MAPS 2015

From Maps to Circuits
Models and Mechanisms for Generating Neural Connections

MISHA Amphitheater, University of Strasbourg, France

7-9 December 2015

Catering : coffee breaks will be hosted in the main hall of the MISHA building. Lunch will be hosted at the university restaurant ***Le 32*** (5' walking distance from the venue – voucher are provided your welcome package).

Posters : posters can be put up on Monday morning and left up for the duration of the meeting. Formal poster session will be held on Tuesday. Poster can be A0 portrait.

Sunday, December 6th : for anyone arriving on Sunday, we will have an informal gathering (place to be communicated soon).

http://maps2015.org

Sponsors

This meeting is supported by the University of Strasbourg Institute for Advanced Study (USIAS), Neurôpole Strasbourg, City of Strasbourg (Communaute Urbaine de Strasbourg), Idex Joint Master in Neurosciences — University of Strasbourg, Institute of Cellular and Integrative Neurosciences (INCI), Strasbourg, Wellcome Trust, The Company of Biologists and Région Alsace.

Idex - Joint Master in Neuroscience
BASEL-STRASBOURG-FREIBURG

Monday, December 7th 2015 - Chairs: F. Wolf (Max Planck) / U. Drescher (King's College)

9.00-9.45: Registration

9.45-10.00: Introduction/Welcome

10.00-10.45: **J. Cang (Northwestern University)**: *Visual Response Properties of Mouse Superior Colliculus.*

10.45-11.30: **S. Eglen (Cambridge University)** : *Using competitions to evaluate theoretical tools: understanding map formation and beyond.*

11.30-12.00: ***J. Triplett (Children's National Health System,):*** *Orientation- and direction-selectivity in the superior colliculus are driven by Islet2 + and Islet2 - retinal ganglion cell inputs, respectively*

12.00-14.00: lunch-Restaurant Le 32

14.00-14.45: **S. Lowel (University of Gottingen)**: *The dynamic architecture of the adult visual cortex or how can I keep my brain young ?*

14.45-15.30: **M. Feller (UC Berkeley)**: *You are what you see:a surprising role for activity in the development of retinal direction selective circuits.*

15.30-16.00: coffee break

16.00-16.45: **A. Huberman (UC San Diego)**: *Mapping visual direction selectivity in the brain*

16.45-17.30: **H. Baier (Max Planck)**: *From vision to action in the zebrafish midbrain*

17.30-18.30: General discussion

Evening: free visit of the Christmas market + gathering (sciences cafeteria, University of Strasbourg)

Tuesday, December 8th 2015 - Chairs: M. Crair (Yale) / D. Feldheim (UC Santa Cruz)

9.00-9.45: **R. Datta (Harvard)**: *Higher-order sensory maps for olfaction.*

10.00-10.30: **C. Stevens (Salk Institute)**: *Maps and Anti-maps.*

10.30-11.00: coffee break

11.00-11.45: **P. Gaspar (Institut du Fer à Moulin/INSERM)**: *Organizing a neuromodulatory system : topography in the ascending raphe neurons.*

11.45-12.15: ***P. Isope (CNRS UPR3212)****: Functional spatial maps of cerebellar granule cell inputs to Purkinje cells, Golgi cells and molecular layer interneurons in the cerebellar cortex*

12.15-14.00: lunch-Restaurant le 32

14.00-14.45: **T. Marquardt (University of Gottingen)**: *Motor neuron functional diversification and movement control.*

14.45-15.30: **F. Rijli (Friedrich Miescher Institute)**: *Epigenetic and Transcriptional Regulation of Cortico-Ponto-Cerebellar Circuit Formation.*

15.30-16.00: coffee break

16.00-16.45: **J. Rodger (University of Western Australia)**: *Electromagnetic brain stimulation to reorganise neural pathways : molecular, structural and behavioural effects*

16.45-17.15: ***X. Nicol (Institute of Vision)***: *Lipid rafts compartmentalize cAMP signals required for the refinement of retinal maps.*

17.15-17.30: **Posters Lightning session (1' talk highlighting the poster)**

17.30-18.30: **poster session**

19.15: Gala Dinner – Le Set Restaurant (20 rue Pierre de Coubertin - 67000 Strasbourg)

Wednesday, December 9th 2015 - Chair: D. Willshaw (University of Edinburgh)

9.00-9.45: **D. Holcman (Ecole Normale Supérieure)**: *Modeling neuro-glia interactions from synapses to network*

9.45-10.30: **Y. Sweeney (Imperial College)**: *Synaptic plasticity in neural network*

10.30-11.00: coffee break

11.00-11.45: **C. Lohman (Netherland Institute for Neurosciences)**: *Spontaneous network activity shapes neuronal connectivity with single synapse precision*

11.45-12.30: general discussion/conclusion-good byes
buffet-snacks

Poster titles (click on title to view corresponding abstract; ** denotes short-talk)

A Modified Topographic Product Reveals 'True' Order in Data Modelled on Multi-subject Retinal Inputs to the Optic Tectum.

Andrew Bard[1*], Aenea Hendry[1], Gareth Barker[2] and Andrew Lowe[1]

* Presenting Author (andrew.bard@kcl.ac.uk)

[1] Department of Developmental Neurobiology, King's College London. UK

[2] Centre for Neuroimaging Sciences, Institute of Psychiatry, King's College London. UK

Within the visual system, how individual retinal ganglion cell (RGC) types topographically map to, and integrate within, central targets is largely unknown. Deriving the topographic organisation of distinct retinal inputs to central targets that span the whole of visual space within a single experimental subject would require a technical tour de force, even in convenient model systems like the larval zebrafish. An alternative strategy would be to derive the topographic organisation of distinct RGC types by acquiring limited samples within a single animal and pooling data from many independent subjects. However, inter-subject map variability poses additional problems for the quantification of such datasets.

The topographic product (P_T) is a metric for topographic order derived from graph theory. It provides an estimate of order across all scales by examining the ratio of distances in matched spaces (for the application described here, visual and tectal) for all pairs of points representing the map. Using data modelled on the zebrafish retinotectal projection we have explored the consequences of map shape and different sources of variability (inter- and intra-subject) on P_T. As expected, P_T was resistant to changes in map shape but vulnerable to inter-subject variability.

We have explored two alternative formulations for analysis of group datasets: P_{Ts}, the mean of P_Ts from individual subjects; and P_{Tdist}, in which the ratios are pooled according to the distance between points in either map. While both of these derivations are insensitive to inter-subject map variability, P_{Tdist} outperforms P_{Ts}. We apply our method to real zebrafish functional imaging data, revealing topographic order in populations of zebrafish RGC axon terminals derived from multiple fish.

Nonlinear growth: An origin of hub organization in complex networks

Roman Bauer[1] and *Marcus Kaiser*[1,2]
[1]*Interdisciplinary Computing and Complex BioSystems ResearchGroup (ICOS), School of Computing Science, Newcastle University, Newcastle upon Tyne, UK*
[2]*Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK*

Highly connected nodes or hubs are observed across a wide range of complex networks, in particular neural networks. Their degree is higher than expected from regular, random networks. Often, this structural peculiarity goes hand in hand with a special functional role in the network. For example, hub regions in the human brain have been shown to be central in brain communication and neural integration [1]. Therefore, shining light on the developmental process of hub formation is a crucial step towards understanding network functionality in general. Many well-established models that can explain the development of hubs, such as preferential attachment [2] (for scale-free networks) rely on non-local information exchange, which renders them biologically unplausible. In this work, we propose and characterize a novel model of network growth that accounts for the development of hubs. Moreover, this model can account for rich-club organization, i.e. the manifestation that hubs often tend to preferentially connect with one another, rather than with lower-degree nodes. Finally, we analyze several real-world datasets, e.g. the brain connectivity of macaque monkey and C. elegans, as well as protein interaction networks. We then demonstrate that our "non-linear growth model" is well in-line with the experimental observations, and so provides a general principle for hub development.

References

[1] van den Heuvel MP and Sporns O, 2013. An anatomical substrate for integration among functional networks in human cortex. The Journal of Neuroscience.
[2] Barabási AL and Albert R, 1999. Emergence of scaling in random networks. Science.

Push and pull mechanisms of CNS-confined compact anterior migration of pontine neurons during development

Heike Blockus[1,2], Pavol Zelina[1], Chloé Dominici[1], Thomas di Meglio[1] and Alain Chédotal[1].
1 INSERM, UMRS_U968, Institut de la Vision, Paris, F-75012, France. 2 Ecole des Neurosciences de Paris, F-75006 Paris, France

During development, differentiated neurons often migrate long distances from their birthplace following stereotypic routes. These stereotypic patterns of neuronal network formation are not established in a random manner, but are encoded by environmental and neuron-specific cues in a highly controlled spatiotemporal fashion. Mammalian evolution was accompanied by the emergence of novel migratory pathways underlying new functional outcomes. These include the compact migratory stream of precerebellar pontine neurons. Dorsally born rhombic-lip derived pontine neurons first travel anteriorly across several rhombomeres before making an almost right-angled turn towards the ventral midline in rhombomere 4. Push-and-pull mechanisms are at play in these two distinct phases of migration and both the superficial, as well as the CNS-confined migration are controlled individually. We show here that pontine neurons fail to be confined to the CNS in the absence of Netrin-1 and DCC. Ectopic pontine neurons exit the brain at the level of the trigeminal nerve root and migrate into the ganglion alongside Sox10-positive Schwann cell precursors. Furthermore, in Robo3/DCC double mutants, displaced pontine neurons invade the inner ear, suggesting a regulatory barrier delineating the PNS/CNS boundary is missing in these mutants. Contrarily, after cell-autonomous deletion of the chemokine receptor Cxcr4, pontine neurons disperse from their compact superficial anterior stream and migrate deep inside the hindbrain tissue as thin chains in ectopic posterior positions. Concomitant deletion of Cxcr4 in a Robo3- or DCC-deficient background rescues midline attraction of posteriorly displaced pontine neurons. Altogether, our findings show that the compact anterior migration of pontine neurons requires balanced molecular control by different mechanisms ensuring superficial, but CNS-confined trajectories during development.

Increasing retinal waves accelerates visual development.

Zachary W. Davis, Barbara Chapman, Hwai-Jong Cheng

Center for Neuroscience, University of California, Davis; Davis, California, 95618, USA

ABSTRACT

Visually evoked activity is necessary for the development of the visual system. However, little is known about the capacity for spontaneous activity to drive the maturation of receptive fields prior to visual experience. Retinal waves provide instructive retinotopic information for the anatomical organization of the visual thalamus. In order to determine whether retinal waves can also drive the maturation of functional responses, we increased the frequency of retinal waves pharmacologically in the ferret (*Mustela putorius furo*) during a period of retinogeniculate development prior to eye opening. The development of geniculate receptive fields after receiving enhanced spontaneous retinal waves was measured using single-unit electrophysiology. We find that increased spontaneous activity accelerates the maturation of geniculate receptive fields. The maturation is caused by sharpening the receptive field center rather than by strengthening the inhibitory surround. This work reveals an instructive role for spontaneous activity in guiding the functional development of neural circuits.

Re-definition of a recently discovered midbrain structure: the tVTA (tail of the ventral tegmental area) or RMTg (rostromedial tegmental nucleus).

Fanny Faivre, Pierre Veinante, Michel Barrot.
Institut des Neurosciences Cellulaires et Intégratives, CNRS & Université de Strasbourg, Strasbourg, France.

In the past decade, a new mesopontine structure was described in the rat brain: the tail of the ventral tegmental area (tVTA) or rostromedial tegmental nucleus (RMTg). This new brain region attracted a lot of attention as it densely innervates the VTA and substantia nigra, providing the most potent inhibitory GABA control of dopamine systems, it was proved to be the anatomical target by which opiates recruit dopamine systems, it is the main output of the lateral habenula and its relay toward dopamine systems, it controls avoidance behaviors and aversive responses, it encodes reward prediction errors… However, this structure is not yet present in rat and mouse brain atlases, and some questions regarding the definition and boundaries of the tVTA remain. Thus, we did a side-by-side comparison of the various parameters defining the tVTA, by doing immunohistochemistries based on different protein markers of the tVTA, μ opioid receptor, glutamate decarboxylase 67, NeuN, and FosB/ΔFosB after an acute administration of cocaine. The results allowed us providing a 3D reconstruction of the structure. In a second step, we verified, by tract-tracing, the lateral habenula-tVTA-VTA connections. The results show that: 1) the various neurochemical markers of the tVTA define a bilateral structure with same localization and boudaries within the midbrain; 2) the tVTA contains about 2500 neurons per side and most of them can be recruited by cocaine (~60%); 3) the neurochemistry-based and connectivity-based definitions are not matching perfectly, and the neurochemical definition seems to be more relevant. These data provide a better anatomical definition of this newly described structure, which is a necessary step for developing functional studies concerning the role of the tVTA.

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Engineering and characterising neural network connectivity in 3D alginate scaffolds

Neurodegenerative disorders are a primary cause of ailment in older populations, with several neurological and neurodegenerative disorders resulting from the loss of cell populations [1,2]. The field of tissue engineering is driven by demand for healthy, functional tissues and cell populations [3-5]. In a therapeutic setting the goal is successful transplantation and integration with a host neural network; for research purposes, the goal is to generate artificial tissues in vitro, for investigating the intricate mechanisms of development and regeneration within a physiologically relevant platform [6,7].

In vivo, tissues develop as a result of complex spatial and temporal interactions of growth factors, chemokines and transcription factors, generating highly specialised neural networks [3,8]. Traditionally, two-dimensional (2D) cell cultures are used to investigate cell behaviour in vitro, but it is increasingly evident that dynamic three dimensional (3D) cultures can better represent the in vivo microenvironment, compared to 2D cultures [3,9]. This lab has previously generated 3D cultures from human neural stem cells using Alvetex®, a synthetic polystyrene substrate. The resulting cultures had heterogeneous neuro-glial populations including glutamatergic and gaba-ergic neurons, and astrocytes. Cultures were physiologically active, demonstrated by spontaneous activity on multi-electrode arrays and whole-cell patch clamp recordings.

Given the results using Alvetex®, current research focuses on developing a 3D neuro-glial network within an alginate hydrogel, and with a primary goal to characterize neural network connectivity in the resulting network. Alginate is a natural polymer derived from algae, inherently biocompatible and with an average pore size of ~5um in diameter (in 1% w/v alginate) [10,11]. Contrastingly, Alvetex® has no inherent biocompatibility and an average pore size of ~40um, much larger than the average cell diameter (~20um) [12-15]. The elastic modulus of alginate 1% w/v is 1000Pa, close to that of brain tissue, and due to the small pore size, alginate hydrogels surround and encapsulate the cell body similar to the in vivo extracellular matrix [9,11]. Cell viability in alginate is high, as indicated by flow cytometric analysis, and cultures are positive for neuronal markers MAP2 and β-Tubulin at four days post-harvest from the alginate (Figure 1).

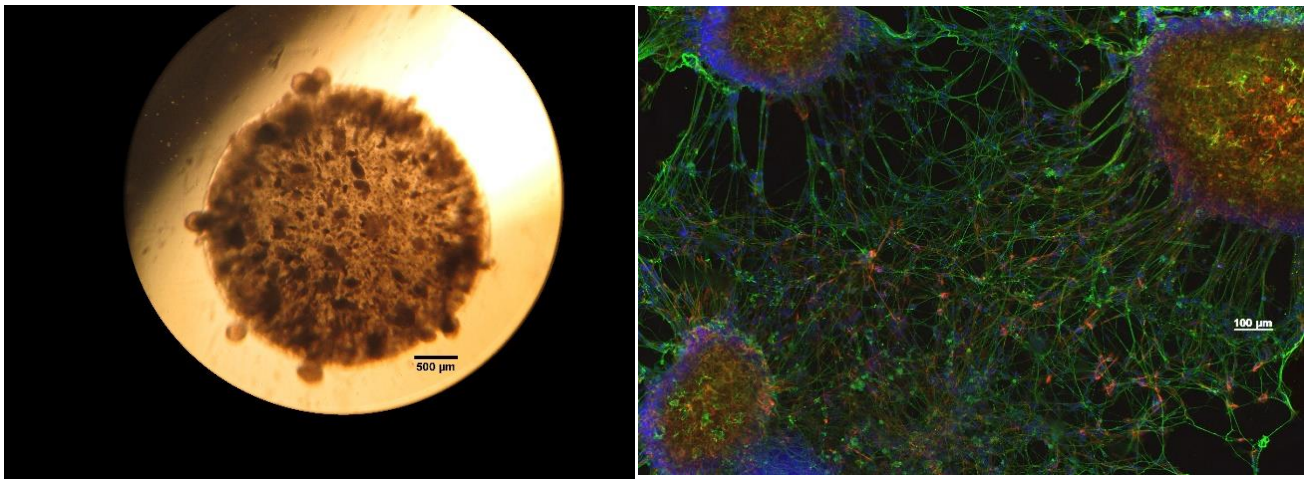

Figure 1. Representative images of alginate bead containing cell aggregates (left), and subsequent image of harvested aggregates replated onto laminin coated coverslips, div 10 (right).
Blue: DAPI, Red: Nestin, Green: MAP2 and β-Tubulin

Selection of salient stimuli by zebrafish midbrain networks

Miguel Fernandes[1], Marco Dal Maschio[1], Herwig Baier[1]

[1]Department Genes-Circuits-Behavior, Max Planck Institute of Neurobiology, 82152 Martinsried, Germany

The ability to selectively focus on a particular object ignoring other competing information is a crucial task for animals. By detecting the most salient feature from the visual environment, animals can efficiently respond to it.
In birds, "attention" is a dynamic process that seems to depend on interactions between deep tectal and isthmic populations of neurons in the midbrain. Previous studies pointed to the role of these populations for encoding stimulus saliency. It has been proposed that stimulus selection could be mediated by global inhibitory interactions. How this is accomplished and if it is relevant for behavior is not well understood.
Using transgenic approaches, we identified the corresponding midbrain neuronal populations in zebrafish and found that the circuit architecture is conserved, along with its molecular and functional properties. We imaged, with single-cell resolution, the responses from large ensembles of neurons in the deep tectum and isthmic circuits during presentation of competing visual stimuli. Presentation of a "competitor stimulus" leads to suppression of responses to the less salient stimulus within the receptive field. As for birds, we interpret this reduction of activity as a correlate of selective attention at the neuronal level.
To test if this phenomenon can be observed at the behavioral level, we established a behavior choice paradigm for zebrafish larvae. Fish are confronted with competing stimuli of different sizes that each trigger robust avoidance when presented alone. Preliminary results show that zebrafish quickly adapt their behavior to the relative saliency of stimuli and avoid the stronger stimulus, ignoring the weaker one.
We intend to use our transgenic tools to selectively manipulate the function of excitatory and inhibitory components of the midbrain networks. With this approach, we hope to identify fundamental mechanisms governing selective attention.

A novel co-adaptation mechanism reconciles growth cone adaptation and topographic mapping.

Felix Fiederling, Markus Weschenfelder, Martin Bastmeyer and Franco Weth

Karlsruhe Institute of Technology, Zoological Institute, Department of Cell- and Neurobiology, D-76131 Karlsruhe, Germany

The retinotectal projection is a major model to investigate the embryonic development of topographic axonal maps, defined by the preservation of neighborhood relationships upon projection. It is well established that counter-graded distributions of ephrin-As and EphAs along both, the retinal temporo-nasal and the tectal antero-posterior axes are involved in this process. A complex cross-talk of ephrin/Eph signals, involving fiber/target as well as fiber/fiber forward and reverse interactions guides the growth cones (GCs) to their targets. By combining computational simulation and in-vitro reconstitution, we have recently suggested a comprehensive model based on the global balancing of forward and reverse signaling to explain the major experimental findings in this system.

Topography formation strongly relies on the faithful reading of guidance cue concentrations by the GCs. Surprisingly, however, we found that retinal GCs can adapt to the respective signals. On tailored micro-structured growth substrates, GCs desensitize towards homogeneous ephrin-A5 forward as well as EphA3 reverse signals. Back on a neutral substrate, they quickly regain their sensitivity.

Updating our computational model to include adaptation, we propose strictly proportional co-variation of forward and reverse signaling sensor activities on the GC surface ("co-adaptation") to be the crucial mechanism reconciling adaptation and topographic mapping. The new model faithfully reproduces our in-vitro adaptation assays as well as accurate topographic mapping. Most importantly, however, we experimentally confirmed the counterintuitive co-adaptation hypothesis. We show that GCs desensitize towards ephrin-A5 forward signaling not only when exposed to homogeneous ephrin-A5 but also when migrating on EphA3 substrates and vice versa.

To address the molecular mechanisms of co-adaptation, we transfected axons with a SNAP-tagged ephrin-A5 construct and show a massive reduction of surface ephrin-A5 on GCs growing on either EphA3 or ephrin-A5 fields. As resensitization proves independent of protein synthesis, co-adaption might involve recycling endosomal compartments.

Modeling results suggest a critical role for (co-)adaptation in primary target innervation, possibly explaining how retinal axons can first enter the anterior tectum, a region of highly concentrated repulsive EphAs.

Mapping of inputs-outputs organization of areas 24a and 24b of the mouse anterior cingulate cortex

Clémentine Fillinger, Ipek Yalcin, Michel Barrot, Pierre Veinante
Institut des Neurosciences Cellulaires et Intégratives, CNRS UPR3212, Strasbourg, France

Depression is the most common mood disorder estimated to become the foremost contributor to the worldwide burden of disease by 2030. Because the morphofunctional substrate underlying depression is still not well understood, there is a need to investigate in greater detail the anatomical circuitry of depression. The anterior cingulate cortex (ACC) is known, in human and rodent, to play a major role in depression. The connectivity of the ACC, constituted by Brodmann's areas 25, 32, and 24 has been studied in primate and rat, but a complete mapping is still missing in the mouse. Thus, we analyzed areas 24a and 24b connectivity by injecting retrograde (Fluorogold, FG; beta-subunit of the choleric toxin, CTb) and anterograde (biotine dextran amine, BDA; leucoagglutinin of *Phaseolus Vulgaris*, PHA-L) tracers in the dorsal area 24b and ventral area 24a. These areas were found to be strongly interconnected with five groups of structures: (1) cortical areas, (2) thalamus, (3) subcortical forebrain, (4) hypothalamus and (5) brainstem. In addition to specific ACC intra-connections, main cortical reciprocal connections occurred with retrosplenial and orbital cortices, parietal associative and secondary visual areas. Among thalamic nuclei, the anteromedial and mediodorsal nuclei appeared strongly interconnected with areas 24a/24b. Midline and intralaminar nuclei, especially paracentral, reuniens and rhomboid nuclei were moderately labeled in both anterograde and retrograde studies. In subcortical forebrain, the claustrum, the cholinergic corticopetal system and the basolateral amygdala were found to be interconnected with ACC, but the striatum only receives inputs. In the hypothalamus (4), scant connections were found in lateral and posterior areas. Finally, the brainstem provided the most singular pattern of connections between afferents and efferents. Afferents to 24a/24b only came from monoaminergic centers but efferents also targeted the superior colliculus, PAG, laterodorsal tegmental nucleus, reticular areas, and extended to the spinal cord. Several differences in topography and/or labeling density were observed between 24a and 24b, especially in cortical, striatal and thalamic targets, as well as in midbrain and pontine projections. These results disclose the organization of ACC outputs in mice and emphasize its position at the center of a circuit relevant for pain and depression.

Lability and constancy of orientation tuning in the visual cortex depends on the functional architecture

Juan Daniel Flórez Weidinger[1,2] & *Fred Wolf*[1,2]
[1]*MPI for Dynamics and Self-Organization, Göttingen, Germany*
[2]*Bernstein Center for Computational Neurosciene, Göttingen, Germany*

A fundamental question in the function of cortical sensory systems is how information is represented by neuronal ensembles to be processed by higher cortical areas. In the primary visual cortex the spatial arrangements of tuning properties show fundamental interspecies differences. While in primates and carnivores neurons of similar orientation preference are clustered in iso-orientation domains, in rodents and lagomorphs they are spatially disordered. Little is known about the dynamic stability of these representations under livelong plasticity and how it depends on the underlying functional layout.
Here, we study mathematical models of circuit dynamics where the tuning parameters and the intra-cortical interactions of the network evolve dependent on the current architecture. Our previous work shows that columnar designs quantitatively matching the biological systems naturally emerge when orientation selective long range interactions are present, while disordered layouts are stabilized when local circuits are predominantly inhibitory [1]. When subject to temporally random perturbations we find that receptive field properties in disordered layouts exhibit a pronounced lability compared to maps. This difference is maintained even near pinwheel centers, where neurons with very different orientation preferences are in close proximity. We find that the drift of orientation preferences in disordered layouts is reduced when biologically relevant conditions are implemented in the tuning dynamics, such as orientation selective excitatory interactions [2], dynamical matching of binocular orientation preferences [3] and orientation tuned input from the LGN [4]. An examination of the energy landscape of the model in the different interaction regimes explains this quantitative difference. In disordered layouts because of the high number of distinct disordered solutions the energy barriers between them seem shallow, such that small perturbations can cause transitions to a different organization. Iso-orientation domains, in contrast, have higher energy barriers between solutions, such that a collective change in the tuning of many neurons is necessary to elicit a transition.
Taken together our study indicates that maps and disordered layouts differ in the lability of orientation representations and lays the basis for an experimental assessment of this difference.

References

[1] Flórez et al, Maps2014 Meeting

[2] Ko et al, Nature, **473**, 7345 (2011)

[3] Wang et al, Neuron, **65**, 2 (2010)

[4] Cruz-Martn et al, Nature, **507**, 7492 (2014)

Early cortical spontaneous activity displays the spatial structure of mature sensory evoked cortical responses

Bettina Hein[1,2], *Philipp Huelsdunk*[1], *Gordon B.Smith*[3], *David E. Whitney*[3], *David Fitzpatrick*[3] & *Matthias Kaschube*[1,2]

[1]*Frankfurt Institute for Advanced Studies & Goethe University, Frankfurt, Germany*

[2]*IMPRS for Neural Circuits, Frankfurt, Germany*

[3]*Max Planck Florida Institute for Neuroscience, Jupiter, Florida*

Numerous models of cortical map formation have attributed a critical role to activity dependent interactions within developing cortical circuits. It is plausible that correlated activity in the early cortex could establish the networks of spatially distributed yet functionally co-tuned neurons present in the mature cortex, but there is so far no experimental evidence supporting this hypothesis.
Here, we perform the first longitudinal study of correlation structures in ferret visual cortex across development, starting at an age when layer 2/3 cells are starting to receive feed-forward input and extending to a stage when circuits reach full maturity. By measuring the correlation structure of both spontaneous and stimulus-evoked cortical activity, we are able to relate correlations to tuning properties as they emerge across time. We show that spontaneous correlations are higher between locations which develop similar orientation preferences in the mature cortex and are lower for locations developing orthogonal tuning. Notably, this structure is already apparent in the highly immature cortex over 10 days prior to eye opening, and is not evident from stimulus-evokedcortical activity through closed-eyelids.
Together, these results suggest that early spontaneous activity is suitable to fulfill the instructive role proposed by models of cortical development.

Optogenetic induction of orientation behavior in the zebrafish tectum.

Thomas Helmbrecht[1,2], Marco Dal Maschio[1], Herwig Baier[1]

[1]Max Planck Institute of Neurobiology, Dept. Genes - Circuits - Behavior, 82152 Martinsried, Germany

[2]Graduate School of Systemic Neurosciences, LMU, Munich, Germany

Sensory information is integrated and converted into a pattern of activity in downstream premotor areas, in order to generate target-oriented behavior. While it is known that the optic tectum performs this sensorimotor transformation, the circuits driving it remain unclear. We tested the role of the optic tectum in orienting responses (e.g. tail movements) and investigated the underlying neuronal circuitry.

To explore the involvement of tectal cells in initiation of orientation swims, we combined two-photon calcium imaging with a behavioral assay. We imaged larval zebrafish at 5-6 dpf, when they start to show consistent visual behavior, and found tectal neurons with activity correlated to either the visual stimulus or to turning movements.

Next we asked if the neuronal activity in the tectum is sufficient to cause orientation initiation. Therefore, we used light-fiber stimulation to optogenetically map the tectum for different induced behaviors. Analysis of the simultaneously recorded tail movements revealed two main motor outcomes, approaches and escapes (small angle contraversive swims vs. large angle ipsiversive bouts). Results indicate that these two behaviors tend to be evoked by stimulating different parts of the tectum.

In order to determine the morphologies of tectal neurons governing the different behaviors, we used a single cell mosaic labeling technique. Taking advantage of a highly variegated GFP transgene (*BGUG*), single neurons can be labeled in the tectum. This is allowing us to classify e.g. the ipsilateral and contralateral tracts at single cell resolution. Screening for neurons localized in behaviorally different tectal zones will reveal distributions of projection neurons and their targets in the reticular formation.

Combining this information will eventually reveal the wiring diagram underlying different sensorimotor transformations.

Functional spatial maps of cerebellar granule cell inputs to Purkinje cells, Golgi cells and molecular layer interneurons in the cerebellar cortex

Antoine M Valera, Francesca Binda, Sophie A Pawlowski, Jean-Luc Dupont, Jean-François Casella, Jeffrey Rothstein, Bernard Poulain & Philippe Isope[1]
[1]*Institut des Neurosciences Cellulaires et Integratives CNRS UPR 3212, Strasbourg*

Despite its apparent uniformity, the mammalian cerebellar cortex is highly compartmentalized into distinct functional and anatomical modules. Mossy fiber and climbing fiber inputs carry sensorimotor information to the cerebellar cortex with a highly specific topographic organization. Climbing fiber inputs were delimited using zebrins, a family of biochemical markers confined to specific subsets of Purkinje cells, while mossy fiber inputs were identified using injection of AAV in the external cuneate nucleus or in the spinal cord. Recent studies suggest that cerebellar afferences and patterns of zebrin bands reflect a common organizational scheme within the cerebellum, suggesting a modular information processing. We postulate that this columnar information processing will lead to a specific regulation of functional synaptic organization. We focused on the spatial organization of granule cell inputs onto Purkinje cells, Golgi cells and molecular layer interneurons in the vermal region of the anterior cerebellum. We investigated how synapses onto these cell types are affected by the segregation of incoming information, using ZebrinII as a coordinate system, to localize accurately recorded and stimulated cells. Experiments were performed using transgenic mice expressing GFP under the control of the EAAT4 promoter, allowing for the vizualisation of ZebrinII bands during the experiment. Connectivity was studied combining whole-cell patch clamp recordings and RuBi-glutamate uncaging onto granule cells. Our results showed distinct inputs patterns for each cell types, suggesting a modular and cell-type dependent organization of the granular inputs in the cerebellar cortex. This topographical and modular organization is conserved between animals, and could be central in motor coordination.

Functional analysis of a genetically defined visual pathway

Yvonne Kölsch[1,2] and Herwig Baier[1]
[1] Department Genes - Circuits - Behavior, Max Planck Institute of Neurobiology, Martinsried, Germany
[2] Graduate School of Systemic Neurosciences, LMU, Munich, Germany

The visual system processes incoming information in multiple channels, each representing a specific feature of the visual scene. Retinal ganglion cells (RGCs), the output neurons of the eye, parcel these visual features and relay the information to the brain. In zebrafish, RGCs terminate in ten distinct neuropil areas called arborization fields (AFs). Each AF is innervated by a unique complement of RGC subtypes and hypothetically initiates a different behavioral output. However, what function individual RGC subtypes have and which parallel processing channels converge in an AF to control behavior is poorly understood.

We generated a BAC transgenic *slit1a:Gal4* line, which drives expression in a subset of RGCs. An intersectional genetic approach provides us with experimental access to specific RGC subtypes. By single RGC labeling, in conjunction with confocal *in vivo* imaging, we classified RGCs based on their morphology. *slit1a* is a marker for RGCs of six out of the fourteen distinct dendritic stratification patterns within the retina. A substantial fraction of *slit1a*$^+$ RGCs innervates the pretectal nucleus AF9. Restrained larvae expressing the calcium indicator GCamp6s are being used for 2P functional imaging of RGC axons during visual stimulation. We develop experimental strategies involving the presentation of a diverse range of visual stimuli to elucidate the tuning of *slit1a*$^+$ RGCs. Future studies will be aimed at the ablation of this genetically defined visual pathway for subsequent behavioral analysis.

A functional description of individual RGC subtypes is expected to provide detailed insights into how the visual system combines input from parallel processing channels to generate visually evoked behavior.

A theory for the three dimensional organization of orientation domains

Joscha Liedtke[1,2] & *Fred Wolf*[1,2]
[1]*MPI for Dynamics and Self-Organization, Göttingen, Germany*
[2]*Bernstein Center for Computational Neurosciene, G̈ttingen, Germany*

The neocortex is composed of 6 different layers. In the primary visual cortex (V1), the functional architecture of basic stimulus selectivity is experimentally found to be similar across these layers [1]. The organization in functional columns justifies the use of cortical models describing only two-dimensional layers and disregarding functional organization in the third dimension.
Here we show theoretically that already small deviations from an exact columnar organization can lead to non-trivial three-dimensional functional structures. Previously, two- dimensional orientation domains were modeled by Gaussian random fields allowing for an exact calculation of pinwheel densities [2]. Pinwheels are points surrounded by neurons preferring all possible orientations and these points generalize to pinwheel strings in three dimensions. We extend the previous two-dimensional model characterized by its typical scale of orientation domains to a three-dimensional model by keeping the typical scale in each layer and introducing a columnar correlation length. We dissect in detail the three-dimensional functional architecture for flat geometries and for curved gyri-like geometries with different columnar correlation lengths. The model is analyzed analytically complemented by numerical simulations to obtain solutions for its intrinsic statistical parameters. We find that (i) pinwheel strings are generally curved, (ii) for large curvatures closed loops and reconnecting pinwheel strings appear and (iii) for small columnar correlation lengths a novel transition to an rodent-like interspersed organization emerges.
This theory extends the work of [2] by adding a columnar dimension and supplements the work of [3] by a rigorous statistical treatment of the three-dimensional functional architecture of V1. Furthermore, the theory sheds light on the required precision of experimental techniques for probing the fine structure of the columnar organization in V1.

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Enhancing functional recovery after stroke: Identifying neuro-stimulation targets

Sol Lim[1] and *Marcus Kaiser*[1,2]
[1]*Interdisciplinary Computing and Complex BioSystems ResearchGroup (ICOS), School of Computing Science, Newcastle University, Newcastle upon Tyne, UK*
[2]*Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK*

Neuro-stimulation has been used in treatment of several brain diseases from the replacement of affected circuits to the re-training of remaining circuits using invasive and non-invasive stimulations [1]. Neuro-stimulation can benefit from brain network information to enhance functional recovery after stroke. Connectome-guided approaches have been used recently and demonstrated post-stroke connectivity changes and possible interventions [2]. The process where remaining brain regions can partially or fully take over functions of the lesioned brain areas is known as vicariation of function. A challenge is to find the regions that would facilitate functional compensation and whose reorganization after a stroke could be facilitated by brain stimulation. These regions might be some of the adjacent regions to the affected tissue but often it could be remote cortical regions within the same hemisphere or regions in the opposite hemisphere. Therefore, we need a more optimised search scheme to find better candidate regions for stimulation that would also assess distant areas which are involved over cortical fibre tracts or through subcortical reorganization. Here, we present a proof of concept study to find candidate brain regions or circuits for neuro-stimulation to restore the lost function after stroke. Possible candidates for functional recovery can be areas with similar incoming and outgoing connections. We evaluate how similar the connectivity of a potential target region is to the connectivity of the lesioned area by stroke. First, we use the matching index (or Jaccard coefficient) and non-metric multi-dimensional scaling (NMDS) to measure similarity of the connectivity between regions. Second, we look at the similarity of indirect neighbours. Third, we consider how close a candidate region is to the lesioned area in the hierarchical structure of the network. We hypothesize that the connectivity of the region involved in functional recovery will be similar to the stroke-affected area. We test our hypothesis using data from an animal study in which we could identify the location of the region that showed evidence of functionally compensation [3]. We show that our approach to find optimal target regions for neuro-stimulation using connectome information could be used to enhance the recovery of stroke patients.

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Modulation of visual evoked responses by low-intensity repetitive transcranial magnetic stimulation depends on visual system activity during stimulation

Makowiecki K.[1,2], Garrett A.[1,2], Harvey A. R.[1,3,4], and Rodger J.[1,2,4]
[1]Experimental and Regenerative Neuroscience, [2]School of Animal Biology, [3]School of Anatomy, Physiology and Human Biology, The University of Western Australia. [4]Western Australian Neuroscience Research Institute (WANRI)

Modulation of brain activity, for example by low-intensity repetitive transcranial stimulation (LI-rTMS) has promise for treating neurological and psychiatric disorders. However, clinical outcomes are highly variable, and though rTMS is thought to induce some form of neural plasticity, mechanisms are largely unknown. We previously showed that long-term LI-rTMS improved visual system topography in a mouse model of abnormal circuitry, and a single LI-rTMS session upregulated markers of neural activity. Though this suggests structural plasticity may arise via activity-dependent mechanisms, no studies have assessed the immediate effects of LI-rTMS on neuronal activity, or its interactions with concurrent evoked activity from sensory input. In this study, we recorded visual evoked potentials (VEPs) from anesthetised mice, before and after 10Hz LI-rTMS or sham to examine the interaction between endogenous and induced activity during LI-rTMS. We also explored the role of coordinated and random cortical activity by manipulating 1) synchrony in the cortical response: comparing wildtype to ephrin-A2A5$^{-/-}$ mice, which have disordered visual projections and 2) presence or absence of evoked responses: comparing LI-rTMS applied in the light or dark. Validating our model, before LI-rTMS, VEP response peak amplitudes were significantly smaller in ephrin-A2A5$^{-/-}$ mice than wildtypes, consistent with asynchronous responses from disordered projections. LI-rTMS with concurrent visual input significantly decreased peak to peak amplitudes compared to baseline in wildtypes, such that responses were similar to those of ephrin-A2A5$^{-/-}$ mice. However, LI-rTMS applied in the dark decreased amplitude similarly in sham and LI-rTMS groups, with no change in ephrin-A2A5$^{-/-}$ mice. This decrease was most pronounced in VEP peaks associated with GABAergic inhibition, suggesting LI-rTMS interacts with visually evoked responses and excitation-inhibition balance, which may be permissive for long-term plastic changes. This is the first evidence that degree of coordinated and random neural activity during stimulation affects LI-rTMS response, and has implications for clinical utility of LI-rTMS as an adjuvant therapy, such as in rehabilitation therapy following stroke.

Lipid rafts compartmentalize cAMP signals required for the refinement of retinal maps

Stefania Averaimo, Ahlem Assali, Sandrine Couvet, Yvrick Zagar, Ioana Genescu, Alexandra Rebsam and Xavier Nicol.

cAMP regulates a wide range of cellular processes and has a key role in neuronal development. It is critical for the modulation of axonal response to guidance molecules, including ephrin-As, that refine retinotopic maps. How cAMP can achieves specific signalling pathway activation in axonal growth cones is poorly understood. Recent studies suggested that the spatial compartmentalization of cAMP signals in subcellular microdomains is critical to exert specific responses. However, the identity of these compartments is still unknown. We hypothesized that cAMP signals generated and restricted to the plasma membrane microdomain lipid rafts are required for the development of retinal connections.
We used genetically encoded tools to monitor and manipulate cAMP signals restricted to subcellular microdomains, and evalutate the role of local cAMP for the guidance of retinal axons *in vitro* and the ephrin-A-dependent remodelling of neuronal connections in the early post-natal period *in vivo*. Our data provide evidence that lipid raft-restricted cAMP signals are essential during the development of precise neuronal connectivity. Local cAMP modulates ephrin-A5-induced axon retraction *in vitro*, and the elimination of misplaced axonal branches in the superior colliculus *in vivo*. Lipid rafts segregate cAMP signals in developing axons and provide specificity for axon response to guidance cues.

Early pheromone-experience modifies a functional circuit to influence pheromone-mediated behaviors of adult *C. elegans*

Leesun Ryu*, Myeongjin Hong*, Kyuhyung Kim

Department of Brain and Cognitive Sciences, DGIST, Daegu, Republic of Korea

*These authors contributed equally to this work

Connectomics, the description of neuronal circuits based on anatomically defined synapses, is an ongoing venture in neuroscience. The next intriguing question is how the connectome circuits function and generate context-dependent outputs. The nematode *C. elegans*, of which connectome has been fully constructed (White et al., 1986), provides an excellent system in which to investigate structural and functional basis of neural circuit mechanisms. *C. elegans* secretes pheromone mixtures, which affect development and behavior of worms. In the adult stage, pheromones elicit sexually dimorphic responses; hermaphrodites are repelled whereas males are attracted. Previously, we identified a novel avoidance circuit to pheromone; hermaphrodites exhibit acute avoidance to a distinct pheromone components (called C9) and this behavior is mediated by the nociceptive ADL neurons (Jang et al., 2012). Here we show that early C9 experience enhances C9 repulsion of adult hermaphrodites via the functional modification of the C9 avoidance circuit. Animals that have been exposed to C9 at a time right after birth (first larval stage), exhibit increased C9-specific repulsion at the adult stage, indicating that C9 experienced animals form a long lasting memory for C9. Since the memory for a specific C9 pheromone is acquired only at the critical developmental period, we define this learned C9 avoidance behavioral plasticity as imprinting (Lorenz, 1970). We next found that Ca^{2+} responses to C9 in the ADL sensory neurons are not altered in C9-imprinted animals, suggesting that C9 memory forms at the downstream circuit levels. To identify the genes and molecules required for this pheromone imprinting, we examined candidate genes and identified an *odr-2* Ly-6-related GPI-linked signaling gene. While *odr-2* mutants show normal C9 repulsion, the early C9 experience of *odr-2* mutants fails to leave a C9 imprint. Surprisingly, *odr-2* is expressed in the SMB sensory/inter/motor neurons and its expression is strongly increased in the SMB neurons of the C9-imprinted animals. The SMB neurons elicit Ca^{2+} responses to C9 in C9-imprinted but not naïve animals. These results indicate that the early C9 experience recruits a single neuron and/or its circuitry to the C9 avoidance circuit and thus shapes the sensitized backgrounds to C9 responses.

Differential requirement of presynaptic release for eye-specific and topographic retinal maps

Alexandra Rebsam[1], *Ahlem Assali*[1], *Mohamed Bennis*[2], *Pascal Kaeser*[3], *Thomas Südhof*[4], *Patricia Gaspar*[1]
1: Institut du Fer Moulin, INSERM, U839, Paris, France.
2: Cadi Ayyad University, Marrakesh, Morocco
3: Harvard Medical School, Boston, USA
4: Howard Hughes Medical Institute, Stanford university, USA

Projections of Retinal Ganglion Cells (RGCs) in their main targets, the dorsal Lateral Geniculate Nucleus (dLGN) and the Superior Colliculus (SC), are organized in eye-specific domains and with precise topography. Projections are initially intermingled and are refined into their final territories during the first postnatal weeks. Alteration of spontaneous neural activity in the retina disrupts both eye-specific segregation and retinotopy. However, the cellular mechanisms linking neural activity to map refinement remain poorly understood.
Here we examine the role of presynaptic release on the refinement of retinal projections. To distinguish between the synaptic and non-synaptic effects of activity blockade, we perturbed specifically the presynaptic release at retinal terminals by a conditional deletion of *Rim 1 *and* 2 *in RGCs. The removal of Rim proteins is known to strongly reduce calcium-dependent neurotransmitter release, without affecting spontaneous release. Our tracing studies indicated that Rim conditional double knock-out (Rim cDKO) mice have defects in eye-specific segregation in the dLGN but no major topographic defects in the SC. This result suggests that segregation but not gross topography involves calcium-dependent synaptic release. Interestingly, ipsilateral projections in the SC do not form patches and extend more laterally in Rim cDKO compared to control mice, suggesting that ipsilateral projections could be more sensitive to the perturbed presynaptic release. Our results show that retinal synaptic release is important for eye-specific segregation and for the organization of ipsilateral projections.

A new role for retinal ephrin-As in topographic map formation

Elise Savier, Martine Perraut, Frank Pfrieger & Michael Reber
Institute for Cellular & Integrative Neuroscience, CNRS UPR3212, Strasbourg, France.

Accurate processing of the sensory stimuli relies on neural maps present throughout the brain. The superficial layers of the superior colliculus (SC) in the midbrain receive projections from retinal ganglion cells (RGCs) and V1 cortex that are aligned and in register, forming a visuotopic map. The molecular mechanisms of visuotopic map alignment in the SC are unknown. We describe a new mouse model, the Isl2-ephrin-A3, wherein ephrin-A3 expression is specifically elevated in an alternating subset of RGCs, producing two mixed populations of cells with distinct levels of ephrin-As. We find that these populations form a single coherent map in the SC, demonstrating that retinal ephrin-A3 is not directly involved in retino-collicular mapping. Unexpectedly, V1 cortico-collicular projections are duplicated in Isl2-ephrin-A3 animals, leading to a visuotopic mismatch in the SC. This is further confirmed when in vivo inactivation of retinal ephrin-A3 restores a single wild-type cortico-collicular map. Our data strongly suggest that retinal ephrin-A3, carried to the SC by RGC axons, provides positional information for ingrowing cortical axons. This work identifies a new molecular mechanism supporting the retinal-matching model of visuotopic map formation and alignment in the midbrain.

Computer generated holography for optogenetic modulation of neural network activity *in-vitro*

Manuel Schottdorf[1,2,3], *Hecke Schrobsdorff*[1,3], *Walter Stühmer*[2,3], & *Fred Wolf*[1,3]
[1]*MPI for Dynamics and Self-Organization, Göttingen, Germany*
[2]*MPI for Experimental Medicine, Göttingen, Germany*
[3]*Bernstein Center for Computational Neurosciene, G̈ttingen, Germany*

Randomly plated primary cultures of neurons resemble to some extend *in-vivo* neural tissue in structural features, activity and development and have been used for various studies of learning, memory, plasticity, connectivity, and information processing. The activity of neurons in a culture can be measured with multi-electrode arrays. However, providing the cell culture with precise and spatially complex input patters is a standing challenge.

Here, we address this problem using holography. A laser and a spatial light modulator, assembled in the beam path of an inverted microscope, are used to generate holographic interference patterns in the object plane. These precise and spatially complex patterns excite a cell culture of optogenetically modified cortical neurons of a rat. The neural responses are monitored with a multielectrode array.

We present a performance assessment of our setup. We show that cultured neurons react well to external stimuli and we present some preliminary results on the modulations in network activity by the spatially complex optical excitation.

Orientation- and direction-selectivity in the superior colliculus are driven by Islet2^{+} and Islet2^{-} retinal ganglion cell inputs, respectively

Rachel B. Kay and Jason W. Triplett
Center for Neuroscience Research, Children's National Health System, Washington, DC USA

Perception of complex visual scenes requires precise connectivity between specific subtypes of neurons as visual information is propagated through the brain. Retinal ganglion cells (RGCs) convey all visual information to the brain and have diverse receptive fields (RFs), two of which are center-surround and direction-selective RGCs (DSGCs). A major target of retinal output is the superior colliculus (SC), where neurons have RFs distinct from those of RGCs, including orientation-selective (OS) cells. To elucidate the wiring mechanisms utilized to establish distinct RFs in the SC, we recorded visual responses in the SC of *Islet2-EphA3* knock-in mice (Isl2$^{EphA3/EphA3}$). We previously demonstrated that distinct subtypes of RGCs project to two independent subdomains of the SC in these mice. Specifically, Isl2^{+} RGCs, which are predominantly non-DSGCs, terminate in the anterior half of the SC, while Isl2^{-} RGCs terminate posteriorly. In the Isl2$^{EphA3/EphA3}$ SC, we were able to identify functional cell types with receptive field properties similar to those found in wild type SC, including, On-, Off-, On-Off, DS and OS. However, the distribution of cell types found in the anterior and posterior SC of Isl2$^{EphA3/EphA3}$ mice was dramatically altered compared to control. Strikingly, we found no DS neurons in the anterior SC of Isl2$^{EphA3/EphA3}$ mice, suggesting that direction-selectivity in the SC is conveyed primarily by Isl2^{-}, DSGC inputs. In addition, we found substantially more OS cells in the anterior SC (45.2% of visually-responsive cells) than in the posterior SC (11.2%), suggesting that orientation-selectivity in the SC is constructed primarily from Isl2^{+}, non-DSGC inputs. Taken together, these data elucidate a novel understanding of the wiring strategies utilized in the SC.