYNAPSES IN SPIKE TRAINS STATISTICS OF LINEAR INTEGRATE AND FIRE NEURAL NETWORKS

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Communication between neurons involves chemical synapses as well as electric synapses. On theoretical grounds, the role of gap junctions in encoding and shaping collective dynamics as well as spike train statistics is quite less understood than the role of chemical synapses. In previous work [1] the collective spike train statistics in conductance-based Integrate and Fire neural networks was studied rigorously. It was especially shown that this statistics is characterized by a Gibbs distribution whose potential can be explicitly computed. This provides moreover a firm theoretical ground for recent studies attempting to describe experimental rasters in the retina [4] as well as in the parietal cat cortex [2] by Gibbs distributions and maximal entropy principle. The work presented at AREADNE will extend the mathematical analysis of previous work [1] to conductance-based Integrate and Fire neural networks with chemical synapses as well as electric synapses, in the presence of noise. In opposition to previous paper dealing with this subject [3] we do not consider mean field approximations and the analysis is not limited to pulse type chemical synapses.

The core of the analysis is to show how multiple single neurons interact in the presence of gap junctions. In conductance based models coupled with gap junctions, the sub-threshold dynamics is ruled by a coupled set of linear, non-autonomous and non-homogeneous stochastic differential equations of Ornstein-Uhlenbeck type, where conductances depends upon the spike-history of the network. We compute explicitly the evolution operator and show that given the spike-history of the network and the membrane potentials at a given time, the further dynamical evolution can be explicitly written in a closed form. Under a moderate assumption on the evolution operator the system has a unique strong solution. From this we obtain a family of transition probabilities for spike dynamics, corresponding to a Gibbs distribution. This results emphasizes the role of gap junctions on spike statistics with strong effects on space time correlations and memory. This work suggest that electric synapses could have a strong influence in spike train statistics of biological neural systems, especially the retina where gap junctions connections between several cells-type (e.g. amacrine and ganglion cells or amacrine-bipolar) are ubiquitous.

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NEURONAL ENSEMBLE ORGANIZATION IN THE PREFRONTAL AND POSTERIOR PARIETAL CORTEX

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The dorsolateral prefrontal and posterior parietal cortices play distinct functional roles in the cortical network controlling attention, working memory, and executive function, though little is known about how the specialization of these two areas is achieved. In the sensory pathways, the cortical hierarchy is characterized by stereotypical feed-forward connections transmitting the output of one area into the input layers of the next. A long standing theory posits that the elemental transformation of information in each cortical area is essentially the same, leading to progressively larger receptive fields and more complex neuronal properties by virtue of increasing numbers of steps of processing. On the other hand, no obvious hierarchical pattern of information processing is present between the parietal and prefrontal cortices, whose connections are largely reciprocal rather than strictly serial. It is unclear therefore how functional specialization can be achieved beyond the posterior parietal cortex into the frontal lobes. One possible factor that may account for the functional specialization is unique intrinsic connectivity. By some accounts prefrontal pyramidal neurons exhibit the most extensive dendritic trees and highest number of spines of any cortical neurons. It is possible that unique patterns of effective connectivity account for identified neurophysiological properties, although the functional implications of this reported anatomical difference have not been investigated until now. If prefrontal cortex is characterized by a unique organization of its intrinsic synaptic inputs, we reasoned, different strengths of functional connectivity across a range of distances would be observed in the two areas. We therefore computed the strength of effective connectivity of simultaneously recorded neurons to infer any characteristic differences between neuronal ensembles in the two areas.

We analyzed a large database of neuronal recordings consisting of 1078 pairs of neurons recorded from area 7a of the posterior parietal cortex and 1909 pairs from areas 46 and 8 of the dorsolateral prefrontal cortex. All pairs analyzed were recorded from different microelectrodes, separated laterally by 0.18 to 1.50 mm. Our study found reliable differences between the dorsolateral prefrontal and posterior parietal cortices in the extent and strength of such intrinsic connections. In agreement with prior studies, both parietal and prefrontal cortex demonstrated a decrease in effective connectivity as a function of distance. However, neurons in the posterior parietal cortex shared a larger percentage of their functional inputs when they were located at short (less than 0.5 mm) distances, compared to pairs of neurons recorded at equivalent distances from the prefrontal cortex. This was true for both short cross-correlation lags, comparable to the time scale of synaptic interactions, and longer time scales of functional connectivity, shaped by polysynaptic interactions. Effective connectivity was also influenced by the similarity in stimulus selectivity between cells (signal correlation) and in the temporal envelope of their responses across the task (temporal correlation), although the effect of distance could not be fully explained by these factors alone. Modeling of the differences in effective connectivity in the two cortical areas provides further mechanistic insights into their different functional roles.

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THREE-DIMENSIONAL RANDOM ACCESS MULTIPHOTON IMAGING OF NEURAL POPULATIONS

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An important goal in systems neuroscience is to record the behavior of large populations of neurons in order to understand how these populations represent and transform information. Electrophysiology provides the highest temporal resolution of available methods, but suffers from difficulty isolating individual neurons as well as problems scaling to higher numbers of neurons. It also doesn't provide fine scale positional information. A more recent method is two-photon imaging using bulk-loaded calcium indicators, which allows imaging from on the order of one hundred neurons, but is limited by the temporal resolution of the scanning system (on the order of 10 Hz for galvometric methods) and can only record from cells within the optical plane. We have implemented a 3-D random access scanning system for in vivo two photon imaging using acousto-optical components instead of the mechanical components and a custom FPGA-based scanning controller. With this system we demonstrate high quality recordings at hundreds of Hertz from 50–400 neurons in a 3D volume. The data from the neurons is interleaved with structural imaging to provide parallel tracking of the movement of the preparation. This allows characterizing the neural dynamics across a 3-D microcircuit with high spatial and temporal resolution as a mouse observes visual stimuli to capture the correlated dynamics from larger population sizes than have been recorded before.

THE SPATIOTEMPORAL STRUCTURE OF ONGOING AND EVOKED ACTIVITY INVESTIGATED USING OPTICAL IMAGING OF VOLTAGE SENSITIVE DYES IN AWAKE MONKEY V4

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Increasing evidence suggests that spontaneous, ongoing activity in a given cortical area shows characteristics that reflect its functional organization, which, in turn, reflects the area's critical information processing features. For example, Kenet et al. (Nature 2003) have shown that the functional maps obtained in cat area 17-18 in absence of stimulation at certain times display the same typical orientation patches obtained upon stimulation with oriented gratings. More recently, Berkes et al. (Science 2011) have shown that, in adult ferret V1, the firing patterns recorded within a group of neurons during spontaneous activity is more similar to that evoked by natural stimuli than to that evoked by artificial ones. This raises the question if the structure of spontaneous activity in a given area could not be taken as a reference to classify stimuli into sets of more or less "natural-like" ones. By comparing elementary stimuli to natural ones, this classification might then allow to identify the stimulus features that are critically processed by that specific area (*e.g.* orientation in V1).

Here, we report first results obtained applying this approach to data obtained using optical imaging of voltage sensitive fluorescent dyes (VSD) in awake macaque visual area V4. The functional organization of V4 is still largely unknown. Therefore, defining "reference" spatial patterns is less evident than in the case of V1, which shows typical orientation maps. As a more general approach, we thus studied the structure of pair-wise correlations, for all pairs of points in space, in single-trial responses. We compared the correlation structure of ongoing neuronal population activity to that evoked by various visual stimuli. Those consisted of luminance and isoluminant (color) full-field drifting gratings of various contrast levels. Ongoing activity was recorded during a fixation-dot-only condition ("blank"). We found that: (*i*) the spatial extent of these correlations obtained during stimulation was larger than in absence of stimulation; (*ii*) it increased with stimulus contrast; (*iii*) this effect tended to be stronger for luminance than for isoluminant stimuli. Our results indicate that a simple, correlation-based approach is sensitive enough to discriminate between the activity patterns observed during spontaneous and evoked activity. They also suggest that it should be possible to classify stimuli into categories on the basis of the correlation structure of their evoked responses and its comparison to the blank.

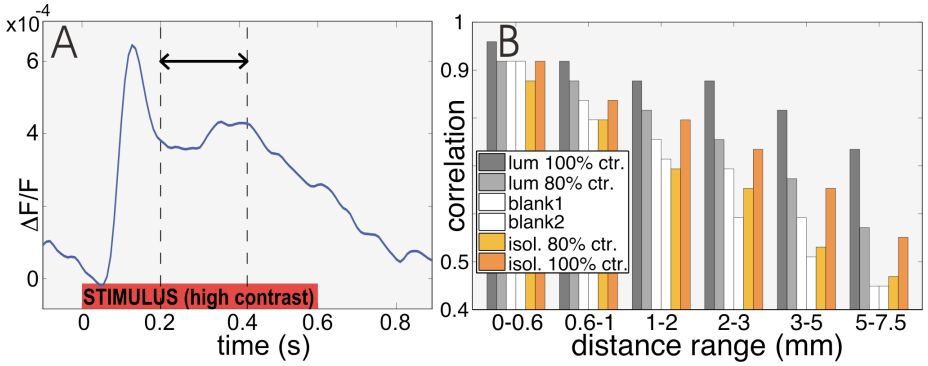

Figure 1. (**A**) Average (n ~ 16) VSD response to a visual stimulus in V4. The arrow shows the time period used to calculate histograms of correlations (see B) between pixel pairs. (**B**) Likeliest correlation values in histograms, for 6 distance ranges between pixel pairs.

PREPLAY OF SPATIAL EXPERIENCE IN THE RAT HIPPOCAMPUS

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During sleep and rest states, the activity of ensembles of place cells from the CA1 area of the rat and mouse hippocampus is organized into temporal sequences. Some of these temporal sequences reflect past spatial experiences in the form of replay of familiar place cell sequences or spatial trajectories. In addition, our previous work with experimentally naive mice has shown that during sleep and rest a significant number of temporal sequences correlate with the corresponding future place cell sequences formed subsequently during the first time exploration of a novel linear track, a phenomenon called preplay. Here we confirm and extend our previous findings in the mouse by showing that in experimentally naive rats temporal sequences fired during sleep preplay the order in which corresponding place cells subsequently fire during the first time exploration of a novel linear track. This preplay occurred before the linear track was first introduced into the room where the rats were sleeping. Bayesian decoding of the preplay temporal sequences during sleep revealed in some cases virtual spatial trajectories through the novel linear track which was only subsequently explored for the first time. These results indicate that hippocampal network is preconfigured to rapidly encode and represent novel spatial information.

THE CORRELATION STRUCTURE INDUCED BY FLUCTUATIONS IN ATTENTION

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How attention shapes the structure of population activity has attracted substantial interest over the past decades. Attention has traditionally been associated with an increase in firing rates, reflecting a change in the gain of the population. More recent studies also report a change in noise correlations, which is thought to reflect changes in functional connectivity. However, since the degree of attention can vary substantially from trial to trial even within one experimental condition, the measured correlations could actually reflect fluctuations in the attention-related feedback signal (gain) rather than feed-forward noise, as often assumed.

To gain insights into this issue we analytically analyzed the standard model of spatial attention, where directing attention to the receptive field of a neuron increases its response gain. We assumed conditionally independent neurons (no noise correlations) and asked how uncontrolled fluctuations in attention affect the correlation structure.

First, we found that this simple model of spatial attention explains the empirically measured correlation structure quite well. In addition to a positive average level of correlations, it predicts both an increase in correlations with firing rates, as observed in many studies, and a decrease in correlations with the difference of two neurons' tuning functions — a structure generally referred to as limited range correlations.

Second, we asked how fluctuations in attention would affect the accuracy of a population code, if treated as noise by a downstream readout. Based on previous theoretical results, it would be expected that they negatively affect readout accuracy because of the limited range correlations they induce. Surprisingly, we found that this is not the case: correlations due to random gain fluctuations do not affect readout accuracy because their major axis is orthogonal to changes in the stimulus orientation.

Our results can be readily generalized to include feature-based attention. The model has very few free parameters and can potentially account for a large fraction of the experimentally observed spike count (co-)variance.

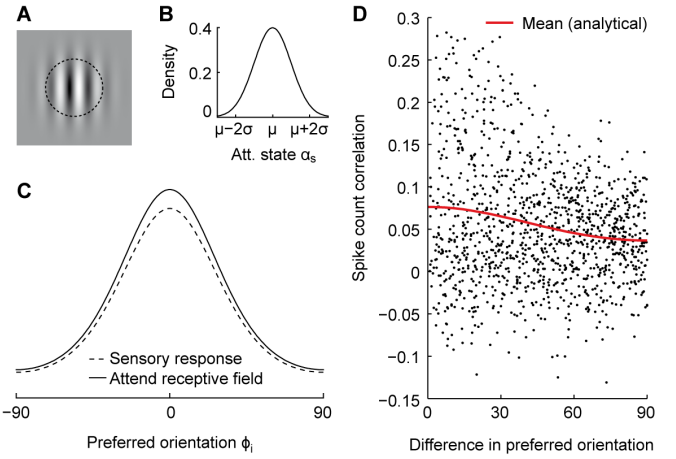

Figure 1. Model of spatial attention. (**A**) Example stimulus. The neurons' receptive fields are assumed to be at the same location (dashed circle). (**B**) Distribution of attentional gain fluctuations. (**C**) Population response under sensory stimulation (dashed) and with attention directed to the stimulus in the receptive fields (solid). (**D**) Spike count correlations as a function of difference in preferred orientation.

NEURAL CODING IN THE CORTICO-STRIATAL SYSTEM IN A DECISION MAKING TASK: INSIGHTS FROM RESERVOIR COMPUTING

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The cortico-striatal system, a striking component of primate neuroanatomy, plays a major role in decision making and sequence processing. Quilodran *et al.* (Quilodran, Rothe, Procyk, 2008, Neuron, 57(2):314-25) developed a decision making task with a clear separation between an exploration phase where monkeys explored targets to find that which was rewarded by fruit juice, and a exploitation phase where monkeys could repeat the rewarded choice. Activity in the anterior cingulate cortex (ACC) and lateral prefontal cortex (LPFC) was recorded. A significant number of neurons showed a clear dynamical shift between the search and repeat phase. Certain neurons specifically encoded the first reward, which crucially indicated the shift from exploration to exploitation. However, equally important, the last chosen target was not explicitly represented in neuronal activity at the time of target choice.

We simulated the cortico-striatal system in the framework of reservoir computing (Jaeger, 2001, GMD Report 148, German Nat. Res. Inst. for Computer Science). The reservoir, a recurrent network of leaky integrator neurons with non-modifiable connections develops a non-linear activity over time that reflects the history of its inputs. A readout layer fully connected to the reservoir uses this activity to produce the desired output associated with the input sequence by linear regression learning. We considered that the reservoir models the cortex and the readout represents the striatum. Our objective was to assess the ability of the model to reproduce the behavior and the cortico-striatal dynamics observed in the electrophysiological results exposed above.

The reservoir was trained with random versus ordered strategies for exploration of the targets. Random search elicited poor performance while ordered exploration was almost perfect. Secondly, we trained the reservoir with the behavior from a monkey efficiently performing the task. The results, while slightly inferior to those for ordered search showed that the monkey had a rather structured behavior since the reservoir was able to learn the task from that behavior. Reservoir activity displayed similarities with unit recordings from monkeys, and also explained certain paradoxical observations. We found neurons showing a shift in activity between the exploration and exploitation as seen in biological neurons. While no reservoir neuron responded only to the first reward, neurons could be successfully trained to respond to it, demonstrating that the crucial information to shift from exploration to exploitation was present in the reservoir even if it was not explicitly expressed by single neurons. Similarly, while as in the monkey, no single units encoded the previously chosen target (crucial for deciding the next choice), trained neurons demonstrated that this information was robustly present in the reservoir, an important results emphasizing that unexpressed information may be sparsely encoded in the activity of neural populations.

Reservoir computing can be considered an interesting tool for the study of higher cognitive function, including characterization of primate behavior and neural activity. Indeed, our model provides a novel response to an open question concerning the coding of previous behavior in planning for the future.

EXPLAINING NEURAL VARIABILITY IN THE VISUAL CORTEX THROUGH SAMPLING-BASED NEURAL REPRESENTATIONS

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It is well-documented that neural responses in sensory cortices are highly variable: the same stimulus can evoke a different response on each presentation. Traditionally, this variability has been considered as noise and eliminated by using trial-averaged responses. Such averaged responses have been used almost exclusively for characterizing neural responses and mapping receptive fields with tuning curves, and accordingly, most computational theories of cortical representations have neglected or focus on unstructured Poisson-like aspects of neural variability. However, the large magnitude, characteristic spatio-temporal patterns and systematic, stimulus-dependent changes of neural variability suggest it may play a major role in sensory processing.

We propose that sensory processing and learning in humans and other animals is probabilistic following the principles of Bayesian inference, and neural activity patterns represent statistical samples from a probability distribution over visual features. In this representational scheme, the set of responses at any time in a population of neurons in V1 represents a possible combination of visual features. Variability in responses arises from the dynamics that evokes population patterns with relative frequencies equal to the probability of the corresponding combination of features under the probability distribution that needs to be represented. Consequently, the average and variability of responses encode different and complementary aspects of a probability distribution: average responses encode the mean, while variability and co-variability encode higher order moments, such as variances and covariances, of the distribution.

We developed a model derived from this sampling-based representational framework and showed how it can account for the most prominent hitherto unexplained features of neural variability in V1 related to changing variability and the pattern of correlations without necessarily changing mean responses. Besides providing the traditional mean responses and tuning curves, the model replicates a wide range of experimental observations on systematic variations of response variability in V1 reported in the literature. These include the quenching of variability at stimulus onset measured either by membrane potential variability or by the Fano factor of spike counts, contrast-dependent and orientation-independent variability of cell responses, contrast-dependent correlations, and the close correspondence between spontaneous and evoked response distributions in the primary visual cortex. Crucially, current theories of cortical computations do not account for any of these non-trivial aspects of neural variability. The framework also makes a number of key predictions related to the time-dependent nature of the sampling-based representation.

These results suggest that representations based on samples of probability distributions provide a biologically feasible new alternative to support probabilistic inferential computations of environmental features in the brain based on noisy and ambiguous inputs.

NEURONAL POPULATION DYNAMICS OF AUDITORY CORTEX IN STIMULUS-DRIVEN AND UNDRIVEN-RESTING STATES IN THE AWAKE MACAQUE

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To understand the neuronal mechanisms of auditory perception, it is essential to examine how populations of neurons process incoming sounds over time. Like human auditory cortex, the auditory cortex of macaques consists of several highly interconnected subareas on the supratemporal plane (STP) of the lateral sulcus and adjacent superior temporal gyrus (STG). While neural responses in some of these subareas have been studied extensively, the spatiotemporal dynamics of the neural activity in response to acoustic stimuli are still unknown. This requires recording activity from a large expanse of the cortex with high temporal resolution in the sulcus, which is difficult to achieve with conventional extracellular recording or functional imaging. To overcome this problem, we adopted the technique of intracranial electrocorticography and designed a micro-electrocorticographic (μECoG) array to record field potentials simultaneously from multiple areas of macaque auditory cortex with high temporal and spatial resolution. Each μECoG array had 32 recording sites on a 3×7 mm grid with 1 mm spacing. We chronically implanted four such arrays, allowing for 128 parallel measurements of field potentials from the surface of the STP as well as the caudal STG. We first examined the auditory frequency tuning of auditory evoked potentials to pure tone stimuli. The stimulus-evoked power in the high-gamma band revealed tonotopic maps that reversed frequency direction at putative areal boundaries. Next, we estimated when each site showed significant discrimination among different stimulus frequencies by evaluating the high-gamma power in a moving window with an ANOVA. We found that the onset time of the discrimination increased along the caudal-to-rostral as well as the medial-to-lateral axes, consistent with the hypothesis that auditory information is serially processed in these two directions in parallel. Taking further advantage of the simultaneous recordings, we next evaluated the undriven-resting activity by using principal components analysis. The results indicated that the spontaneous fluctuations in the resting activity of the auditory cortex reflects this region's functional architecture, including its areal subdivisions and their tonotpic maps, thereby demonstrating a close relationship between functional organization and spontaneous neural activity in sensory cortex of the awake monkey.

CAN NETWORK STRUCTURES BE DERIVED FROM CALCIUM IMAGING DATA? — A SIMULATION STUDY

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Information processing in the brain has remained enigmatic, largely because of methodological constraints in measuring neuronal circuit activity and connectivity. Two-photon calcium imaging now enables functional analysis of local neuronal populations under in vivo conditions. We present a simulation framework for the quantitative evaluation of reconstruction performance under different experimental constraints. First, we simulated spike-evoked calcium transients and noisy fluorescence imaging, and then applied a state-of-the-art reconstruction algorithm to recover the underlying spike train. We examined the effect of signal-to-noise ratio, imaging speed and indicator properties on the fidelity of spike reconstruction under conditions commonly observed in cortical pyramidal cells. Furthermore, we explored how spike train reconstruction impacts on estimates of the connectivity structure in statistical neural network models.

Reliable methods of network reconstruction are important for the testing of hypotheses about the functional organization of neural networks. Based on our extensive simulations, we show that it is possible to determine which experimental conditions are necessary to infer how well individual hub neurons can be identified, whether the network has a scale-free structure, and to what extent the network possesses a small-world, effective connectivity. Whether a network characteristic can be accurately reconstructed depends on the balance of different experimental control parameters — therefore our findings provide a valuable set of recommendations for calcium imaging experiments aimed at faithfully characterizing network properties.

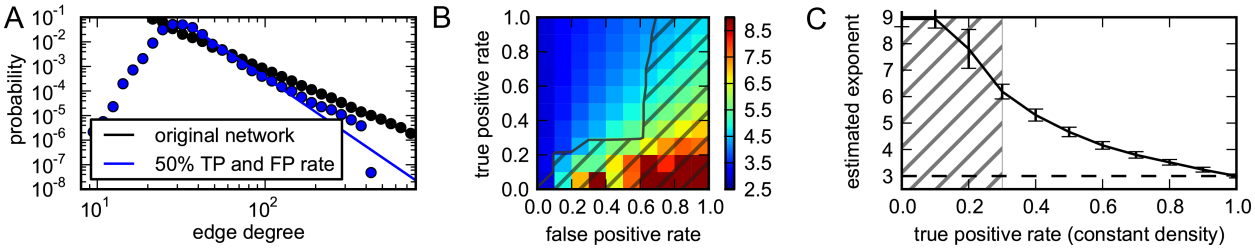

Figure 1. Detection of scale-free structure under imperfect connectivity reconstruction. (**A**) Sample degree distributions of original and reconstructed networks. The original degree distribution follows an inverse power law with exponent 3 (black). Reconstructed networks were obtained by assuming that 50% of all links can be reconstructed with an equal number of false positive links (blue). (**B, C**) Estimated power-law coefficients as a function of varying degree of reconstruction performance: In B, color encodes the value of the fitted power-law exponent. In hatched areas the median p value of the goodness-of-fit test was lower than 0.05 indicating that the best power-law fit was inconsistent with a scale-free assumption. In C, a line section through B is shown for which the reconstructed connection density is constant. The scale-free exponent is systematically overestimated.

Acknowledgments

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LEARNING ENHANCES POPULATION CODING IN THE AVIAN AUDITORY CORTEX BY INVERTING THE INTER-NEURONAL CORRELATION STRUCTURE

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Learning to recognize important features in our environment, such as faces, objects, voices, and words, is normally effortless and reliable. The neural activity that encodes these features, however, is noisy: repeated presentations of the same stimulus elicit variable responses. To generate reliable behavior from such variable sensory representations, the brain is thought to pool activity from large populations of neurons. Consequently, it is critically important to study the neurophysiological basis of sensory learning in populations of neurons.

The ability of neural populations to convey sensory information depends critically on the relationship between shared noise (“noise correlation”) and tuning similarity (“signal correlation”) between neurons. Positively correlated noise between similarly tuned neurons cannot be removed because the shared noise cannot be “averaged out”. In contrast, correlated noise between oppositely tuned neurons can be substantially attenuated with an inhibitory interaction: the signal is amplified while the shared noise is subtracted out. In heterogeneous populations, therefore, the information encoded depends on how noise correlations relate to signal correlations. A positive relationship limits the information that can be encoded by the population, while a negative relationship expands this information. Flexibility in this relationship has long been hypothesized as a potent mechanism for learning-dependent cortical plasticity, yet empirical evidence is lacking.

Here we investigate how learning alters neural population representations by measuring the simultaneous activity of multiple auditory cortical neurons in songbirds trained to discriminate between segments of natural song (“motifs”). We find that populations of neurons can discriminate better between behaviorally relevant motifs than between irrelevant motifs or novel motifs. This plasticity derives from an inversion of the relationship between signal and noise correlations between pairs of neurons. Behavioral relevance decreases the fraction of shared noise between similarly tuned neurons (for which shared noise is detrimental) and increases the fraction of shared noise between dissimilarly tuned neurons (for which shared noise is beneficial). These results reveal that learning-dependent plasticity can target the inter-neuronal correlation structure, yielding substantially enhanced sensory encoding in populations of neurons.

SPECIFYING LONGITUDINAL SYNCHRONIZATION OF SUBTHALAMIC OSCILLATORY ACTIVITY IN PARKINSON'S DISEASE

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It has been established that the parkinsonian state is characterized by an increased incidence of beta oscillatory activity (13–30 Hz) in the dorsolateral region of the subthalamic nucleus (STN), whereas gamma activity (31–100 Hz) predominates in the ventral part [1]. Furthermore, a high degree of neuronal synchrony in the STN seems to be associated with pathophysiological aspects of Parkinson's disease (PD) [2]. However, the exact synchronization pattern of oscillatory activity along the STN has not been characterized yet.

To this aim we analyzed 127 microelectrode recordings obtained intraoperatively from 14 STN trajectories in 7 PD patients undergoing deep brain stimulation intervention. Specifically, we examined the distribution of synchronization — along the STN trajectories — between the local field potential (LFP) activity, the single-unit activity and the high-frequency background activity. LFP activity represents the synaptic input of a broad neuronal population and is linked to an intermediate level of interaction. On the other hand, background activity reflects the multi-unit spiking activity of the local population in the neuron's immediate vicinity, *i.e.* close to the recording electrode [3]. As such, in relation to single-unit oscillations, it is expected to embody the network's co-activity at the most microscopic level [4]. Thereafter, on the basis of non-linear dynamics theory, both standard spectral and phase synchronization analyses [5] for LFP, single-unit and background oscillations were applied along each microelectrode track.

Synchronous oscillatory dynamics in the beta frequency band was found to be exalted dorsolaterally, *i.e.* the motor territory of the STN, where single-unit and background oscillations were predominantly found to be statistically coherent ($p < 0.05$) over the recording period (10 s). Interestingly, coherence frequency range proved to be patient-specific as is the case for the beta peak observed in the LFP power spectral density function [6]. Absence of both significant coherence and phase-locking indicated de-synchronization phenomena. Particularly, synchronization between LFP and single-unit/background activity was significantly weaker as compared to the correlation between single-unit and background activity. Moreover, our results emphasize an indication of synchronicity ventrally, specific for frequencies in the gamma frequency band.

The findings suggest that neural population synchrony along the STN in the parkinsonian state tends to capture the behavior of dorsal beta and ventral gamma oscillatory activity appearing stronger within a small vicinity of the recording electrode. This kind of knowledge might be appropriate considering into studies designed to optimize targeting in DBS procedures and to treat PD by suppressing pathological beta-band synchronization in the STN.

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NEURAL REPRESENTATIONS OF LOCATION COMPOSED OF SPATIALLY PERIODIC BANDS

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The mammalian hippocampal formation (HF) provides neuronal representations of environmental location, but the underlying mechanisms are unclear. We report a class of cells with spatially periodic firing patterns composed of plane waves (or bands) drawn from a discrete set of orientations and wavelengths. The majority of cells recorded in parasubicular and medial entorhinal cortices of freely moving rats belonged to this class. Grids cells form an important subset, corresponding to hexagonal configurations of bands, and having the most stable firing. Occasional changes between hexagonal and non-hexagonal firing patterns imply a common mechanism underlying the various spatial patterns. Our results indicate a Fourier-like spatial analysis underlying neuronal representations of location, and suggest that path integration is performed by integrating displacement along a restricted set of directions.

BURST RELATED SPIKE AMPLITUDE ATTENUATION IN THE HIPPOCAMPUS

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In neuronal communication not all spikes are created equal. Bursts of spikes appear to be especially important, partly because they trigger synaptic transmission more reliably than single spikes and can selectively engage synaptic plasticity. While bursting has been studied extensively both theoretically and in vitro, the role bursts play in the circuits of the intact brain remain poorly understood, at least in part because of the difficulty in isolating the spikes of bursting neurons recorded extracellularly. In this work, we discuss the systematic spike amplitude changes associated with bursting in the hippocampus and present a corresponding simple mathematical description. Accounting for spike amplitude changes in the context of single unit isolation leads to a state space model (SSM) formulation of clustering. While the clustering SSM is non-linear, it can be seen as a switching linear Gaussian model, allowing tractable estimation using sequential Monte Carlo techniques. We present the resulting clustering algorithm and discuss its performance on real and simulated data. Finally, we consider the role bursts may play within hippocampal circuits during the process of memory consolidation.

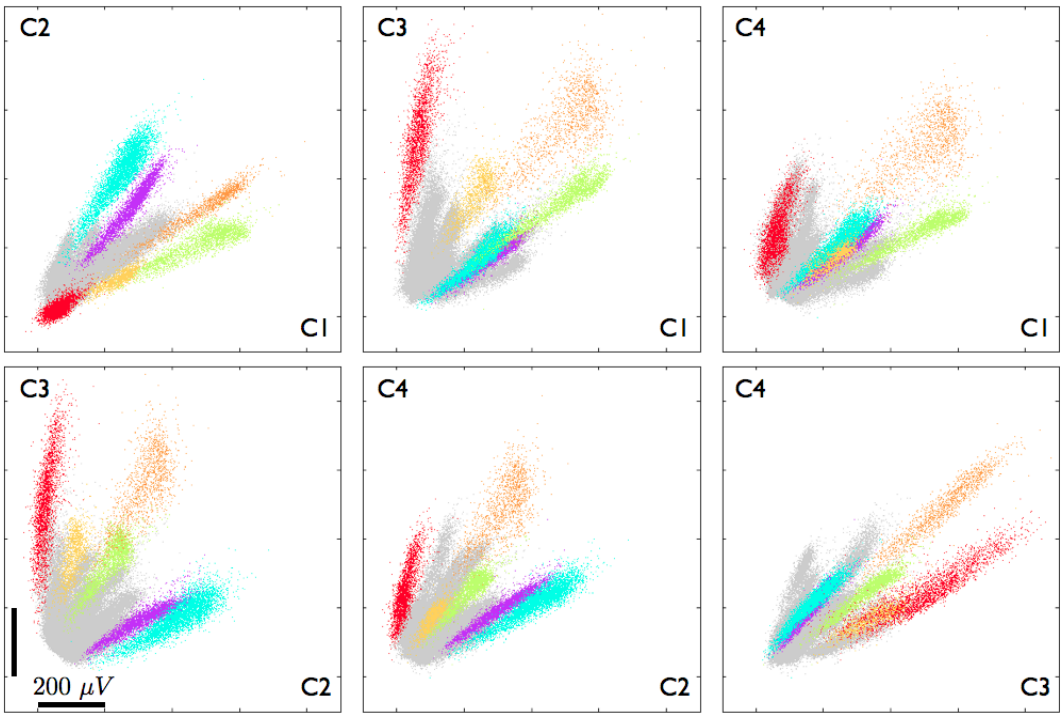

Figure 1. Spike amplitudes of neurons recorded extracellularly from the hippocampus using a tetrode. Each panel shows a scatter plot from two tetrode channels (C1-C4). Notice the elongation of clusters from bursting neurons (color) due to burst related spike amplitude attenuation. Spikes occurring later within bursts are lower in amplitude and consequently are subject to systematic omission and misclassification errors. We present methodology to address this issue.

SPATIOTEMPORAL STRUCTURE IN MOTOR NEURON ACTIVITY IN ISOLATED MOUSE SPINAL CORD

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The firing patterns of motor neurons represent the product of neural computation in the motor system. EMG recordings are often used as a proxy for this activity, given the direct relationship between motor neuron firing rate and muscle contraction. However, there are a variety of motor neuron subtypes with varied synaptic inputs and intrinsic properties, suggesting that this relationship is complex [1]. Indeed, studies have shown that different compartments of individual muscles are activated asynchronously during some motor tasks—implying heterogeneity in firing across single motor pools [2]. To measure the activity of many identified motor neurons simultaneously, we have combined population calcium imaging at cellular resolution with the use of a deconvolution algorithm that infers underlying spiking patterns from Ca^{++} transients (based on [3]). Using this approach, we set out to examine the firing properties of neurons within an individual pool of motor neurons, and in particular, to compare the activity of individual neurons belonging to synergist (*e.g.* flexor-flexor) and antagonist (flexor-extensor) pools.

We imaged motor neurons in the spinal cord of neonatal mice. The motor neurons were either loaded with synthetic calcium indicator or conditionally expressed GCaMP3. To identify the muscle targets of the loaded motor neurons, we injected two fluorophore-conjugated variants of the retrograde tracer cholera toxin B into specific antagonist or synergist muscles. To examine the correlated firing of motor neurons during network activity in our in vitro preparation, a current pulse train was delivered to a sacral dorsal root in order to evoke a locomotor-like state. The onset and evolution of this rhythmic state was recorded from multiple ventral roots using suction electrodes. To calibrate optical measurements, and to determine the upper limit of correlated firing, motor neurons were antidromically activated via ventral root stimulation. The optical responses to the antidromic train were used to directly fit a model to our data that related the fluorescence measurements to an approximate spike train. Preliminary observations suggest heterogeneity in neuronal firing within individual pools, as well as alternation in the firing between antagonist pools. We are currently examining the relationship between firing patterns and spatial position, cell body size, and genetic subtype of motor neuron. In the future, this approach will be used to examine the activity patterns of molecularly-defined interneuron subpopulations as a function of the firing of identified motor neurons.

Acknowledgement

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MODELING CORTICAL POPULATION RECORDINGS: LATENT DYNAMICS OR DIRECTED COUPLINGS?

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Neurons in the neocortex appear to participate in coding and computational processes that span local populations. With the advent of large-scale multielectrode recording it has become possible to access these processes empirically by fitting statistical models to unaveraged data. What sort of statistical model best describes the concurrent spiking of cells within a local network?

We argue that in the cortex, where firing exhibits extensive correlations in both time and space and where a typical sample of neurons still reflects only a very small fraction of the local population, the most appropriate model captures shared variability in firing by a low-dimensional latent process evolving with smooth dynamics, rather than by models of direct coupling.

We test this claim by comparing a dynamical system model with realistic spiking observations to the coupled generalized linear spike-response models (GLMs) using extracellular recordings from motor cortex. We find that the dynamical system approach outperforms the GLM in terms of goodness-of-fit, and reproduces the temporal correlations in the data more accurately. We also compare latent process models with Gaussian and with non-Gaussian count conditional probabilities, finding that the non-Gaussian count-based approach provides slightly better goodness-of-fit and more realistic population spike counts.

INFERRING MOVEMENT INTENTION FROM WIDEBAND MULTIUNIT ACTIVITY IN THE BRAINGATE NEURAL INTERFACE SYSTEM

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Neural interface systems offer the potential to restore communication and movement ability in people with motor disorders following spinal cord injury, brainstem stroke, neuromuscular diseases such as ALS, or limb amputation. Neural interfaces record neural activity from the motor cortex, decode it to estimate movement intention, and control assistive devices accordingly. For this purpose, single-unit activity (SUA), obtained from motor cortical neurons, is well established as a useful signal due to its extensively studied relationship to voluntary movement. Despite its rich information content, SUA poses practical challenges for chronic neural interfaces, since it involves a frequent and time-consuming process of spike sorting and decoder recalibration. One approach to addressing these challenges may be to use a signal that samples from broader collections of neural activity, namely the wideband multiunit activity (MUA). Besides improving decoder robustness and stability, MUA can help avoid neuronal spike sorting, obviating the need for expert intervention and reducing the computational complexity. Following recent primate studies suggesting that MUA encodes movement intention, our objective is to investigate the feasibility of harnessing MUA for motor decoding in a clinical neural interface for people with tetraplegia.

We analyzed MUA decoding performance as part of the ongoing BrainGate† pilot clinical trial with a participant with brainstem stroke. We recorded analog wideband neural activity, sampled at 30 KHz, using an intracortical array of 96 microelectrodes implanted in the precentral gyrus in the region of arm representation. The wideband neural signal on each electrode was bandpass filtered (0.3–6 KHz), integrated (50 msec non-overlapping windows), and downsampled to obtain MUA. For comparison, we computed the SUA as the firing rate within identical time-bins from approximately 29 sorted units. First, the participant imagined moving a computer-controlled cursor on a two-dimensional screen during a 4-target center-out-back task under open-loop conditions. Neural activity and cursor kinematics recorded during this period were used to calibrate a Kalman filter. In the subsequent closed-loop assessment phase, the filter was used to decode neural activity and control the velocity of the cursor in an 8-target center-out-back task.

From cross-validated offline open-loop decoding of the participant's MUA on two different days, we found that the actual (computer-controlled) and decoded cursor velocity had an average correlation coefficient of 0.9 and RMSE of 3.2°/sec. In online closed-loop sessions on four different days, we found that the target acquisition rate using an MUA-based neural cursor was 77% with an average acquisition time of 8 sec and path efficiency of 0.75. From our open- and closed-loop analysis, we found that the MUA and SUA decoding performance were comparable.

Our analysis demonstrates the feasibility of using MUA in a neural interface to estimate intended movement kinematics. As MUA-based decoding can reduce the complexity and improve the robustness of a neural decoder, it can boost the potential of clinical neural interfaces for long-term function restoration and rehabilitation of people with tetraplegia.

† Caution: Investigational Device. Limited by Federal Law to Investigational Use.

PRECISE DECODING OF DYNAMICAL MOTION FROM A LARGE RETINAL POPULATION

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Retinal ganglion cells perform several non-linear computations on moving objects. However, it is unclear how the representation of moving objects is distributed across the entire population of ganglion cells. To address this issue, we recorded a large (100–200) population of ganglion cells with a large, dense array, while displaying a bar animated with random, Brownian motion. The position of the bar could be reconstructed from retinal activity with very high precision using a linear decoder taking a large population of cells as input. Reconstruction using a second order decoder did not lead to a significant improvement in quality. We estimated the decoding error as a function of both bar position and trajectory frequency. We found the minimal error to be below the average spacing between pairs of cones for a broad range of frequencies, indicating that the decoding performance was in a regime of hyperacuity.

This high precision was made possible thanks to the large number of cells recorded: performance increased with the number of cells used for decoding, slowly reaching a plateau of high correlation between real and estimated trajectories ($r = 0.9$) towards 70 cells. We estimated the mutual information between real and estimated stimulus trajectories for subsets of cells with different sizes. For up to 10 cells, the mutual information estimated this way could be predicted by summing the mutual information obtained for each cell individually, indicating there was little redundancy between them. However, for larger groups, a significant and increasing redundancy was found. These large-scale recordings showed that the cells did not carry the information about a moving object independently. Rather, they conveyed redundant information, and accumulating a large number of these redundant cells was necessary to decode precisely the stimulus trajectory.

IMPROVEMENT IN SENSORIMOTOR PERFORMANCE VIA STOCHASTIC RESONANCE

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Several studies about noise-enhanced balance control in humans support the hypothesis that stochastic resonance can improve transmission in the sensorimotor system during a motor task. The purpose of the present study was to test and extend these findings in a simple controlled task.

We explored whether a special level of a mechanical noise (0-15 Hz) applied on the index finger can improve the performance during the compensation of a static force generated by a manipulandum. The finger position was displayed on a monitor as a small white point in the center of a green circle. We considered a good performance when the subjects maintained the white point in the center of the green circle with only small deviations and when less variation over time occurred. Several intensity levels of mechanical noise were applied on the manipulandum and an optimal level was selected for each subject. We compared the performance during zero noise (ZN), optimal noise (ON) and high noise (HN).

In all subjects (8/8) the data disclosed an inverted U-like graph between the mean variation in position and the input noise level (Fig. 1A). The mean variation was significantly smaller during ON than during ZN or HN (Fig. 1B). The mean absolute deviation was also smaller during optimal noise but without reaching the significance level (Fig. 1B).

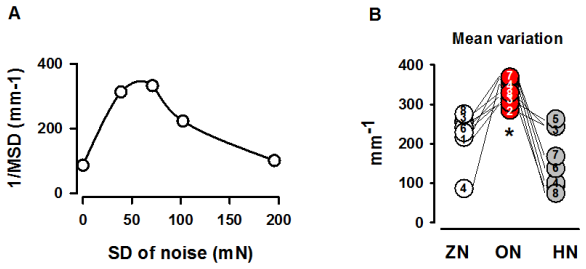

Fig. 1. (A) Inverted U-like graph between the mean variation and the input noise for one of the subjects. (B) Inverted graph of the mean variation of all subjects for ZN (zero noise), ON (optimal noise) and HN (high noise).

The findings suggest that the application of a tactile-proprioceptive noise can improve the stability in sensorimotor performance via stochastic resonance. One possible explanation of this improvement in motor precision can be the suppression or reduction of the physiological tremor by supraspinal centers which exhibit oscillations in neuronal activity at a tremor frequency occurring in antiphase with the oscillations generated by the spinal interneuron circuits. The mechanical noise can have an impact on these supraspinal regions. Another likely explanation of the better performance during optimal noise can is the stronger synchronization induced by stochastic resonance. Therefore, the addition of optimal noise would increase cortical motor and corticomuscular synchrony. Preliminary data showing stronger beta-range corticomuscualr coherence during optimal noise favour this prediction.

Acknowledgments
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DECODING KINETIC PARAMETERS OF GRASPING MOVEMENTS FROM SINGLE UNIT ACTIVITY IN MONKEY MOTOR CORTEX

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Development of neuronal prosthetics, where neuronal activity is used to control artificial limbs, has so far relied on decoding kinematic parameters of movements, such as movement position or velocity. In addition to kinematic control, proper control of forces exerted by the prosthetic device is necessary for successful interaction with the environment, *e.g.* when picking up and handling different objects. In our study, we analyzed the possibility of classifying and decoding different grasp related forces during active grasping.

Two macaque monkeys were trained to reach, grasp and pull an object mounted on a low friction horizontal board in response to visual cues presented in front of the animal. Visual cues instructed the monkeys to grasp the object with one out of two grip types (precision or side grip) and pull the object with one of two different forces (0.5 N or 2 N). Monkeys obtained a food reward after successfully performing the instructed grip and pull. After reaching satisfactory performance, monkeys were implanted with a 100 electrode Utah microelectrode array in the hand and arm area of the motor cortex. Following post-surgery recovery period, monkeys continued to perform the task on a daily basis. During the task execution, we recorded electrophysiological signals from the multielectrode arrays, along with the visual cues and the behavioural events. Six different parameters of the grip, four pressure forces on each side of the object, pull force on the object and the object displacement, were recorded simultaneously with the neuronal activity. We extracted the activity of single neurons from electrophysiological recordings and used it to either classify different grip types or loading forces, or to decode the continuous traces of different forces during the grip.

Grip types were classified with an accuracy of 95% to 100%, whereas the classification of pulling force were not as accurate, reaching a level between 70% and 80%. When decoding traces of kinetic grip parameters, r^2 values were similar for all 6 grip parameters, ranging from 0.55 to 0.85. Our results show that kinetic grip parameters can be decoded with high accuracy, thereby improving the feasibility of constructing fully functional anthropomorphic neuronal prosthesis.

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GIBBS DISTRIBUTION ANALYSIS OF TEMPORAL DYNAMICS IN LARGE-SCALE RETINAL RECORDINGS USING MONTECARLO METHOD

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Recent experimental advances have made possible to record several hundred neurons simultaneously in the retina as well as in the cortex. Analyzing such a huge amount of data requires elaborate statistical mathematical and numerical methods, to describe both the spatiotemporal structure of the population activity and its relevance to sensory coding. Among these methods, the maximal entropy principle has been used to describe the statistics of spike trains. Simple forms of Gibbs potential [3], with only first and second order terms, have been successful in predicting the probability of patterns lying within one time bin. However, the same models are not able to predict the temporal statistics of the neural activity.

We have extended the maximal entropy principle to predict spatio-temporal statistics [2]. This generalization made use of transfer matrix results in ergodic theory [1, 5]. The approach avoids the computation of the normalization factor (partition function) and directly provides the moment generating function (free energy density). We first developed a numerical method to learn the parameters of a maximal entropy model with spatio-temporal constraints on real spike train data [2, 5]. However, this exact method could only be applied to small subsets of neurons, since it required construction of huge matrices whose size increases exponentially with the number of neurons [6].

To circumvent this combinatorial explosion, we then adopted a Monte-Carlo approach [4] to compute the observable averages for a given set of model parameters. We first tested the efficiency of this new algorithm in the case where a raster plot is generated from a known Gibbs distribution. We then let the algorithm find back this Gibbs distribution from that raster. This allowed us to quantify both convergence rate and model accuracy as a function of the number of neurons. We are currently applying these methods to large-scale recordings of retinal neurons responding to natural movies.

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THETA BURST STIMULATION TO MEDIAL SEPTUM ENHANCES SPATIAL COHERENCE OF HIPPOCAMPAL PLACE CELL REPRESENTATION

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Neuronal ensemble activity in the hippocampus is the basis of the cognitive spatial map; the firing properties of hippocampal place cells define the long-term encoding of spatial information. We investigated here if the spatial fields of hippocampal place cells can be shaped by the activity of septal projections. Medial septum (MS) is theta rhythm generator (King et al., 1998); septo-hippocampal lesions abolish hippocampal theta (Buzsaki et al., 1983) and alter hippocampal single unit representations (Leutgeb and Mizumori, 1999). After baseline recording and identification of place fields, we triggered bursts of pulses at theta-frequency (theta-burst stimulation, TBS) to MS every time the animal entered unit's place field and compared the firing properties of the targeted unit with the firing properties of the units with place fields in a distal location (controls) (Fig 1 A, B). We represented the CA1 place field properties as ratios of the measured values from the stimulation session over the values of the baseline session. Our data show that spatial coherence has significantly higher values (paired t-test, $p<0.05$, $n=25$) for TBS-stimulated units in comparison to controls (Fig 1 C, left). Spatial coherence consists of a spatial autocorrelation of the place field map and measures the extent to which the firing rate in a particular bin is predicted by the average rate of the eight surrounding bins (Muller and Kubie, 1989). We also found that place field size is reduced as a result of TBS stimulation (Fig 1 C, right). We computed place field size as the region of the arena in which the firing rate of the place cell was 20% or greater of the maximum firing frequency (Hollup et al., 2001). Importantly, spatial information content (expressed in bits per spike), which is the fundamental property of place fields (Skaggs et al., 1993), remained constant (Fig 1 D, left). Our data reveal that the modulatory role of theta-frequency septal activation on the hippcampal place field representation is linked mainly to spatial coherence.

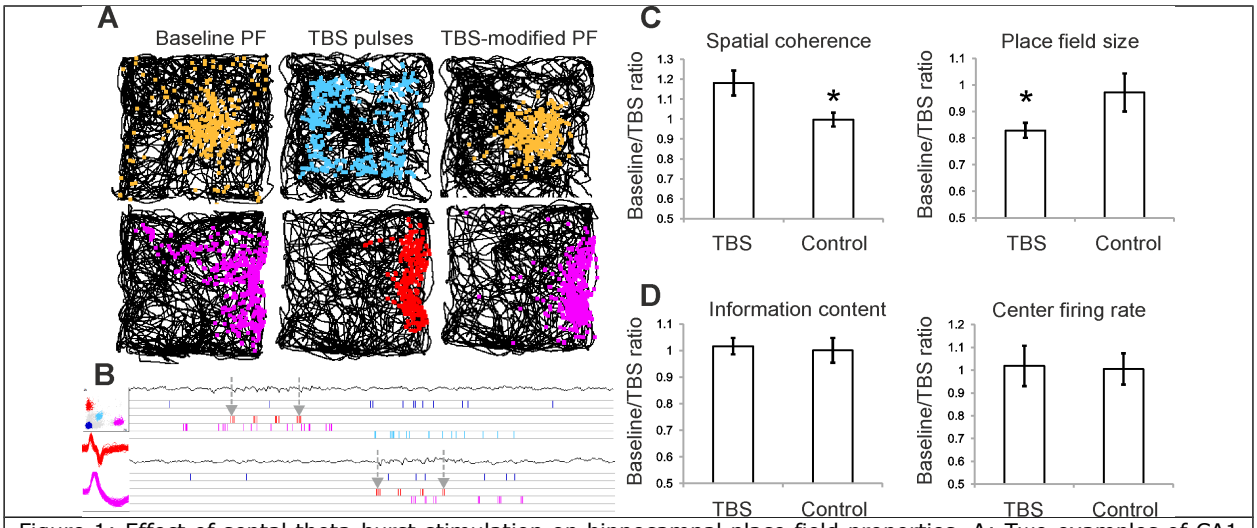

Figure 1: Effect of septal theta-burst stimulation on hippocampal place field properties. A: Two examples of CA1 place fields (yellow and purple) during baseline recordings (left panels) and TBS recordings (right panels); Location of TBS pulses application (blue and red, respectively, middle panels). B: Spike shapes and sample epochs. C: Spatial coherence and place field size ratios. D: Information content and center firing rate ratios.

DIFFERENT ENCODING OF REWARD SIZE AND MOTOR EFFORT IN THE MONKEY STRIATUM AND EXTERNAL PART OF THE GLOBUS PALLIDUS

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Motivation to perform an action can be defined by the subjective value of this action, and quantified by the ratio between its cost and its benefit. It requires convergence and integration of limbic, motor and associative information to adapt behaviors accordingly. The basal ganglia (BG) are known for their implication in processes involving these different types of information. The striatum, the main input structure of this subcortical system, is functionally divided into 3 different areas, sensorimotor, associative and limbic, based on the distribution of the cortical inputs. The external segment of the globus pallidus (GPe) is well positioned to play a key role in the integration of information from the different striatal territories before their transmission to the BG output structures and, consequently to encode information about motivation to perform an action. We recorded the activity of 308 neurons in the striatum, 149 TANs (Tonically Active Neurons, supposed to be cholinergic interneurons) and 159 PANs (Phasically Active Neurons, striatal projection neurons), and 92 neurons in the GPe of two monkeys performing a visuomotor task which requires a motor effort (development of a force) to get a reward. Four distinct associations of visual stimuli determine four cost (force to develop: small or big)/benefit (reward size: small or large) ratios for the animal. Behavioral data (reaction times and error rates) showed that animals discriminated the different conditions of the task and modulated their behavior among these conditions. Sixty-eight percent (101/149) of the recorded TANs were modulated at the occurrence of the visual stimuli, 61% (91/149) at the reward and 46% (68/149) responded to both. We have not found any differences in term of number or magnitude of these responses among the four different conditions of the task. A large majority of the recorded PANs showed a peak of activity to the occurrence of the visual stimuli (27/159, 17%), the development of the force by the animal (73/159, 46%) or the reward occurrence (38/159, 24%). In these last 2 populations, the neuronal activity was modulated by the task conditions (55/73, 75%; 30/38, 79%). The activity of a large population of PANs was, as expected, modulated by the amount of force at the time of the force development (52/73, 71%) and by the reward size at the reward occurrence (29/38, 76%). Interestingly, 45% (33/73) of the PANs also showed an effect of the size of the upcoming reward at the development of the force, and 66% (25/38) an effect of the amount of force exerted at the time of reward occurrence. In GPe, the neuronal activity was modulated by an increase or a decrease in the firing rate, in response to the occurrence of the visual stimuli (50/92, 54%), the development of the force (78/92, 85%) and/or the reward occurrence (73/92, 79%). Most of the recorded GPe neurons responded to multiple events of the task (79/92, 86%). Seventy-one percent (65/92) of the recorded neurons were modulated by the task conditions. At the occurrence of the visual stimuli, 17% (16/92) of the neurons were modulated by the size of the future reward, and at the development of the force, 38% (35/92) were modulated by the amount of force. At the reward, however, neurons were modulated by the force to develop, the size of the reward or the interaction between these 2 variables (20, 13 and 9% respectively). Our results suggest that the motor and motivational information, encoded separately and independently by striatal neurons at different events of the task, converge in GPe where one single neuron can be modulated by these events. Thus, the GPe, considered hitherto as a relay structure, seems to play a role in the integration of these different types of information.

CO-ADAPTIVE BMIs: COMBINING NEURAL AND DECODER PLASTICITY

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Brain-machine interfaces (BMIs) have great potential for motor rehabilitation but require significant performance improvements for clinical viability. Recent work suggests that treating BMIs as closed-loop, co-adapting systems may be beneficial. Here, we review BMI studies of neural plasticity and adaptive decoding. We then present preliminary evidence that these mechanisms can be combined and argue the benefits of a hybrid approach.

In a BMI, an algorithm ("decoder") translates neural activity into a control signal. In closed-loop (CL) BMI, feedback from the controlled device allows the subject to volitionally modulate neural activity. Performance is determined by the user *and* the decoder, making understanding brain-decoder interactions critical to improving performance. Research shows that either brain or decoder adaptation can improve performance. In [1], pairing stable neural ensembles with a fixed decoder allowed subjects to learn a stable neural "map" of the decoder, facilitating performance improvements. Similar to natural motor learning, BMI control was rapidly recalled across days and was robust to interference [1]. Moreover, the dorsolateral striatum—a structure implicated in motor learning—has been shown to be necessary for arbitrary transform learning [2]. These results suggest that neural plasticity can improve BMI performance, and may provide BMIs with desirable learning properties. An alternate approach is to improve performance via decoder adaptation, using a subject's known or inferred task goals to modify the decoder in CL (Closed-Loop Decoder Adaptation, CLDA) [3]. We recently showed that the CLDA time-scale is particularly important design consideration [4]. A CLDA algorithm operating on a 1-2 minute time-scale was able to improve performance independent of the initial decoder in as little as 20 minutes [5].

We conducted preliminary experiments showing that decoder and neural plasticity can be combined. CLDA was used to improve initial BMI performance; this decoder was then held fixed with stable neural activity as one rhesus macaque performed a center-out BMI task. Performance was maintained across days (A) and did not require re-learning (B), suggesting that the neural map for the decoder could be recalled, as in [1]. In cases where CLDA performance was low, the subject also showed intra-session learning (B, grey). As BMI control complexity increases and the ability to fully span the control-space for decoder or neural training alone becomes infeasible, this type of hybrid brain-decoder adaptation may be able to capitalize on the strengths of each adaptation method, reducing learning time while taking full advantage of the motor-learning properties provided by neural adaptation.

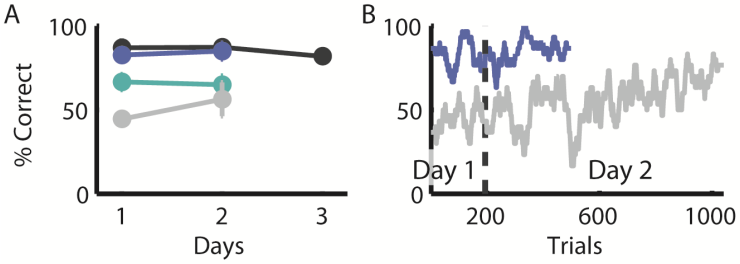

Figure 1. (**A**) Mean BMI performance across days with a fixed decoder created via CLDA. (**B**) sliding average of performance (30-trial window) for example sessions; trace color matches A, black dashed line marks day-breaks.

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FACE AND CAR INDIVIDUATION IN THE OCCIPITOTEMPORAL CORTEX BASED ON MULTI-VOXEL PATTERN ANALYSIS

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It is well-established that certain cortical regions respond preferentially to specific classes of stimuli such as faces (*e.g.* FFA, OFA and STS) and generic objects (*e.g.* LOC). It is yet unclear, however, what specific function is served in these areas with some hypotheses proposing OFA as an early stage, feeding into FFA for identity, and STS for identity-invariant expression processing for faces. To clarify the functional roles these regions play, we examined whether spatial patterns of activation within face- and object-selective regions contain exemplar identity information for faces and cars. In our experiment, subjects (n = 8) viewed two different faces and two different cars displayed at randomly-varying visual sizes. We chose our stimuli using an ideal observer analysis to ensure that the physical difference between the two car exemplars matched that of the two faces. We first localized all three face-selective regions of interest (the core network) and the LOC bilaterally using independent scans. We then performed a multi-voxel pattern analysis (MVPA) to evaluate discrimination accuracy based on patterns of activity across the top 200 voxels of each region-of-interest (ROI) using a support vector machine based linear classifier. In addition, we determined the most discriminative collection of voxels in all tasks by submitting a large cortical area including the core network, LOC and anterior temporal regions to recursive feature elimination (RFE).

Our results can be summarized as follows: all ROIs, bilaterally, contain information sufficient to discriminate faces from cars with significantly above chance accuracy (typical $p < 0.05$), with the exception of STS. Since core-network ROIs were localized (independently) using a face-object contrast, successful between-category MVPA results validate our methodology. The lack of classification in the STS was consistent in both hemispheres and was most likely due to the fact that our MVPA protocol used static images while STS (localized using video clips) is mainly responsive to dynamic stimuli. The car discrimination task showed no classification in the left hemisphere ROIs. Overall, the only individual ROI that discriminated cars was the right LOC, consistent with results by Eger *et al.* (2008). Although classification accuracy for cars in the right FFA and OFA did not reach significance individually (p = 0.1 and 0.07), when combined, this OFA-FFA network performed significantly above chance on the right side (p = 0.006). This finding suggests car individuation as a potential function of the core network and thus challenges the “domain specificity” claim on exclusively face-dedicated processing. Moreover, it suggests that individuation may be occurring in networks of regions rather than in single regions. Consistent with this idea, none of the individual ROIs were able to discriminate the two face exemplars. However, our RFE analysis returned a distributed network of cortical regions, which included the core network and the anterior temporal regions, that classified faces with better than chance accuracy ($p < 0.05$). Classification accuracy for bilateral networks was significantly larger than that of left-hemisphere only ($p < 0.05$), but was not significantly larger than the accuracy of right-hemisphere only. Left hemisphere only networks did not discriminate the face exemplars.

Collectively these results suggest that individuation of cars and faces are right-lateralized while no lateralization was apparent for the between-category face/car discrimination. In addition, results showing OFA and FFA involvement in car discrimination challenge claims of exclusively face-dedicated processing in regions such as FFA.

POPULATION RECEPTIVE FIELD MAPPING IN HUMAN SUBJECTS AFTER LESIONS OF THE VISUAL PATHWAY

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Cortical damage of the visual pathway as a result of stroke typically leads to a loss of conscious vision in the affected region of the contralateral visual hemifield (scotoma). The most common visual injury involves the primary visual cortex (V1), the major relay of visual information to the rest of the cortex. However, in spite of this, several higher visual areas have been shown to be modulated by visual stimuli presented inside the scotoma. This suggests that there are alternate pathways to transmit information from the retina to the cortex that bypass V1 and transmit information directly to extrastriate visual areas. A much debated issue is whether adult visual cortex is able to reorganize after injury, and if so, what is the extent and the mechanism of the observed reorganization. The purpose of this study is to map visual cortex organization after injury, gathering information about the role that specific networks of brain areas play in cortical reorganization and recovery. To this end, we use functional magnetic resonance imaging (fMRI) methods to study several subjects with quadrandanopia and hemianopia and compare them to a group of normal controls. FMRI measurements were obtained during the presentation of a moving bar stimulus, which traverses the visual field while the subjects are fixating. These measurements are used to estimate voxel based population receptive field centers and radii using a direct isotropic Gaussian method introduced by Dumoulin and Wandell (1). In select controls an area of the stimulus is obscured ("artificial scotoma") to simulate as much as possible the real scotoma of each patient. Preliminary results suggest that receptive field measurements obtained both in patients and in subjects examined under the artificial scotoma condition differ from measurements obtained in controls. In general, there appear to be no significant retinotopic map alterations in the borders of early visual areas of patients suffering from cortical lesions. However, there are some differences in the organization of higher visual areas such as hV5/MT+ compared to those of normal subjects. This may in part reflect the fact that some of the input to hV5/MT+ receptive fields has been lost with the V1+ lesion, but there are also suggestions that V1 bypassing pathways contribute. In addition, population receptive field size of some of the patients' spared visual areas show deviations from the normal range of population receptive field sizes derived from the control subjects with and without the artificial scotoma condition.

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UPDATE ON LOWER MOTOR NEURON DISEASES — THE CHILDHOOD-ONSET SPINAL MUSCULAR ATROPHY — A RETROSPECTIVE STUDY OF 75 CASES

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The childhood-onset spinal muscular atrophy (SMA) are a clinically heterogeneous group of autosomal recessive neuromuscular disorders characterized by degeneration of the anterior horn cells, with subsequently weakness and atrophy of limb muscles. After the genetic mapping of childhood-onset spinal muscular atrophy locus to chromosome 5q11.2-13.3, we have been among the members of the International SMA Collaboration Consortium which in 1993 has proposed diagnostic criteria and clinical classification of different types of autosomal recessive SMA. The Consortium Consensus led indeed to a comprehensive clinical classification scheme which currently include three different types or forms of childhood-onset SMA: Type I SMA is the most severe form with onset of symptoms prior to six months of age, and death expected in the majority of cases by two years of age. SMA type II (intermediate form) is defined by onset between 6 and 18 months, with patients never able of standing and walk and death expected after age of two years. SMA type III, by definition have onset of symptoms after 18 months and patients gain ability to stand and walk. Subsequently, from 1995, since the identification and characterization of two SMA determining genes (SMN and NAIP), there are been many advances in the understanding this disorder; the diagnosis is now easily made by genetic testing, and the deletion of the SMN1 gene (telomeric copy) is found in most patient (but not all) affected by SMA; clinical severity seems determined by the copy number of the SMN2 gene (centromeric copy). In 1996 we reported a third multicopy gene in the SMA genes, encoding the p44 subunit of basal transcription factor (BTFF2p44), which is deleted in at least 15% of SMA all cases. Finally, in 1998 a fourth SMA modifying gene (H4F5) has been identified, confirming genetic instability of the SMA region. Up to date, even though many advances in the understanding this disorder have been made, the pathogenesis of SMA is still incompletely understood, including clear explanations for interfamilial phenotypic variability as we observed in two siblings respectively affected by SMA type I and SMA type II. The mainstay of treatment is SMA is mainly based on supportive care, with emphasis to a multidisciplinary approach. Pulmonary support, physical therapy and nutrition support, have drastically improved time expected survival of patients affected by SMA type I and type II. Several drugs have been also tested in preclinical and clinical trials therapy of SMA, especially drugs aimed to increase SMN2 function. In addition to drugs treatments, gene therapy has been also considered for cure of SMA but only in animals model, and much preclinical works will be required before evaluation in human patients. The retrospective study of 75 patients affected by the different types of SMA, including two siblings affected respectively by SMA type I and SMA type two, was mainly based to review of medical records, clinical and neurological examinations, EMG and neuropathological findings, and genetic testing results. All patients were observed at the Division of Pediatric Neurology, Department of Pediatrics, University of Catania, Italy.

ACTIVE INFERENCE, SLOW PURSUIT AND OCULOMOTOR DELAYS

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We consider the problem of sensorimotor delays in the optimal control of movement under uncertainty. Specifically, we consider axonal conduction delays in the visuo-oculomotor loop and their implications for active inference. Active inference uses a generalisation of Kalman filtering to provide Bayes optimal estimates of hidden states and action in generalised coordinates of motion. Representing hidden states in generalised coordinates provides a simple means of compensating for both sensory and oculomotor delays. This compensation is illustrated using neuronal simulations of oculomotor following responses with and without compensation. We then consider an extension of the generative model that produces oculomotor following to simulate slow pursuit eye movements — in which the system believes both the target and its centre of gaze are attracted by a (fictive) point moving in the visual field. Finally, the generative model is equipped with a hierarchical structure, so that it can register and remember unseen (occluded) trajectories and emit anticipatory responses. These simulations speak to a straightforward and neurobiologically plausible solution to the generic problem of integrating information from different sources with different temporal delays and the particular difficulties encountered when a system — like the oculomotor system — tries to control its environment with delayed signals.

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CARMA: A BETTER LINEAR MAR CAUSALITY MEASURE

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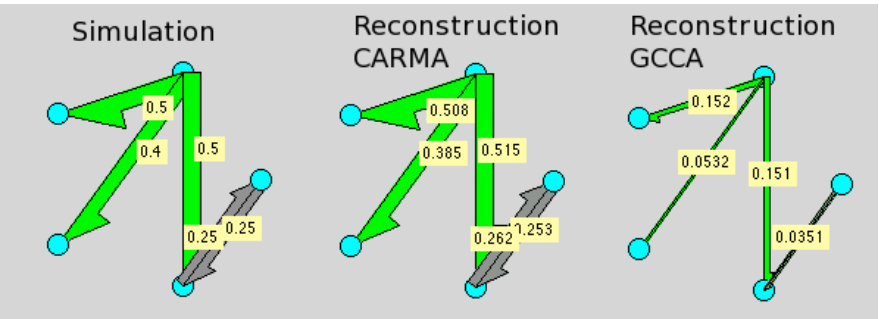
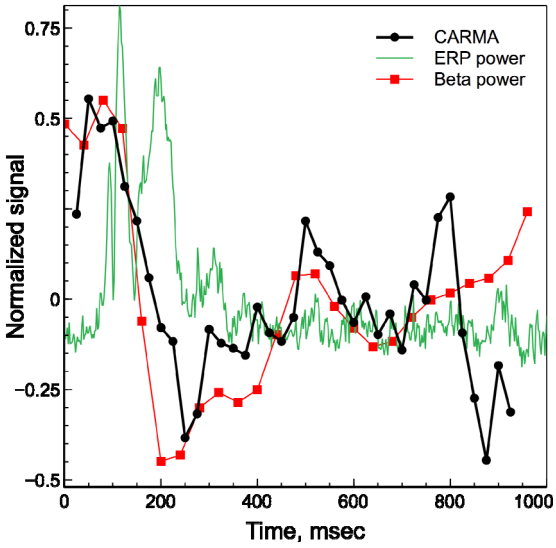
A new causality measure, termed CARMA, which accurately characterizes causal interactions among multiple signals is proposed. The same as for Granger causality (GC) the CARMA measure is based on linear multivariate autoregressive (MAR) fit of the data. Unlike GC and related causality measures CARMA estimates causal input of a variable by zeroing its MAR coefficients instead of leaving the variable out of the MAR fit. Because this approach leaves the remaining coefficients unaffected it allows to correctly estimate relative strengths of causal links, which are commonly misrepresented by GC-based measures. This approach also considerably speeds up calculations for multiple variables, because only one MAR fit is necessary for N variables vs. N fits for GC-based measures. Finally, CARMA measure has a straightforward interpretation: it gives the proportion of a signal's variation due to a causal input from another signal. CARMA showed excellent performance when tested on realistically simulated brain signals, such as produced by EEG or MEG. The algorithm was applied to complex networks of causal interactions with loops and recurrences. The results were not significantly affected by the signal's statistics: CARMA's performances for normal, uniform, and Laplace distributed signals were nearly identical. Although CARMA uses linear MAR fit its performance is not compromised by output-input nonlinearities, i.e. a nonlinear relationship between the actual signals exchanged among neural nodes and the measured signals (logistic and threshold + logistic nonlinearities were tested). The algorithm was also applied to high-density EEG data. The results demonstrated that causal interactions were strongly correlated with beta-band activity rather than with evoked responses.



Results are shown left using simulated causal data comparing CARMA with conditional Granger causality (GCCA), Seth, A.K. (2010)



CARMA measure showed strong correlation with beta-band activity for a high-density EEG experiment. The stimuli used were high-contrast full-field checkerboards reversing their contrast every second. CARMA and EEG power were analyzed in 20 msec steps over 100 msec windows. Six of 128 EEG electrodes used were chosen for the causal analysis. The electrodes were located roughly over V1 areas (1), left and right LOC (2), FEFs (1), and left and right frontal lobes (2). Mean strength of causal interactions among the six nodes is shown as a function of time from the stimulus onset. Visually evoked responses (ERP) and beta-band power were averaged over the same six electrodes.

INFLUENCE OF DENDRITIC MORPHOLOGY ON SINGLE NEURON ARITHMETIC

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Pyramidal cells are the most abundant type of neurons in the cerebral cortex. Their activity has been associated with higher cognitive and emotional functions. Pyramidal cells have a characteristic structure, consisting of a triangularly shaped soma where from two complex dendritic trees and a long bifurcated axon extend. All the morphological components of the pyramidal neurons exhibit significant variability across different brain areas and layers. Pyramidal neurons receive numerous synaptic inputs on the basal, oblique and tuft dendrites, whose integration in space and time can result in the generation of local dendritic spikes. Different modes of the combined subthreshold synaptic effects are observed: linear, when integration is the sum of individual responses, and nonlinear, when synaptic inputs are integrated in a sigmoid or power function. While both experimental and theoretical work has been performed to characterize the arithmetic of synaptic summation in pyramidal neurons, the role of dendritic morphology in this process remains elusive.

To address this issue, we created compartmental neuronal models combining detailed morphology and biophysical properties of 56 rat PFC pyramidal layer V cells. We used these models to investigate the subthershold integration properties of clustered excitatory synaptic inputs delivered to the basal dendritic tree. The simulations were performed in NEURON and the subsequent statistical analysis in MATLAB.

Preliminary results suggest that: (a) different dendritic branches within a model neuron integrate synaptic inputs in distinct manners, (b) the dendritic integration mode can be linear, superlinear or sigmoid-like, (c) the sigmoid response dominates in the dendrites of more complex basal trees and (d) there is a strong correlation between the specific morphological features (*e.g.* length, diameter, branch order), the passive properties of a dendrite and its mode (linear, superlinear or sigmoid) of synaptic integration.

AGE-DEPENDENT CHANGES OF SPONTANEOUS NETWORK ACTIVITY IN MOUSE CORTICAL SLICES

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The cerebral cortex is intrinsically active. In the absence of sensory inputs, as for example *in vivo* during quiescence (*e.g.* non-REM sleep and anesthesia) but also *in vitro*, in cortical slices, the cortex generates spontaneous activity reflecting the dynamics of its neuronal networks. Here we investigated how postnatal development and ageing affect network dynamics in the cortex as reflected in its spontaneous electrical activity. In particular, we recorded field potentials *in vitro*, in cortical slices prepared from mice ranging from the first postnatal week, to adult and aged animals. For comparison, two cortical regions with distinct function and cytoarchitecture are monitored: (i) the primary whisker somatosensory cortex, or barrel cortex, and (ii) the primary motor cortex. We found that spontaneous cortical activity reflect both age-specific and region specific changes. In particular, the spontaneous events of two cortices differed in regard with their occurrence, duration and amplitude. However, in both cortices, the occurrence of spontaneous events changes with age according to an inverted-U shape peaking around puberty. Pharmacological experiments show that these differences could be attributed to a stronger inhibitory modulation during older ages. Thus we propose that spontaneous cortical activity can be viewed as an endophenotype of distinct cortical regions and that its *in vitro* study may serve as an endophenotype of normal brain development which could be used to compare and characterize a number of mouse models of psychiatric diseases with a developmental profile.

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POPULATION RECEPTIVE FIELD MEASUREMENTS IN THE VISUAL CORTEX OF MACAQUE MONKEYS

Yibin Shao [1,*], *Georgios A. Keliris* [1], *Amalia Papanikolaou* [1], *Dominik M. Fischer* [2], *Ditta Nagy* [2], *Herbert Jaegle* [2], *Mark Augath* [1], *Nikos K. Logothetis* [1,3], *Stelios M. Smirnakis* [4]

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Visual receptive fields have dynamic properties that may change with the conditions of visual stimulation or with the state of chronic visual deprivation. We used 4.7 Tesla functional magnetic resonance imaging (fMRI) to study the visual cortex of two adult normal macaque monkeys and one with binocular central retinal lesions due to a form of juvenile macular degeneration (MD). FMRI experiments were performed under light remifentanyl induced anesthesia (Logothetis, *et al.*, Nature Neuroscience, 1999). Standard moving horizontal/vertical bar stimuli were presented to the subjects and the population receptive field (pRF) method (Dumoulin and Wandell, Neuroimage 2008) was used to measure retinotopic maps and pRF sizes in early visual areas. In addition we used a new spatiotemporal dynamic modulation method to measure pRF sizes as comparison. In general fMRI measurements from the normal monkeys agree with electrophysiological results in the literature, with fMRI pRF sizes and electrophysiology measurements showing similar trends. For the MD monkey, the size and location of the fMRI defined lesion projection zone (LPZ) in early visual areas is consistent with the retinotopic projection of the retinal lesion. No significant activity is found within V1 LPZ of the MD monkey, and the retinotopic organization of the non-deafferented V1 periphery is regular without distortion. Higher level visual areas (V5/MT) of the MD monkey show more extensive activation than areas of control monkeys with an artificial scotoma (to obscure part of the stimuli from the visual field as a simulation of the real scotoma) of comparable size. PRF sizes in the non-deafferented V5/MT of the MD monkey are on average slightly smaller than controls. Further investigation using fMRI and standard electrophysiology methods is in progress.

SPONTANEOUS SLOW-RHYTHMIC ACTIVITY IN NEOCORTICAL SLICES OF MICE LACKING THE BETA-2 SUBUNIT OF THE NICOTINIC ACETYLCHOLINE RECEPTOR

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During quiescent brain states, such as non-REM sleep and anaesthesia, a spontaneous slow-rhythm activity develops in the cerebral cortex. This activity is largely maintained *in vitro*, in cortical slice preparations, indicating that it is mainly the outcome of intrinsic properties of the local neural networks. The cholinergic system is believed to regulate the cycling between sleep and wakefulness and activation of the cholinergic system has been associated with REM sleep and arousal. In addition, the beta-2 subunit of the nicotinic acetylcholine receptor (nAChR) has been linked to the high affinity nicotine binding sites of the brain and is thought to be related to cognitive deficits associated with ageing. In the present study we examined the characteristics of spontaneous rhythmic activity in brain slices of adult (3–9 months) and old (over 18 months) mice lacking the beta-2 subunit of the nAChR (b2KO). Field potential recordings were obtained from the somatosensory cortex of wild-type (WT) and b2KO C57BL/6 mice. We found that the duration of individual spontaneous events was longer in the b2KO mice compared to WT, and this was not affected by mouse age. Additionally, we found differences in the power spectrum of individual events: the relative power of the lower gamma frequency band was significantly increased in adult b2KO mice compared to adult WT and old b2KO mice. Furthermore, preliminary pharmacological experiments using carbachol or gabazine indicate differences in the mechanisms supporting the spontaneous rhythmic activity of the b2KO compared to WT mice. Overall, the spontaneous network activity exhibits systematic differences between WT and b2KO mice, suggesting that this network phenomenon could serve as an endophenotype of cortical physiology.

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ELUCIDATING THE NEURONAL CIRCUITRY OF TIMING FOOD INTAKE

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Rodents eat almost exclusively during the night hours when they are most active, but if they are fed in a limited amount during the light cycle they will show a peak of activity in anticipation (usually ~ 2 hrs) of the scheduled meal time. As this activity precedes daily scheduled feeding it is referred to as *food anticipatory activity* (FAA). We have determined that dopamine production solely within the dorsal striatum is sufficient or permissive for the expression of FAA on a calorie restricted diet. Moreover, mice mutant for the dopamine receptor 1 (DrD1) do not successfully anticipate meal delivery. In contrast, mice mutant for the dopamine receptor 2 have normal ability to predict meal time. Interestingly, impairment of serotonin signaling by deletion of either the tryptophan hydroxylase-2 or serotonin transporter does not impair FAA. We are currently conducting in vivo electrophysiology of awake, behaving mice anticipating scheduled meal deliveries in the dorsal striatum and have observed some units with firing patterns that are highly correlated with anticipation or expectation of meal time. We are currently implanting neural probes into the dorsal striatum of additional mice in hopes of capturing more units that correlate with food anticipation. We are also in the process of using virus to restore DrD1 to different sites in the striatum of DrD1 knockout mice to determine precisely where DrD1 is acting in the striatum to promote FAA.

AN FMRI STUDY EXAMINING THE LEARNING AND RETREIVAL OF OVERLAPPING SPATIAL MEMORIES

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Episodic memories are comprised of distinct events in time and space, yet our memories often overlap. Prior modeling work implicates medial temporal lobe structures as critical for retrieving distinct memories based on contextual information, which can be used to distinguish overlapping events. Recent research in animals and humans has demonstrated a critical role for the hippocampus in the retrieval of overlapping sequential representations (Agster, *et al.*, 2002; Brown, *et al.*, 2010). Key structures outside the hippocampus have also been implicated in the successful navigation of overlapping routes, including the parahippocampal cortex and the caudate nucleus (Brown et al., 2010).

The present study used fMRI in humans to examine the role of the hippocampus, parahippocampal cortex, and medial caudate nucleus in the integration of overlapping navigational memories during learning. Sixteen participants were trained outside the scanner to navigate 10 distinct virtual mazes to a criterion of 100% correct. The following day, participants navigated each well-learned maze and learned 10 new mazes while undergoing fMRI scanning. Images were collected on a 3 T Siemens TrioTim MRI scanner (3.5 $\times$ 3.5 $\times$ 4 mm voxels, TR = 2 s, 32 slices, flip-angle = 90°). The mazes were comprised of three hallways and intersections, with unique landmarks at each intersection. There were four experimental conditions. Five mazes comprised the Overlapping Old (OL_{Old}) condition. Mazes of the OL_{Old} condition were learned as distinct, non-overlapping mazes on training day, but become overlapping with five new mazes during scanning. Five mazes comprised the Overlapping New (OL_{New}) condition, which were learned within the scanner and shared their middle hallways with the mazes of the OL_{Old} condition. Overlapping pairs of mazes began at distinct locations from one another so that the starting intersections and their landmarks served as contextual cues to identify the current navigational episode. The other 10 mazes were split between the Non-overlapping (NOL) Old and New conditions. Mazes of the two NOL conditions were completely distinct from every other maze. BOLD signal was contrasted between the navigation of Overlapping and Non-overlapping mazes for the Old and New conditions.

The results demonstrate a specific role for the parahippocampal cortex in representing novel spatial contextual cues, and complementary roles for the hippocampus and medial caudate in navigating familiar routes which become overlapping with novel representations. Our results suggest the hippocampus may be particularly important for flexible decision-making through its ability to uniquely represent or disambiguate overlapping memories, while the striatum can be thought of as supporting disambiguation of actions, helping to flexibly represent alternative behavioral output in different circumstances.

ENCODING OF REWARD VALUE IN AIP AND F5 DURING DECISION-MAKING IN A GRASPING TASK

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When faced with choices that prompt a motor decision, it may be advantageous to include in the neural representations the magnitude of the benefit afforded by each option. This might be especially important in areas of the brain directly involved in motor planning and execution. To investigate the dynamics of this representation, we recorded neural activity in anterior intraparietal area (AIP) and ventral premotor cortex (area F5) while a monkey performed a reward-modulated grasping task. After fixating a red dot on a screen, visual cues appeared guiding the animal (Macaca mulatta) to select one of two possible grip types, *power grip* or *precision grip* for manipulating a target object. We trained the animal to recognize the reward magnitude associated with each of three visual cues representing small, medium, and large liquid rewards. In addition to single-cue trials instructing the monkey to select one of the possible grip types, we presented free-choice trials allowing the monkey to compare both visual cues and then freely select the preferred grip type. The monkey chose the higher-valued reward in 96% of comparison trials.

We recorded single- and multi-unit activity from 128 channels simultaneously using permanently implanted electrode arrays. Of 226 units (123 in F5; 103 in AIP), ~ 60% encoded information about grip type selection and ~ 27% showed differential representation of reward, with ~ 21% displaying both effects. Since a large portion of units exhibiting reward modulation also encoded grip type, we classified activity by *preferred* and *non-preferred* grip to further examine coding dynamics. Two common representations emerged: *up* tuning, showing increased firing rate with increased reward magnitude; and *down* tuning, for which firing rate decreased with increasing reward. Interestingly, we found all combinations of *up* and *down* tuning for *preferred* and *non-preferred* grip conditions. Our preliminary findings suggest significant and complex modulation of motor circuitry by reward value representations. This suggests that differential reward representation within a neural ensemble is necessary to allow decision-making networks to select one of several competing motor behaviors.

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EVIDENCE FOR HIERARCHICAL STRUCTURE IN CORTICAL ACTION REPRESENTATION

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Former work in motor neuroscience suggests the existence of two possible contexts of action description, based on which motor control problems might be defined in the brain. One of these contexts refers to an intrinsic frame of reference centered on the body's actuators and sensors, while the other one refers to an extrinsic frame of reference related to task conditions, environmental settings and object properties. Although these frames have been previously examined [1], it still remains unclear how motor coordination is linked to one or the other and whether both of them can be explained as parts of a hierarchical representation of action in the brain.

Here, we propose a hierarchical bayesian framework to test three possible neural representation schemes of motor learning during object manipulation tasks. (A) Our first scheme suggests that task dynamics are principally learned and represented in an intrinsic joint-based frame of reference. This model reflects the function of a neuronal ensemble which controls the generalization of learned motor tasks over all joint space, but with regard to one specific object configuration. (B) Conversely, the second proposed scheme predicts that learning is realized with regard to an extrinsic object-based frame of reference. This mechanism represents a neuronal process which controls the generalization of learned motor tasks over all possible object configurations, but with regard to one specific joint arrangement. (C) Lastly, our third intermediate scheme points to a neuronal process that controls the generation of motor outputs based on the independent and simultaneous representation of learned task dynamics both in an intrinsic and extrinsic frame of reference. In order to test which of the three candidate mechanisms underlies motor control we conducted a behavioral study. Human subjects were asked to perform a rotational task within a given accuracy inside a 3D virtual reality setup, using a bottle of complex or static internal dynamics. In two different experiments subjects learned a single training task and were subsequently instructed to complete multiple testing tasks, in which object or joint positioning varied (experiment 1 and 2 respectively). Their performance was estimated in terms of pivot point displacement and used to examine how learning is transferred from training to testing conditions. A decreased performance in testing phases demonstrated a poor generalization capability of learned task dynamics to novel task contexts in both experiments. This observation provides supporting evidence for our third scheme of hierarchical motor control in which task representations are realized both in an intrinsic and extrinsic frame of reference.

Our work provides a novel formalization for describing cortical motor representations during object manipulation tasks. The prevailing third model reflects how task dynamics are captured by a weighted contribution of two representation contexts. Its structure calls for further investigation of both the computational and neural foundation of hierarchically structured behavior.

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CORTICAL MICROCIRCUIT DYNAMICS IN VISUAL AWARENESS

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When a subject is dichoptically presented with two conflicting images, only one image is perceived at a time while the other is suppressed from awareness; this paradigm of multistable perception, is known as Binocular Rivalry (BR). Perception, therefore, alternates between the two visual patterns allowing a dissociation of sensory stimulation from conscious visual perception. From a theoretical point of view, most of the computational models proposed to account for BR are rate-like models. The need is nevertheless apparent to employ biophysically plausible neuronal network models in order to connect psychophysics experiments with neurophysiological data. Here we adopted a spiking network with biophysically realistic AMPA, NMDA, and GABA receptor-mediated synaptic dynamics, as well as spike-frequency adaptation mechanisms based on Ca^{++}-activated K^{+} after-hyperpolarization currents.

Noise due to the probabilistic spike times of neurons is crucial for rivalry. It has been shown that competition models based on cross-inhibition and adaptation explain the observed alternations in perception when noise operates in balance with adaptation. In order to gain insights into the cortical microcircuit dynamics mediating spontaneous perceptual alternations in BR, we derived a consistently reduced four-variable population rate model from a recurrent attractor-based biologically realistic spiking network used to model working memory, attention, and decision-making, where neuronal adaptation is implemented, using mean-field techniques. The model accounts for experimental data, collected from human subjects during BR, such as mean dominance duration, coefficient of variation, shape parameter of the gamma distribution of dominance durations and agrees with Levelt's second and fourth proposition. The model replicates the observed data when it operates near the bifurcation that separates the noise-driven-transitions from the adaptation-driven-oscillations dynamical regime. Moreover, we show that spike-frequency adaptation of interneurons is not crucial for the spontaneous perceptual alternations, but affects the optimal parametric space of the system by decreasing the overall level of neuronal adaptation necessary for the bifurcation to occur and generates oscillations in resting state, such as in the absence of external stimuli.

Furthermore, we consider recent experimental data from the macaque lateral prefrontal cortex collected during Binocular Flash Suppression a paradigm of externally induced perceptual alternation. They show a decrease in correlated variability across pairs of neurons sharing similar stimulus preferences when their preferred stimulus is perceived during rivalrous visual stimulation compared to the magnitude of correlation when the same stimulus is perceived without competition. Employing the biophysically plausible spiking network with spike-frequency adaptation, we explore distinct possible computational strategies responsible for the noise correlation decrease under visual competition.

RETINAL METRIC: A STIMULUS DISTANCE MEASURE DERIVED FROM POPULATION NEURAL RESPONSES

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Sensory systems transmit information about the environment to the brain using a population code that consists of combinations of spikes and silences. The organism's view of the external world, and in particular, its ability to distinguish between stimuli, is thus shaped by how various stimuli map into population responses. On a single neuron level, this mapping is often described as linear filtering in the neuron's receptive field followed by a non-linear response function (LN model), indicating that distinguishable responses are produced only when the stimuli differ along a small number of directions in the stimulus space. It is unclear how this picture generalizes to a population of interacting neurons encoding the same stimulus. Does the population use the diversity of neural sensitivities to distinguishably represent all possible stimuli, or is it inherently able to discriminate much better between some pairs of stimuli than between others?

To address this question, we recorded simultaneously from 100 neurons in the salamander retina and measured the population responses to repeated presentations of temporally random and spatially uniform stimuli. From this data we built the stimulus-dependent maximum entropy model for the population and used it to construct a corresponding "retinal distance" function between arbitrary pairs of stimuli. In contrast to previously used choices for the distance measure in the space of stimuli, the retinal distance tells us precisely how distinguishable, given the noise in population neural responses, a pair of stimulus clips is to the retina, thus placing bounds on any downstream decoding layer. We find that the retinal distance strongly deviates from Euclidean, and indeed from any distance with a static metric. This approach allows us to isolate the stimulus features that the population as a whole extracts from the stimulus; in this way, it can be viewed as a generalization of the reverse correlation-type analyses for single neurons. Furthermore, for a given stimulus trace, we are able to create ensembles of similar stimuli that are distinguishable from the given one to within a prescribed level of discriminability of the response. By constructing a mathematical model for the retinal distance we show that its non-Euclideanity has important consequences for decoding and inferring feature sensitivity of whole neural populations.

A BI-DIRECTIONAL BMI ALGORITHM WITH ARTIFICIAL SENSORY INFORMATION

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Brain-Machine Interfaces (BMIs) aim to restore motor functions by mediating the communication between brains and artificial devices. It is therefore fundamental to establish a two-way brain-world communication channel, by both decoding motor commands from neural activity and by providing feedback to the brain through electrical stimulation.

Our group recently proposed a BMI that interacts with an external device, such as a point mass or a multi articulated arm, by generating control policies in the form of force fields (FFs) [1], such as those generated by group of muscles, at the limb/environment interfaces. In our system, bidirectional communication is established through: (a) a motor interface decoding neural activity recorded from a motor cortical area, and (b) a sensory interface encoding the state of the device into a pattern of electrical stimuli delivered to a somatosensory area.

The sensory interface associates a portion of the spatial domain of the force field to each stimulation pattern and is set such that the electrical stimuli encoding neighboring portions of space elicit more similar spike trains. We define these sensory regions during the calibration phase during which we collect many neural responses to each stimulation pattern and we project them onto the sensory domain by Multi-Dimensional Scaling. The motor interface then decodes the evoked activity by measuring its distance with respect to all the calibration trials, projecting it in 2D, and looking up the corresponding force in the ideal force field. That force is then applied to the dynamical system. We run the algorithm to probe the “reaching” ability of the system to drive a simulated point mass from a starting position toward the goal location (*i.e.* an equilibrium point of the FF).

To test and validate the mathematical framework proposed, we implemented such an interface in an anesthetized rat, recording neural responses from the vibrissa motor cortex (M1) evoked by stimulating different locations of the primary somatosensory cortex (S1). We then used this data also to construct a simulated computational model of the interface, generating realistically simulated spike trains with the same first-order stimulus-response statistics as the data. Both in the real experiment and in the computational model, we interfaced the neural responses with a dynamical system represented by a point mass moving in a viscous medium and evaluated the robustness of the algorithm by progressively reducing the amount of information about the stimuli of the recorded neural responses. We demonstrate the progress of the mathematics with respect to previous implementations [2].

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UNIFYING PROCEDURAL MEMORY CONSOLIDATION AND STRUCTURE LEARNING IN MOTOR CONTROL

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Humans can improve their performance in procedural movement tasks through practice, but such motor learning has shown puzzling and seemingly contradictory results. On one hand, a wide variety of proactive and retroactive interference effects have been observed when multiple tasks have to be learned. On the other hand, facilitation and transfer of learning has been reported between different tasks, sometimes based on abstract structure similarities.

Here we show how these different phenomena can all be understood based on generic learning principles in a recurrent neural network model. Specifically, we consider a sparsely connected recurrent network whose activity and connectivity is shaped by three plasticity mechanisms: spike timing-dependent plasticity (STDP), intrinsic plasticity, and synaptic scaling. The network receives stimulus-specific input and is connected to a layer of motor neurons mediating the movement sequences through a winner-take-all mechanism. We use this network to model a series of experiments on movement sequence learning using a single set of parameters in all simulations. The network learns to carry out the correct movement sequences over trials and reproduces differences in behavior between training schedules such as blocked versus random training. The network also shows striking similarity to human performance in tasks with similar training sequences but different training times.

It is shown how psychophysical performance measures are reflective of the learned neuronal representations in the recurrent network. Mutual information and PCA analysis of network activity reveal how input representations and the trajectories of neural activity change with training. Finally, we provide testable predictions for further experiments. Thus, we show how training schedule and task similarity interact to produce a rich set of interference and facilitation effects thereby unifying procedural memory consolidation and structure learning in a recurrent network model with multiple plasticity mechanisms.

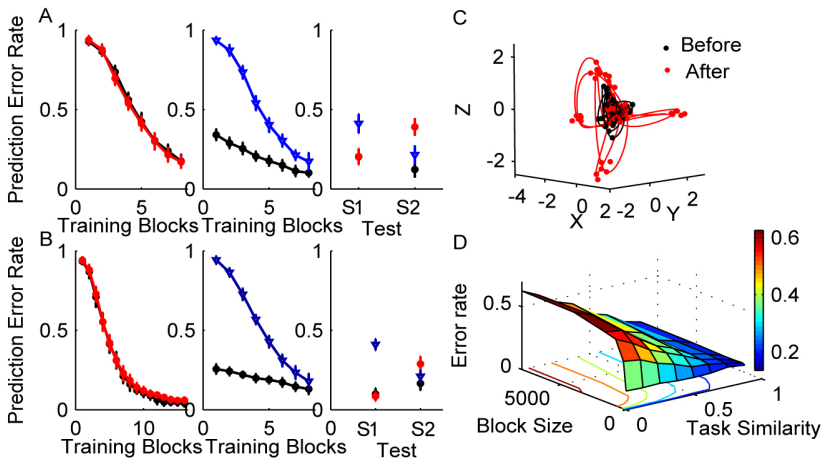

Figure 1: (**A**) Error rate over training time on sequence S1 and S2 and at subsequent testing according to model. Black: experiment group, training S1 and then S2. Red: control on S1. Blue: control on S2. The network shows retroactive interference and proactive facilitation. (**B**) Same as above, with the difference that training on S1 is twice as long. Note that now the retroactive interference is attenuated, as in psychophysical experiments. (**C**) Network activity in low-dimensional embedding space shows separation of sequence states with training. (**D**) Interaction of task similarity and training schedule on error rate in model simulation.

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