Spontaneous Activity in Brain Development (SPONT2018)
Leiden, Amsterdam, Oct. 8th-10th

BROCHURE

SPONT 2018

Spontaneous Activity in Brain Development

8th-10th October 2018 / Museum Volkenkunde, Leiden, The Netherlands

Neurowetenschappen Amsterdam Rotterdam

The Company of Biologists

Organizers:

Guillermina López-Bendito
Institute of Neuroscience, Alicante, ES

Christian Lohmann
Netherlands Institute for Neuroscience, Amsterdam, NL

Programme of the Meeting

The **programme** of the meeting is also available for download on the www.spont2018.org

Neurowetenschappen Amsterdam Rotterdam

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PROGRAM

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Monday, October 8th

13:00-14:15 Arrival & Registration

14:15-14:30 Welcome address

Session 1 Modeling spontaneous activity

Chairperson: Heiko Luhmann, Institute of Physiology, Mainz, Germany

14:30-15:05 1 Julijana Gjorgjieva, *Activity-dependent organization in developing cortical networks*

15:05-15:40 2 Stephen Eglen, *Theoretical models of spontaneous activity driving map formation*

15:40-16:10 Coffee Break

Session 2: Visual system I

Chairperson: Patrick Kanold, Univ. of Maryland, Maryland, USA

16:10-16:45 3 Marla Feller, *Light prior to eye-opening promotes retinal waves*

16:45-17:20 4 Christian Lohmann, *Spontaneous activity in the developing visual cortex: from networks to synapses*

17:20-17:40 # Short Talk 1: Corette J. Wierenga, *Endocannabinoid signaling controls local dendritic coordination between excitatory and inhibitory synapses*

17:40-18:00 # Short Talk 2: Emre Yaksi, *Developmental changes in the architecture, the function and the connectivity of habenular networks*

19:00 Invited Speakers' Dinner

Tuesday, October 9th

Session 3 Olfactory and Auditory Systems

Chairperson: Rosa Cossart, INMED, Marseille, France

09:00-09:35 5 Dwight Bergles, *Homeostatic control of spontaneous activity in the developing auditory system*

09:35-10:10 6 Takeshi Imai, *Formation of discrete olfactory circuits by spontaneous activity*

10:10-10:30 # Short Talk 3: Martijn C. Sierksma, *Development of multi-innervation of principal cells of the rat medial nucleus of the trapezoid body*

10:30-11:00 Coffee Break

Session 4: Large-scale activity patterns

Chairperson: Julijana Gjorgjieva, Max Planck Institute for Brain Research, Frankfurt, Germany

11:00-11:35 7 Rustem Khazipov, *Early patterns of activity in the developing brain*

11:35-12:10 8 Matthias Kaschube, *Distributed network interactions and their emergence in developing neocortex.*

12:10-12:30 # Short Talk 4: Mattia Chini, *Field potential amplitude predicts anesthesia depth in neonatal mice and humans*

12:30-12:50 # Short Talk 5: Michael C. Ashby, *Interactions between spontaneous and evoked pan-cortical activity in the neonatal brain*

13:00-14:15 Lunch

Session 5: Somatosensory system

Chairperson: Michael Crair, Yale University School of Medicine, New Haven, USA

14:15-14:50 9 Guillermina López-Bendito, *Patterned spontaneous activity in the prenatal thalamus instruct cortical map formation*

14:50-15:25 10 Takuji Iwasato, *In vivo imaging of barrel cortex circuit refinement in neonates*

15:25-16:00 11 Heiko Luhmann, *(De)Constructing the neonatal cerebral cortex with spontaneous activity*

16:00-16:20 # Short Talk 6: Nobuhiko Yamamoto, *Patterned neuronal firing regulates promoter activity of brain-derived neurotrophic factor (BDNF) in individual cortical neurons*

16:20-18:15 Poster Session + Coffee

18:15-19:00 Plenary Session: Future directions for the field and the meeting!

19:15 Dinner

Wednesday, October 10th

Session 6: Visual system II

Chairperson: Marla Feller, Univ. California Berkley, Berkley, USA

09:00-09:35 12 David Feldheim, *Sensory mapping in the mouse Superior Colliculus*

09:35-10:10 13 Kenichi Ohki, *Gap junctions control synaptic density and maturation of cortical functions*

10:10-10:45 14 Michael Crair, *Spontaneous activity across development and spatial scales*

10:45-11:15 Coffee Break

Session 7: Subplate, Hippocampus, Neocortex

Chairperson: Kenichi Ohki, University of Tokyo, Japan

11:15-11:50 15 Patrick Kanold, *Early cortical circuits and early sensory experience.*

11:50-12:25 16 Rosa Cossart, *Hidden GABAergic assemblies in the developing mouse barrel cortex in vivo*

12:25-13:00 17 Matthew Colonnese, *Conservation and transformation in the development of spontaneous activity*

13:00-13:20 # Short Talk 7: Knut Kirmse, *Hippocampal network dynamics in the conditional absence of NKCC1*

13:20 Concluding Remarks

13:30-14:30 Light Lunch & Departure

ABSTRACTS

Spontaneous Activity in Brain Development

8th-10th October 2018 / Museum Volkenkunde, Leiden, The Netherlands

1 - Interactions between spontaneous and evoked pan-cortical activity in the neonatal brain

Michael C. Ashby & Christine M. Cross

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The interaction between internally-generated spontaneous neural activity and that evoked by sensory experience is thought to be crucial for maturation of the cerebral cortex. However, the characteristics of the interplay between evoked and spontaneous activity across early life brain development are not well defined. To assess the spatiotemporal dynamics of spontaneous and evoked activity, we have used macroscopic fluorescence imaging to measure neuronal calcium elevations across the entire cortical surface of the awake neonatal mouse. Characterisation of these pan-cortical activity patterns highlighted clear differences between spontaneous and sensory-driven activity. To directly investigate how sensory drive might influence spontaneous activity, we manipulated sensory experience by delivering various stimuli and by disrupting sensory receptors acutely and chronically. Over short time scales, sensory stimulation dramatically suppressed spontaneous activity. This suppression persisted for several seconds after the end of the sensory stimulus within related cortical areas and in apparently unrelated parts of the cortex, suggesting cross-modal interactions. Over longer timescales, chronic disruption of sensory experience, by whisker trimming, had effects at the local level within the barrel cortex, but did not appear to alter coordination between larger somato-motor networks. Further investigations will aim to target the mechanisms by which spontaneous and evoked activity interact, and how this interaction shapes neonatal behaviour and maturation of cortical function.

2 - Hippocampal network dynamics in the conditional absence of NKCC1

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NKCC1 is known to be the primary transporter mediating chloride uptake in immature principal neurons, but its role for network dynamics in the developing brain remains controversial. To address this question, we generated mice lacking NKCC1 in the vast majority of forebrain glutamatergic cells. Using a combination of electrophysiological and optical approaches *in vitro* and *in vivo*, we demonstrate that NKCC1-dependent GABAergic depolarization promotes spontaneous network activity during early postnatal development in a model-, event type- and region-specific manner. Unexpectedly, long-term effects of a chronic absence of NKCC1 on synaptic development, network dynamics and performance in hippocampus-dependent tasks are subtle or absent. Our data provide first evidence for a neural network function of NKCC1 *in vivo* and, at the same time, challenge the idea that NKCC1 expression by cortical principal neurons is indispensable for major aspects of hippocampal development.

3 - Endocannabinoid signaling controls local dendritic coordination between excitatory and inhibitory synapses

Hai Yin Hu*[1], Dennis L. H. Kruijssen*[1], Balázs Rózsa[2], Casper C. Hoogenraad[1], Corette J. Wierenga[1]
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Dendritic inhibitory synapses are most efficient in modulating excitatory inputs localized on the same dendrite, but it is unknown if their location is random or regulated. Here we show that formation of inhibitory synapses is directed by local synaptic activity. We stimulated dendritic spines close to a GABAergic axon crossing by pairing two-photon glutamate uncaging with postsynaptic depolarization in CA1 pyramidal cells. We found that repeated spine stimulation promoted growth of a new GABAergic bouton onto the same dendrite. NMDA receptor activation was required, but not sufficient, to induce inhibitory bouton growth. The dendritic feedback signal was mediated by CB1 receptors and we could induce inhibitory bouton growth by local, brief applications of the endocannabinoid 2-AG. Together, our findings reveal a dendritic signaling mechanism to trigger growth of inhibitory boutons at dendritic locations with strong excitatory synaptic activity, which may serve to ensure inhibitory control over clustered excitatory inputs.

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4 - Developmental changes in the architecture, the function and the connectivity of habenular networks

Stephanie Fore, Mehmey Ilyas Cosaca., Carmen Diaz, Maximillian Hoffman, Caghan Kizil, Emre Yaksi
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Abstract: The habenula is a midbrain nucleus that is involved in modulating behaviors ranging from associative learning to social interactions. Many of such complex behaviors develop with age. For example, juvenile zebrafish display increased social interactions and perform better during associative learning tasks, compared to larvae. The maturation of neural circuits, including habenula, could underlie an increase in cognitive capacity and the development of such complex behaviors. Previously, we have shown that the habenula exhibits spontaneously generated ongoing activity that is spatially structured into functional subdomains, which are specifically driven by the activity of sensory and limbic brain regions. These results indicated that ongoing habenular activity could potentially influence the processing of sensory stimuli depending on the animals' internal behavioral state. It is however less clear how these neural computations and ongoing habenular activity are altered across development, as animals gradually expand their behavioral repertoire.

To investigate the function of the developing habenula we used a combination of molecular and functional imaging tools. We observed that as the habenula grows in size, neurons are integrated with a spatial order and new inhibitory connections are formed. Moreover, while the habenular sensory responses are already present at early developmental stages, the nature of the habenular ongoing activity changes drastically as zebrafish develop. Our results highlight the increased spatial structure, faster temporal kinetics and robustness of ongoing habenular activity in the juvenile stages. We propose that this functional refinement underlies the transition of developing zebrafish larvae into a mature animal with an expanded cognitive capacity.

5 - Patterned neuronal firing regulates promoter activity of brain-derived neurotrophic factor (BDNF) in individual cortical neurons

Yumi Miyasaka and Nobuhiko Yamamoto*
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During development, neuronal activity is known to remodel cortical circuits. Our previous study has demonstrated that netrin-4 and BDNF are expressed in cortical cells in an activity-dependent manner and promote thalamocortical axon branching. However, what physiological activity efficiently alters gene expression in various cortical cells remains unknown. To address this issue, we performed live imaging of BDNF promoter activity, which is well characterized, in individual cortical cells by applying various patterned stimulation.
For this, cortical slice cultures were prepared from perinatal mouse brain. To visualize the promoter activity, a luciferase (luc) vector containing a BDNF exon4 promoter was transfected sparsely into upper layer neurons together with a DsRed2 vector, which was used for morphological analysis. The luc signal was observed by an EMCCD camera every 30 minutes for up to 24 hr. First, the promoter activity of cortical cells was examined by depolarizing them with KCl treatment. The luc signal in each transfected cell started to increase within a few hours after KCl addition and reached a plateau after around 10 hr, although the plateau level varied among cells (ranging from 1- to 13-fold changes). Conversely, treatment with tetrodotoxin or glutamate receptor blockers which suppress spontaneous activity reduced the luc signal in most cortical cells. Next, the firing patterns that effectively induce the promoter activity were studied using optogenetic stimulation. For this, cortical cells were transfected with a channelrodopsin-2 (ChR2) vector by in utero electroporation prior to culturing. After confirming that ChR2-positive axons surrounded the luc transfected cells, photostimulation with various frequency was applied to the culture. As a result, high frequency stimulation (2-10 Hz) significantly increased the luc signal in a fraction of upper layer cells. The signal began to increase within a few hours, peaked around 6 to 8 hr after the photostimulation, and then gradually decreased. In contrast, low frequency stimulation did not change the luc signals. Thus, the luc activity was increased in synaptically activated cortical cells in responding to high frequency stimulation.
The present live imaging of the luc signal demonstrated temporal patterns of BDNF promoter activity of cortical cells at a single cell level. The results suggest that BDNF expression is modulated depending on the pattern of neuronal activity and is regulated differentially according to cell types.

6 - Mother-pup interactions and oxytocin during early brain development

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Spontaneous network activity occurs before birth and during early postnatal brain development. This type of activity regulates the establishment of synaptic connections and subcellular compartments in order to prepare the brain before it can fully experience the environment. Though the senses of vision and hearing and most motor abilities become functional around the second postnatal week in rodents, tactile and odor cues are already perceived at birth, playing a significant role during mother-pup interactions in the nest. Moreover, natural occurring differences in maternal care behaviors such as licking and grooming affect adult brain functions. How brain development is affected by this type of early social experience has not yet been investigated. Associated with adult social behaviours and already expressed during prenatal development, the neuropeptide oxytocin (OT) and OT receptors (OTR), are good candidates to mediate the effects of mother-pup interactions on brain development. Thus, here we aim to address the role of OT on spontaneous neuronal activity of primary visual cortex (V1). As shown by *in vivo* 2-photon calcium imaging recordings in layer II/III of V1, OT decreases the frequency of spontaneous calcium network events. *In vitro*, OT increases the frequency of inhibitory postsynaptic currents (IPSCs) without affecting excitatory postsynaptic currents (EPSCs). This OT-mediated increase in inhibition is concomitant with an increase in the excitability of somatostatin interneurons upon OTR activation. Moreover, by performing large-field calcium imaging recordings we observed that OT-mediated inhibition is selective to V1, without affecting somatosensory cortex (S1). Consistently with this observation, OT has a balanced effect in S1, increasing the frequency of both IPSCs and EPSCs, therefore leading to a zero net effect of OT on synaptic activity. Finally, we used primi- and multiparous mouse mothers as a model to study the effect of differential maternal interactions on the electrophysiological properties of the neonatal mouse brain. *In vitro* patch-clamp recordings show that pups raised by a primiparous mother exhibited a higher firing rate when comparing with pups raised by multiparous mothers.

Together, our results reveal that OT exerts specific cellular and network effects in the developing V1, changing the inhibitory-excitatory balance towards inhibition. Moreover, these results give evidence for a role of maternal interactions on postnatal brain development

7 - GABAergic interneurons excite hippocampal, but inhibit cortical, activity in neonatal mice.

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The developing iso-cortex and hippocampus spontaneously generate unique age- and region-dependent activities, the underlying circuit mechanisms of which have not been fully characterized.
Here we investigated the role of GABAergic interneurons in cortical and hippocampal network activity using chemogenetics and *in vivo* electrophysiology. hM3D(Gq) for enhancement and KORD for suppression, were expressed in the majority of GABAergic neurons by locally injecting Cre-dependent AAVs into the visual cortex or hippocampus of GAD2-Cre mice at postnatal day (P) 0-1. This approach allows us to bi-directionally manipulate activity of GABAergic neurons in un-anesthetized mice as early as P3, while simultaneously monitoring the effects of manipulation on LFP and neuronal firings using multi-electrode recordings.
In the hippocampus, on P3 suppressing GABAergic neuronal activity decreased multi-unit firing rates in the pyramidal cell layer of CA1 and reduced the amplitude of early sharp waves. Enhancing GABAergic neuronal activity had the opposite effects. However, in the second postnatal week, such 'excitatory' GABAergic action was not observed, and suppression of GABAergic interneurons increased firing rates in the pyramidal cell layer, suggesting the acquisition of mature inhibitory action of GABAergic interneurons.
By contrast, in the visual cortex, on P3 suppressing GABAergic interneuron activity increased cortical multi-unit firing rates without substantially altering the amplitude or frequency of LFP oscillations. Enhancing GABAergic neuronal activity had the opposite effects and decreased cortical firings at all ages examined. Thus, in visual cortex GABAergic interneurons exert inhibitory actions as early as P3, and its main role during early development is likely to control the activity level rather than pattern early oscillations.
Our preliminary results suggest that GABAergic neurons have diverse, age- and region-specific roles in modulating excitability and network oscillations in the developing cortex and hippocampus.

8 - The Netrin receptor Unc5c controls the formation of the retino-retinal connection

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The existence of a retino–retinal (R-R) connection has been reported in different vertebrates but its function remains unknown. Here, we demonstrate that, in mice, a subpopulation of retinal ganglion cells (RGCs) located in a region of the retina that is positive for the guidance receptor Unc5c, project to the opposite retina. Loss of Unc5c function prevents retinal axons of entering the opposite optic nerve and conversely, ectopic expression of this receptor forces retinal axons to join the contralateral nerve. In addition, the expression pattern of Netrin1, the ligand for Unc5c, at the optic chiasm region, pinpointed Unc5c/Netrin1 repulsive signaling as a candidate mechanism to guide R-R axons to the other retina. In line with these observations, visual axons that traverse the Netrin1 positive area, such as those projecting ipsilaterally to the brain, do not express Unc5c and, in fact, the transcription factor Zic2, which specifies the ipsilateral pathway, represses Unc5c expression. We have also generated a mathematical model that predicts the requirement of a R-R connection for the proper layout of binocularly coordinated retinotopic maps in species with a substantial dependency of axonal remodeling during circuit assembly, but not in species where retinal axons experience direct targeting into the correct terminal zone. According to this model, we found a correlation between the expression of Unc5c in the developing retina, the magnitude of the R-R projection and the extent of axonal refinement at the visual targets, in multiple species.

9 - Structured patterns of embryonic activity from thalamic neurons governs the emergence of functional cortical maps

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In the mammalian brain, cortical sensory areas are organized as a topographical array of discrete, but interacting, functional modules. This implies that for a given cortical neuron, sensory tuning to certain stimulus properties can be predicted by its location. The retinotopic, somatotopic and tonotopic maps of primary visual, somatosensory and auditory areas are classical examples of this type of organization. In mice, the best characterized example of such maps is the posteromedial barrel subfield of the primary somatosensory cortex, in which each facial principal whisker is represented by a particular domain in the layer 4, the barrel. Extensive research regarding the postnatal ontogeny of such functional maps, including the barrel cortex, has demonstrated that thalamocortical projections, the main source of peripheral input to the cortex, impose this particular arrangement. However, and despite accumulated evidence on the existence of thalamocortical interactions at prenatal stages, little is known with respect to their role in the formation of cortical sensory maps. Here, we show that the somatosensory cortex shows modularity and functional topography already at prenatal stages. Moreover, we demonstrate that altering the intrinsic activity of the embryonic thalamus promotes a large increase in the gain of cortical circuits before birth that is maintained postnatally. As a consequence, functional and structural cortical maps are lost in the adult brain. Our findings therefore demonstrate the existence of a spatially organized functional map that is present embryonically, is sculpted by specific patterns of thalamic spontaneous activity, and that determines the correct assembly of cortical circuits for sensory processing.

10 - Development of multi-innervation of principal cells of the rat medial nucleus of the trapezoid body

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The formation of synapses is a critical step in the development of the brain. The calyx of Held-synapse is among the best studied central synapses due to its exceptional size. This synapse develops from a conventional bouton comparable to many other axonal endings, and in a few days the terminal rapidly expands over the soma of a principal neuron in the medial nucleus of the trapezoid body, resulting in a one calyx-one soma innervation. Anecdotal evidence suggests that multiple calyces on a soma form in this period, indicating a form of competition. Here, we use an in vivo approach to record the spontaneous activity and describe the functional changes that coincide with the expansion of the calyx of Held. We used a stimulation electrode to identify different inputs by their size, activation threshold and delay. At early developmental stages, bursts of spontaneous activity were relayed by many synaptic inputs of the principal cell. Prespikes, a hallmark of a giant terminal, were observed only for the strongest input per cell and allowed us in three principal cells to distinguish two strong inputs by their association with a prespike. In the first postnatal week the strongest input increased in strength, while the second strongest input did not change in strength between cells. To relate these functional changes to synaptic structures, we immunolabeled recorded cells for active zone protein Piccolo and vesicular glutamate transporters. The strength of the strongest input *in vivo* correlated with the size of the somatic terminals. Prespike-associated inputs were only recorded from cells with a large terminal. For the converse, two exceptions were found of principal cells with a large somatic terminal, but no input with a prespike. We therefore conclude that the formation of multiple giant terminals on a single principal neuron is rare. Our results suggest a model where one axon rapidly grows and becomes the calyx of Held while at earlier stages the activity of multiple inputs ensures that the postsynaptic neuron fires during bursts of presynaptic activity.

11 - Light prior to eye-opening promotes retinal waves and eye-specific segregation

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Retinal waves are bursts of correlated activity that occur only during development and provide a critical source of activity that drives the refinement of retinofugal projections prior to eye-opening. Retinal waves are thought to be initiated spontaneously with their spatiotemporal features dictated by immature neural circuits. Here we demonstrate that, during the second postnatal week in mice, changes in light intensity reliably trigger retinal waves via activation of conventional photoreceptors. Propagation properties of triggered waves are indistinguishable from spontaneous waves, indicating that they are activating the same retinal circuits. Using whole brain imaging techniques, we demonstrate that light deprivation prior to eye-opening diminishes eye-specific segregation of the retinal projections to thalamus but not other retinal targets. These data indicate that structured light that passes through the closed eyelids plays a critical role in the development of the image-forming visual system.

12 - Coordinated activity in the developing entorhinal-hippocampal network

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The correlated activity in entorhinal-hippocampal neuronal networks, supported by oscillatory and intermittent population activity patterns, is critically involved in learning and memory. However, when and how the correlated activity in entorhinal cortex and hippocampus emerges during development remains largely unknown. We found, that during the first postnatal week in rats, the activity in superficial layers of medial entorhinal cortex (MEC) and hippocampus was highly correlated with intermittent population bursts in MEC followed by early sharp waves (eSPWs) in hippocampus. Neurons in the superficial MEC layers fired before hippocampal neurons in the dentate gyrus, CA3 and CA1. The current source density profile of eSPWs indicated that perforant and temporoammonic entorhinal inputs, and intrinsic hippocampal connections are co-activated during the entorhinal-hippocampal activity bursts. Finally, a majority of the entorhinal-hippocampal activity bursts were triggered by spontaneous myoclonic body movements that are characteristic of the neonatal period. Thus, during neonatal period, the activity in entorhinal cortex and hippocampus is highly synchronized with the entorhinal cortex leading hippocampal activation.

13 - Two distinct spontaneous activity patterns guide different aspects of network refinement in the developing visual cortex

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Spontaneous activity is commonly encountered in different sensory systems during brain development and is known to contain important cues for the establishment of appropriate network connectivity and functional maps. Multiple studies have shown that from early development until the onset of sensory experience spontaneous activity progressively sparsifies, and the trend is observed in different sensory areas. In the visual system, patterned spontaneous activity is first generated in the retina and propagates to downstream areas including the visual cortex. Calcium imaging recordings in the mouse primary visual cortex in vivo before eye opening have revealed two distinct patterns of spontaneous activity (Siegel et al. 2012): (1) low-synchronicity events with small amplitude largely originating in the retina, and (2) high-synchronicity events with large amplitude involving almost all recorded neurons largely originating in the cortex. Combining theory and modeling, we sought to understand how these two distinct activity patterns jointly shape network connectivity between the sensory periphery and the cortex under different plasticity rules. We found that low-synchronicity events shaped the emergence of cortical input selectivity and topographic organization of connectivity. In contrast, high-synchronicity events normalized synaptic weights ensuring continued sensitivity of the cortical network to peripheral inputs. However, we found that the robustness of receptive field formation was sensitive to the properties of learning rules. We then examined a scenario where the amplitude of a cortical cell during high-synchronicity events is adaptive to its own recent activity. This adaptive mechanism resulted in (1) much more stable and refined receptive fields, and (2) a progressive sparsification of cortical activity as the developmental stage was changed in the simulation. We conclude that a combination of two patterns of spontaneous activity during development can improve receptive fields and promote network refinement without relying on changes in the learning rule. Furthermore, as the network refines during development, the patterns of spontaneous activity change accordingly, in agreement with the time course of changes in spontaneous activity patterns measured in the visual cortex (Rochefort et al. 2009).

14 - Cochlear purinergic receptors contribute to *in vivo* spontaneous activity in the developing auditory system

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Spontaneous electrical activity is a prevalent feature of the developing nervous system, which has been shown to influence the maturation and survival of neurons, as well as refinement of circuits in the brain. In the auditory system, bursts of activity are initiated in the cochlea when ATP is released by inner supporting cells (ISCs) within Kölliker's organ (greater epithelial ridge). This periodic release of ATP induces inward currents, crenations (cell shrinkage), and calcium waves in ISCs, ultimately leading to depolarization of inner hair cells (IHCs). Subsequent release of glutamate and activation of spiral ganglion neurons transmits these bursts into the central nervous system, where it propagates through developing auditory centers. While key components of this signaling pathway have been explored, the receptors that mediate the effects of ATP remain undefined, limiting our ability to define functional consequences of this activity. Our studies indicate that activation of purinergic autoreceptors on ISCs is a critical initial step in the cascade of events that lead to efflux of potassium into the extracellular space and depolarization of IHCs. Using whole cell patch clamp and DIC imaging, we found that spontaneous currents and crenations of ISCs were inhibited by chelation of intracellular calcium or by inhibition of phospholipase C, suggesting that metabotropic, Gq-coupled receptors are required. ISC activity was abolished by the P2ry1 antagonist MRS2500 and dramatically reduced in P2ry1$^{-/-}$ mice. Moreover, confocal imaging of cochleae from mice expressing GCaMP3 revealed that spontaneous calcium waves in Kölliker's organ were eliminated by MRS2500, indicating that P2ry1 is responsible for initiating spontaneous activity in ISCs. Loose patch recordings from SGNs in cochlear whole mounts from P2ry1$^{-/-}$ mice or in the presence of MRS2500 revealed a marked reduction in SGN burst firing. Additionally, *in vivo* administration of MRS2500 dramatically reduced cochlear-driven neuronal calcium transients in the auditory midbrain of mice expressing the genetically encoded calcium indicator GCaMP6s, indicate that P2ry1 is responsible for triggering bursts of activity in ISCs and adjacent hair cells prior to hearing onset. Unexpectedly, inhibition of P2ry1 with MRS2500 eventually led to tonic firing of SGNs, and spontaneous, non-burst firing of SGNs was enhanced in P2ry1$^{-/-}$ mice, suggesting that P2ry1 also suppresses IHC excitability. Together, these results indicate that P2ry1-dependent signaling is a key regulator of IHC excitation in the cochlea, responsible for both triggering bursts of action potentials and limiting tonic firing.

15 - Field potential amplitude predicts anesthesia depth in neonatal mice and humans

Mattia Chini[1], Sabine Gretenkord[1], Johanna K. Kostka[1], Jastyn A. Pöpplau[1], Laura Cornelissen[2,3], Charles B. Berde[2,3], Ileana L. Hanganu-Opatz[1] & Sebastian H. Bitzenhofer[1]

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Monitoring anesthesia depth during surgeries is critical to prevent intraoperative awareness and reduce adverse side effects. In adults, these monitors are based upon recordings of brain activity that complement measures of autonomic functions and behavioral responses. However, when it comes to neonates, the correlation between brain activity and anesthesia depth is still unclear. Here, we characterize the effects of different anesthetics on brain activity in different cortical areas of neonatal mice and identify electrophysiological features predicting anesthesia depth. We show that similar features can predict anesthesia depth from electroencephalographic recordings in human neonates. Hence, we propose that brain activity measurements combined with online-analysis may improve monitoring of anesthesia depth also in human newborns.

16 - Late stage spontaneous waves and their role in downstream visual areas in vivo

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In the developing mammalian visual system, neighboring retinal ganglion cells (RGCs) fire in correlated bursts of action potentials that are observed as propagating waves across the retina. These spontaneous waves of activity, which in mice begin around the time of birth and last until eye opening, are thought to be crucial for normal formation of visual system circuitry. The features of retinal waves have been described in detail in a number of species *in vitro*, but little is known about their properties in the epoch just prior to eye opening ('Stage III' or P9-P13 in mice) *in vivo*. Using optical imaging techniques with genetically encoded Ca^{2+} indicators, we report here on experiments examining the spatiotemporal and pharmacological properties of Stage III retinal waves in RGCs, the superior colliculus, lateral geniculate nucleus and visual cortex in mice *in vivo*. In comparison to Stage II waves, Stage III waves are smaller, faster, of shorter duration, which is simultaneously observed in their downstream targets. We also describe the results of novel dual wavelength and fluorophore (RCaMP, GCaMP) experiments to simultaneously image presynaptic axons and postsynaptic neuronal activity. Both Stage II and Stage III waves show faithful transfer to postsynaptic targets in the SC, however Stage III wave transfer is less predictable, likely due to increased post-synaptic activity at older ages. Our data also suggest that Stage III retinal waves propagate in a wave like fashion in both the colliculus and thalamic afferents, but cortical activity is less tightly correlated to retinal activity in Stage III waves than during Stage II. We also examined the effects of pharmacological manipulations in the eye on the propagation of retinal waves to the superior colliculus and higher order visual circuits. These results demonstrate that Stage III waves have unique properties and trans-synaptic propagation compared to earlier (Stage II) spontaneous activity, which may be essential in the patterning of circuits throughout the visual system *in vivo*.

17 - Modulation of hyperpolarization-activated ion channels by long-term potentiation of local synaptic inputs

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Neurons in the brain receive thousands of synaptic inputs. Integration of synaptic signals in dendrites is regulated by local enrichment of voltage-gated ion channels in the membrane, affecting the summation of excitatory synaptic signals in a nonlinear manner. In particular, activation of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels causes a depolarizing inward current (I_h) which dampens the summation of excitatory synaptic signals. Here, we explore how HCN channel localization influences local dendritic integration with whole-cell patch clamp recordings and two-photon microscopy. We injected hyperpolarizing currents (-100 to -600 pA) and quantified the effect of I_h on membrane potential changes in CA1 pyramidal neurons in organotypic hippocampal slice cultures of mice. We found that stronger hyperpolarizing current injections caused activation of more HCN channels, increasing the voltage sag and rebound voltage, indicating that HCN channels opened during the hyperpolarization and closed right after. Blockade of HCN channels with ZD7288 (10 µM) resulted in larger hyperpolarization of the membrane potential and diminished the characteristic voltage sag. Next, we modulated the expression of HCN channels by long-term potentiation (LTP) of local synaptic inputs. LTP was induced by extracellular stimulation of CA3 axonal bundles with theta burst stimulation (TBS; 50x 5 pulses at 100 Hz, repeated each 200 ms). Before and after TBS, hyperpolarizing current injections were applied to measure HCN channel activation. Cells were filled with Alexa Fluor 568 (via the patch pipette) to visualize dendrites with two-photon imaging and determine the distance between dendrites and stimulation electrode. We are currently examining the regulation of HCN channels after LTP induction of distal and proximal synaptic inputs.

18 - Dendritic plasticity rules in spontaneously active cortical neurons

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Although recent advances in calcium imaging provide a detailed picture of the spatial and functional organization of synapses on individual regions of the dendritic tree ([1]), it is largelyunknown how these structures arise during development. In this study we investigate activitydependent mechanisms that induce the formation of functional clusters during postnatal development. In particular, we focus on a mechanism involving the conversion of proBDNF to mature BDNF (brain derived neurotrophic factor), each respectively governing synaptic potentiation via the TrkB pathway and depression via the p75NTR pathway ([2],[3]). We model a dynamical system of interactions involving pre- and postsynaptic activity, BDNF, proBDNF and the protease MMP9 (matrix metallopeptidase 9) that cleaves proBDNF into BDNF. Interestingly, we demonstrate that this mechanism effectively implements a form of Hebbian plasticity by relating it to a burst-timing-dependent plasticity rule which describes synaptic potentiation and depression identified in developing retinogeniculate synapses ([4]). This biophysical model is capable of unifying several experimental findings within one framework and makes several novel predictions, including a potential link to spike-timingdependent plasticity in adult animals.To perform mathematical analysis and large-scale simulations, we reduced the biophysical model to a minimal model that expresses the burst-timing-dependent plasticity rule on dendritic synapses. In this model we investigate the emergence of cooperation and competition among synaptic inputs depending on the correlation between them. We demonstrate the emergence of functionally specialized clusters of synaptic inputs in early development consistent with experimental literature. Furthermore we are able to interpolate qualitatively between functional clustering in the ferret and the mouse visual cortex by manipulating a single parameter in our model.

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19 - Excitatory/inhibitory balance and somatostatin cell signaling control specificity of spontaneous activity

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Spontaneous activity patterns can be described in terms of frequency, synchronicity, amplitude, the number of cells participating and other characteristics (Ackman and Crair, 2014; Kerschensteiner, 2013). A growing body of work has shown that merely the presence of activity is not sufficient for refinement. Instead, specific characteristics encode and transmit essential information required by the brain to develop normally (Kirkby et al., 2013; Leighton and Lohmann, 2016). For instance, if retinal waves are too large, retinotopic map refinement is prevented, whereas eye-specific segregation can be impaired by changes in event frequency (Burbridge et al., 2014; Xu et al., 2011).

Patterns of activity in the visual cortex occur during the second postnatal week which are driven by retinal waves (Ackman et al., 2012) and reduced upon enucleation (Hanganu et al., 2006; Siegel et al., 2012). We refer to these cortical events as low participation events ('L-events') as they activate relatively few neurons in the field of view. Their retinal origin, combined with their relative sparsity, gives them the potential to shape the network according to the properties of the eye. During the same period, events can be seen which are not affected by retinal manipulations. These high- participation events ('H-events') are highly synchronized in time and drive a calcium response in almost all cells in the field of view. This activity pattern may allow them to perform synaptic homeostasis, bringing synaptic strengths back to a workable range.

Here, we find that the characteristics of spontaneous activity are controlled by the balance of excitation and inhibition during the second postnatal week. During L-events, excitation is tightly matched by inhibition, restraining response amplitude and participation. Moreover, characteristics can be specifically controlled by interneuron subtypes, as somatostatin cells were found to govern the density of activation and the lateral spread of events without affecting other features.

20 - Manipulating cellular chloride levels in order to understand sensory deficits in autism

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Deviant sensory reactivity constitutes a problem for many autism spectrum disorder (ASD) patients. Studies in various ASD rodent models suggest that dysfunctional sensory processing may follow disrupted activity-dependent fine-tuning of synaptic connections in the thalamocortical system. It is unclear yet whether alterations in early activity and connectivity, along with disturbances in sensory processing in the adult, can result from a delayed GABA shift, a phenomenon that has been described in multiple ASD models.

GABA is the main inhibitory neurotransmitter in the brain and GABA release induces chloride-mediated current in postsynaptic neurons. During postnatal development, GABA currents shift from depolarizing to hyperpolarizing, reflecting a developmental shift in intracellular chloride concentrations due to increased expression of chloride exporter KCC2 and reduced expression of chloride importer NKCC1. In many ASD rodent models this GABA shift is delayed due to aberrant expression of chloride transporters and this developmental delay may be an important factor in sensory processing defects. Indeed, promising results of clinical trials with NKCC1 inhibitor bumetanide in ASD patients suggest that correcting a delayed GABA shift constitutes a relevant therapeutic target.

The aim of this study is to assess the effects of delayed GABA shift on synaptic connectivity. As a first step, the potential to manipulate the GABA shift will be assessed in organotypic hippocampal slices using perforated patch clamp to measure chloride reversal potentials in CA1 pyramidal cells and employing lentivirus-mediated gene transfer for overexpression of NKCC1 or pharmacological inhibition of KCC2. Ultimately, we want to use a similar strategy in vivo and test the effects of a delayed of GABA shift on synaptic transmission, network activity and sensory processing and behavior.

21 - Activity changes following monocular deprivation in model networks of visual cortical circuits

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The development of neural circuits involves a manifold of interacting mechanisms activated during multiple stages. After eye-opening, the development of visual circuits is governed by the interaction between plasticity mechanisms and sensory experience. An experimental paradigm to investigate the action of these mechanisms is monocular deprivation (MD), a perturbation that yields profound changes in synaptic connections and response properties of cells in primary visual cortex (V1). Ex-perimental studies uncovered that this plasticity involves changes in intracortical inhibition and in thalamocortical inputs to excitatory and inhibitory cells [3]. We investigate the e_ects of these changes on the activity in local circuit models of V1 which include multiple subtypes of inhibitory nterneurons. We _rst study the e_ects in a sparse random network of excitatory and inhibitory neurons, where inhibitory cells resemble the largest class of interneurons, parvalbumin-positive cells [1]. In this network we _nd that the regime in which the circuit operates determines how the activity is shaped by MD-induced plasticity. In a rate model of the dynamics, we show analytically how this di_erence of responses connects to the \paradoxical e_ect" described in recurrent circuits stabilized by inhibition [2]. Experiments from multiple cortical areas showed that inhibitory interneurons come in a variety of classes and that these shape cortical dynamics in profound ways [4]. To study how it inuences the response to MD-induced plasticity, we extended our model to include a second type of interneurons, somatostatin-positive cells, a second prominent class of interneurons [1] and _nd that this profoundly a_ects activity following MD-induced synaptic changes. Speci_cally, su_cient inhibitory feedback from somatostatin-positive cells can reverse the response of parvalbumin-positive interneurons to plasticity in either intracortical or thalamocortical synapses. These results show that the operating regime of circuits and the multiplicity of interneuron subtypes in cerebral cortex have far-reaching e_ects on how networks respond to the same changes in synaptic connections, with implications for how we interpret experimental results on the activity and plasticity in developing sensory circuits. By investigating the dynamical consequences of circuit changes in di_erent model networks, we might also identify promising targets for future experimental investigation.

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22 - Understanding the mechanisms involved in the migration and circuit integration of GABAergic thalamic interneurons

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Interneurons (INs) are inhibitory GABAergic cells necessary for the maintenance of the stability between excitation and inhibition in the brain. These inhibitory cells are broadly dispersed through the cortex. However, their thalamic distribution varies among species. In rodents, INs are mainly found in the dorsal latero geniculate (dLG) nucleus. Although it has been extensively investigated how cortical INs migrate to populate the cortex, it is still not well known how thalamic INs get into the dLG. In addition, it has been suggested that IN migration into the dLG and its integration depends on retinal activity. In this project we aim to investigate the molecular mechanisms directing IN migration and integration into the dLG, and how these inhibitory cells would be affecting V1 development. We have seen that there are differences in the number of dLG INs in sensory deprived models compared to the controls. These results suggest that thalamic spontaneous activity, and not the retinal waves, might be mediating IN integration into the visual thalamic nucleus.

23 - The contribution of spontaneous thalamic activity to the emergence of cortical sensory maps

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Spontaneous neural activity during development plays a part in establishing thalamocortical circuitry in sensory areas before sensory onset. It is thought that the cortical activity recorded perinatally strengthens synaptic connections that will define sensory maps and function. Although early cortical spontaneous activity and its transition to a mature firing pattern have been well characterized, the thalamic activity profile and its influence on thalamocortical connectivity, function and early plasticity remains largely unknown. Here, we show preliminary results regarding the spontaneous spiking activity of thalamic nuclei from mice aged from P2 to P14 in control and sensory deprived conditions. Spontaneous activity profile becomes more mature during the first postnatal days and, interestingly, our model of cross-modal plasticity induced by depriving the brain from visual information provokes alterations in the thalamic firing by P2. However, we could not appreciate anomalies in thalamocortical connectivity in deprived mice. Thus, our results show that embryonic sensory deprivation induces changes in the thalamic spiking activity that could be recorded during the first days of postnatal development.

24 - The role of network interactions in refining neural response properties in visual cortex.

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Already early in development, the visual cortex produces highly structured, spatially extended patterns of spontaneous activity with pronounced correlations between distant cortical locations. The role of these distributed network interactions in development is currently unclear. Here we ask whether such early network interactions could coordinate the refinement of stimulus response properties across visual cortex. Specifically, we hypothesize that neurons that at early stages in development exhibit strong spontaneous correlations, but are tuned for different stimuli could shift their tuning over time such that it becomes more similar over the course of cortical maturation. To test this hypothesis, we study the development of orientation preference in the visual cortex using chronic imaging and computational modelling.

To assess the emergence and refinement of orientation selectivity and its relationship to spontaneous activity during early development, we use longitudinal wide-field fluorescence imaging of GCaMP6s to record visually evoked responses with moving grating stimuli and spontaneous activity in the developing ferret primary visual cortex. Prior to P30, the natural time of eye-opening, the eye lids are transiently opened when probing the cortex with grating stimuli.
Typically, weak orientation tuning in a layout coarsely resembling its mature organization is evident in the immature cortex a few days prior to the natural time of eye-opening. However, we also observe considerable refinement in orientation tuning over the following week.

To explore whether network correlations evident in early cortical spontaneous activity could predict the observed refinement in orientation tuning, we formulate a phenomenological model. In this model, pairwise, positively correlated neurons are predicted to become more similar in orientation tuning over time; conversely, negatively correlated pairs become more dissimilar. Using this model, the spontaneous correlations together with the layout of orientation preference measured at an early stage in development allows us to correctly predict aspects of the refinement of orientation tuning over subsequent days. Moreover, with age, interactions between more remote network elements become more effective in predicting tuning changes, suggesting a link to long-range horizontal connections known to develop extensively over the temporal period considered here. Notably, we also observe a refinement of spontaneous network correlations over time and an extended version of our model predicts aspects of this process as well, indicating that neurons develop stronger correlations in their spontaneous activity over time if they share similar tuning properties at an early stage in development. Thus, even as network correlations seem to shape tuning properties, we predict that tuning properties in return influence network correlations.
We conclude that visual response properties and long-range network interactions show a considerable degree of coordinated and interdependent refinement in the developing visual cortex. These refinements improve the degree of specificity by which local functional properties are linked through distributed network interactions and potentially reflect a co-development towards a common layout for orientation tuning and correlated network structure.

25 - Organised spontaneous neuronal activity in the premature human brain

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Introduction

The developing animal brain is characterized by bursts of spontaneous neuronal activity which are thought to originate in the subplate and are critical for cortical maturation. Within these bursts, fast frequency activity synchronises local networks while slow activity synchronises global networks. Spontaneous activity is also seen in human preterm infants. Fast spindles (10-20 Hz) riding on a slow delta wave (<2 Hz) are present on EEG recordings, and their persistence or absence is related to brain injury and poor outcome. The aim of this study was to identify spontaneous delta brush activity with EEG and assess scalp distribution at different frequencies.

Methods

We recorded 18-channel EEG in 18 pre-term infants median 35+6 weeks+days corrected gestational age (range 32+6 to 36+6 weeks+days). We identified delta brushes and calculated their power spectral density between DC-40Hz. We then plotted the scalp distribution (topography) at different frequencies.

Results and conclusion

Delta brushes occurred with different coarse topographies. The most common were recorded in the right and left posterior-temporal region. Peaks in the power spectral density of these unilateral delta brushes were evident at DC-2Hz (slow delta) and 10-20Hz (alpha-beta). The topography of the slow delta activity spread bilaterally, while the topography of the alpha-beta activity was unilateral. This suggests that slow activity is associated with large scale networks, while fast activity with more local networks.

26 - Forebrain-specific loss of I (h) in pre-weaning period results in neurodevelopmental disorders in mice

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The hyperpolarization-activated current I(h) has been suggested to contribute to developmentdependent network activity and maturation of the CNS, and is known to be associated with neurodevelopmental disorders, such as early infantile epileptic encephalopathies or autism spectrum disorder. Yet, due to limitations of knockout mouse models that target only specific subunits of the HCN1-4 channel family and do not allow for the temporal regulation of I(h) loss, studies aimed at investigating I(h) during brain development are sparse. Here, we present an approach that is designed to functionally and conditionally ablate I(h), independent of subunit composition, by controlling the expression of a dominant-negative HCN subunit (HCN-DN) with the Tet-off doxycycline system and CaMKII-alpha promoter in forebrain projection neurons. We show that lifelong I(h) deficiency is associated with delayed somatomotor development in neonatal mutants and psychomotor disturbances,including behavioral hyperactivity and stereotypies in adult mutants. Although the loss of I(h) caused neuronal hyperexcitability, no signs of epileptic seizures were detected in electrocorticogram and local field potential recordings from neonatal and adult networks. Instead, LFPs recorded from immature hippocampal and cortical networks in HCN-DN-expressing mice showed signs of reduced excitability and lasting changes in adult hippocampal population activity patterns. Notably, restricting I(h) loss to an early postnatal period, i.e., to the first three weeks of life, did not prevent behavioral hyperactivity, indicating developmental changes that are not reversible by simple re-introduction of the HCN-channel function later in life. In addition, the locomotor hyperactivity could not be ameliorated by the administration of methylphenidate, which is commonly used to treat attention-deficit hyperactivity disorder. Instead, I(h)- deficient mutants responded to antipsychotics, suggesting that developmental loss of I(h) in forebrain projection neurons caused persistent changes in cortico-basal ganglia circuits and dopaminergic signaling.

27 - Single Neuron Dynamics in Developing Cortical Networks *in Vitro*

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Despite the versatile applications offered by their lasting nature, extracellular recordings are consistently hampered by a major drawback: the proper association of the signal to specific neurons. *In vitro* planar multi-electrode arrays (MEAs) allow the simultaneous non-invasive electrophysiological recordings of hundreds of neurons over many days. Spike sorting methods are routinely used to assign the action potential waveforms to discrete units. However, only few spiking (active) neurons in the proximity of the electrodes are reliably considered, whereas sparsely or non-firing (silent) neurons are neglected. Furthermore, linking the computed units to actual biological neurons remains a challenge. Combining *in vitro* MEA recordings with high resolution imaging instead enables a clear close-up of single neuron dynamics within complex neural networks.
Here we present a dissociated cortical neuronal model that has been genetically modified to express GCAMP6s, a green fluorescent calcium indicator, and a red fluorescent nuclear marker, nls-dTomato. By culturing the transgenic neurons on MEAs endowed with transparent tracks, we are able to optically identify single cells located in the electrode area and at the same time record spontaneous activity. Additionally, we can derive action potentials from the observed calcium transients and distinguish active from silent cells. In this way, single neuron activity can be accurately traced back by matching the calcium traces with the corresponding electrical signal. Performing longitudinal measurements during the second week *in vitro*, we monitor cell fate of single neurons and investigate the relevance of specific electrical activity patterns for neuronal integration and participation in early network development.

Additional Info

Spontaneous Activity in Brain Development

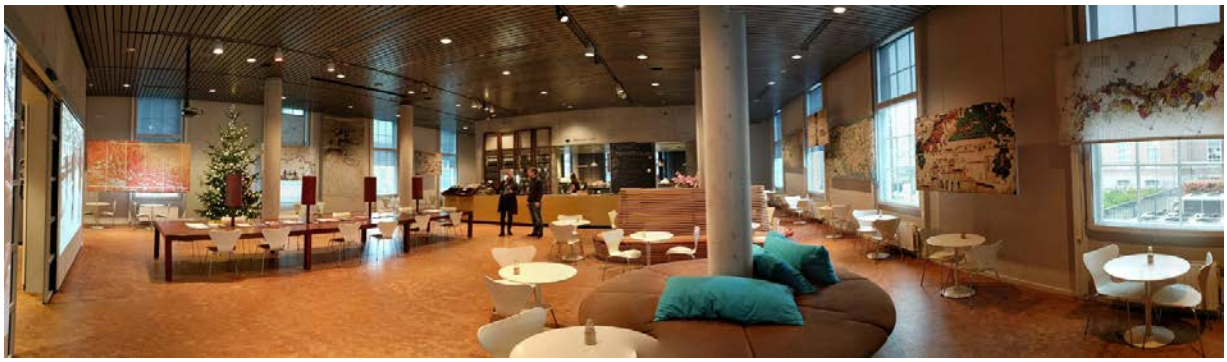
SPONT 2018

Museum Volkenkunde, Leiden, The Netherlands

Venue

Conference meeting will take place in the stunning location of **Museum Volkenkunde** (Leiden, Amsterdam) https://www.volkenkunde.nl/en

Leiden is about 40 km to the south of Amsterdam. You can reach Leiden from the Amsterdam Schiphol Airport by train in about 15 minutes (trains leave every 10 minutes) and from Amsterdam central station in 37 minutes (four times per hour). From Leiden Centraal (central station) you can walk to the venue, **Museum Volkenkunde** in 5 minutes.



Coffee/lunch area

Accommodation

HOTEL For speakers

Boutique Hotel d'Oude Morsch Park de Put 1 2312 BM Leiden

This hotel is within 5-minute walking distance from the Volkenkunde Museum, and located in a historical building (old barrack) next to the old city entrance 'Mors gate'.


HOTEL

IBIS Leiden Centre

Stationsplein 240-242

2312 AR Leiden

This hotel is a simple and good, direct in front of the station. The view is not a romantic one, but the location is perfect. When you walk out the back of the hotel, you can cross the water and you are at Volkenkundig Museum.

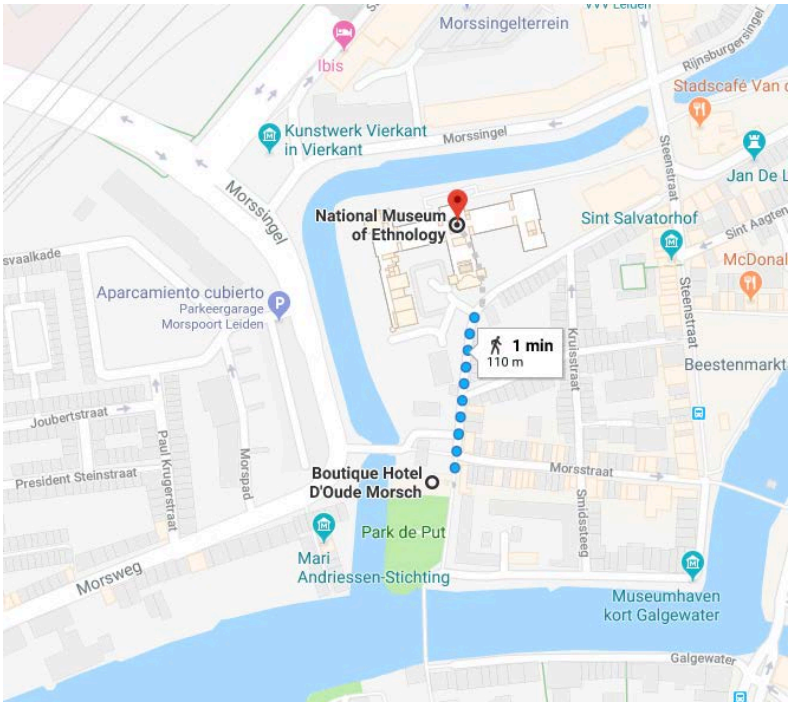
The rooms can be used as singles or doubles

Single € 109.00 breakfast included, plus € 2,50city tax per night

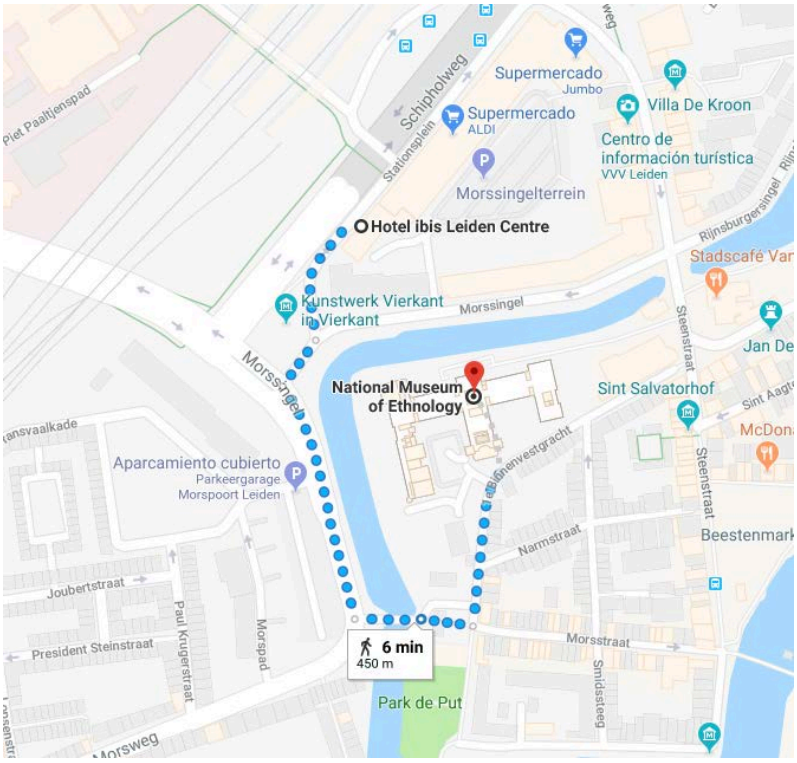
Double € 119.00 breakfast included, plus € 2,50city taks per person per night


Road map, from Hotels to venue:

Boutique Hotel d'Oude Morsch to Venue (Museum Volkenkunde)



IBIS Hotel to Venue (Museum Volkenkunde)



Speakers and posters presenters

Speakers:
Speakers (invited lecturers and presenters of short talks)
Talks are scheduled for 30 minutes + 5 minutes discussion. Short talks are schedule for 15 minutes + 5 minutes discussion. You can present from your notebook or bring your presentation as PowerPoint file. There will be a projector with HDMI cable. If you bring your own computer, please do not forget to bring power adaptors, if you come from outside continental Europe, and/or monitor connectors (e.g. Mac, VGA).

Poster presenters:
All accepted participants who submitted an abstract are invited to have a poster presentation during the meeting.
There will be a poster board available for your poster throughout the meeting. Poster boards are in landscape format and have the dimensions 125 x 100 cm. A dedicated poster session is scheduled for Tuesday 16:20-18:15, but posters can be presented any time during breaks.

Meals during the conference

The registration fee includes: Registration to the meeting, lunches, coffee breaks and a gala dinner on Tuesday 9th at **Stadscafé Van der Werff** (https://www.stadscafevanderwerff.nl)**.** We will have a speaker's dinner schedule for Monday 8th at **Restaurant Het Prentenkabinet** (http://www.prentenkabinet.nl).

Various

The international dialing code to The Netherlands is **31.**

The **wifi** network in the museum is: *volkenkundepubliek*
Password: *bezoeker*

To contact about the meeting, please email spont2018@gmail.com