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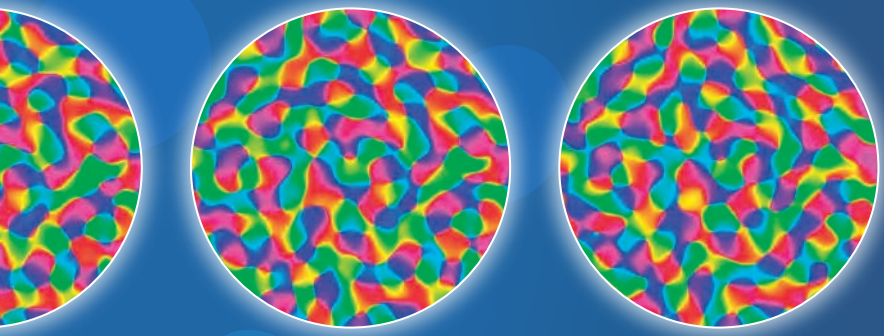

07

Decoding of Hand Movement Directions from Human MEG-Signals

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Abstract Several tasks can be used to drive Brain-Machine-Interfaces (BMI). The usability of center-out movements and corresponding brain activity is analyzed in this study. Subjects were instructed to move a joystick from a center position towards one out of four targets using hand and wrist only. Brain activity was recorded by whole-head Magnetoencephalography (MEG) and investigated in time and frequency domain; time-resolved decoding power (DP, probability to decode correct direction) was calculated on single-trial basis by regularized linear discriminant analysis; and DP was compared to those obtained from other recording techniques. We found significant power variation between rest and movement for sensors located above motor areas in three frequency bands: an increase for $\leq$7Hz and 62-87Hz, a decrease for 10-30Hz. Using MEG activity $\leq$3Hz exclusively of motor area sensors (bilateral), on average significant DP was obtained as early as 100 ms before movement onset and increased to 67% around 400 ms after movement onset. Considered in a direct comparison, MEG allows higher DP than Electroencephalography but less than invasive recording techniques. Our results show that the direction of hand movements can be inferred from non-invasive MEG signals and suggest that movement related brain activity may be used directly to drive non-invasive BMIs.

Altered hippocampal structure reduces synaptic activation of reeler mossy cells

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Abstract The dentate gyrus serves as gateway to the hippocampus and receives feedback excitation from hilar mossy cells. Mossy cells serve as integrators of polysynaptic input from perforant path via granule cells and interneurons, thus playing an important role in balancing the excitability of the dentate gyrus. The reeler mouse, a developmental mutant with dramatic morphological alterations, is expected to show altered network behaviour, and may display an increased propensity for epileptic activity. In order to investigate changes in network function in these mutants, we performed simultaneous whole-cell patch-clamp recordings from mossy cells and extracellular recordings from granule cells during paired-pulse stimulation to characterize the synaptic response to perforant path stimulation. In the mossy cells, we found a stereotypic response comprising short-latency inhibition and longer-latency excitation following the extracellular population spike in slices from wild-type animals. In response to paired pulses, strong potentiation was observed on the second pulse resulting in the regular generation of action potentials. Corresponding to the morphological alterations, reeler mossy cells exhibited short-latency excitation preceding the extracellular population spike. However, both intracellular and extracellular excitatory responses were reduced compared to that in the wild-type. Interestingly, bath-application of bicuculline, a blocker of GABA-A receptor-mediated inhibition, unmasked strong polysynaptic excitation. In conclusion, we did not find an evidence for an enhanced propensity for epilepsy. In contrary, our results suggest that the balance of excitation and inhibition is shifted towards inhibition in mossy cells and the dentate circuit of the reeler mouse. (Supported by the DFG: SFB 505 and TR-3)

Predicting Spontaneous Activity and Modeling Input-Output Relations in Neuronal Networks

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Abstract Spatial resolution of the recordings from neuronal tissues is so far not sufficient to reconstruct the anatomical connectivity and to relate it to activity. Models of functional connectivity, however, can be estimated with machine learning methods and can be used as predictors of the activity dynamics. In this work, we present several machine learning algorithms to estimate functional connectivity models, which predict ongoing activity dynamics and input-output relations of neuronal networks. We present experimental results, which include both simulated cortical random neuronal networks and cultures of cortical slices. Our results indicate that an online gradient descent algorithm can predict the spontaneous spike activity from spike history. We also employ Echo State Networks (ESN) to model input-output relations. In our experiments, Echo State Networks generated a rich dynamics in response to the input sequences, which we also used to stimulate random cortical neuronal networks. Receiver Operating Characteristic curve analysis and cross correlations showed that ESNs are capable of modeling the response of a cortical circuit to random spike trains.

A model for correlation detection based on Ca2+ concentration in spines

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Abstract Understanding the mechanisms of correlation detection between pre- and postsynaptic activity at a synapse is crucial for the theory of Hebbian learning and development of cortical networks. The calcium concentration in spines was experimentally shown to be a correlation sensitive signal constrained to the spine: A supralinear influx of calcium into spines occurred when presynaptic stimulation preceded a backpropagating action potential within a short time window. Its magnitude depended on the relative timing $t_{\mathsf{post}} - t_{\mathsf{pre}}$. There is strong evidence that NMDA receptors are responsible for the supralinear effect. Previous simulation studies related the occurrence of spike time dependent plasticity to this calcium signal. However, these simulations mainly focused on pairs and triplets of pre- and postsynaptic spikes, rather than on irregular activity. Here, we investigate the properties of a biologically motivated model for correlation detection based on the calcium influx through NMDA receptors under realistic conditions of irregular spike trains containing a fraction of events correlated in time. We find that a simple thresholding mechanism acts as a sensitive correlation detector, that works robustly at physiological firing rates. We identify the regime (rate, correlation coefficient, detection time) in which this mechanism can assess the correlation between pre- and postsynaptic activity. Furthermore, we show that correlation controlled synapse pruning acts as a homeostasis mechanism and that cooperation between synapses leads to a connectivity structure that manifests spatial correlations in the input. The detector model allows for a computationally effective implementation usable in large scale network simulations. On the single synapse level most of the results can be obtained analytically.

Functional Optimization for Reliable Transmission in Neocortical Networks

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Abstract The neocortex of higher mammals has a remarkable ability to precisely reproduce behavioral sequences or to retrieve stored information. These abilities are contrasted by measurements of spiking activity in behaving animals, which show a considerable trial-to trial variability and temporal irregularity. This discrepancy has lead to different and even conflicting hypothesis about possible coding schemes which may be employed by the neocortex. A crucial point in this debate is the question where in the complex cortical network variability emerges: if communication between and signal integration within the elements of the neocortical network is unreliable or imprecise, coding schemes that rely on spike timing would be difficult to implement. In the present study, we assessed the precision and reliability of neocortical networks experimentally on a millisecond time-scale. Employing photo-uncaging of glutamate in acute slices, we activated neocortical cells and their synaptic connections in a spatiotemporally precisely controlled manner, while monitoring the resulting sub-threshold membrane potential fluctuations of post-synaptic cells. This approach allowed us to estimate a lower bound for the precision and reliability of neocortical network function. To determine the contribution to the observed variability by different components of the neuronal signal propagation chain, we performed numerical simulations which included or excluded the experimentally measured variability of these various components. We found that signal integration in neocortical pyramidal cells is highly reliable and precise, while the residual variability is most likely due to variability in synaptic transmission. Our data indicate that variability in neocortical activity does not reflect an inherent noisiness of its components but must be attributed to other network properties.

Multi-channel correlations and high frequency components in EEG recordings from kindling and kainate models of temporal lobe epilepsy

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Abstract Multi-channel correlations and high frequency components in EEG recordings from rat kindling and kainate models of temporal lobe epilepsy.

We assessed multi-channel correlations and high frequency (HF, 100-500 Hz) content in EEG recordings from two animal models of temporal lobe epilepsy, hippocampal kindling and intra-hippocampal kainate injection. We found that in the kindling model, HF discharges (ripples, 100-400 Hz) developed over subsequent days and were not limited to the kindling site, but also extended to the contralateral hippocampus with high correlation. In contrast, the HF discharges of the kainate model (fast ripples, 400-500 Hz) occurred only in the lesioned hippocampus. During the afterdischarge (AD) of the kindling model, a behavioral seizure (Racine 5) was observed after 18-25 days of stimulation in all rats. The HF power was always high before and during the initial phase of the seizure, but similar ripples were present in the AD many days before seizures appeared (seizures occurred during the primary AD in most cases). The correlation between all pairs of channels increased during the AD from the first kindling day onwards. We did not find a clear difference when behavioral seizures first appeared. During the AD, sudden inversions of the sign of the correlation occurred between pairs of contacts placed in the right hippocampus as well as between pairs placed in both hippocampii. Overall, our data support a key role of HF discharges and enhanced correlations during the epileptogenic process in both, the kindling and kainate models of temporal lobe epilepsy.

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Testing for higher-order correlations in massively parallel spike trains

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Abstract The cell assembly hypothesis [1] postulates dynamically interacting groups of neurons as building blocks of cortical information processing. Synchronized spiking across large neuronal groups was later suggested as a potential signature for active assemblies [2], predicting higher-order correlations (HOCs) among the spike trains of assembly members. However, the estimation of the necessary parameters of present analysis techniques for HOCs poses serious problems, mainly because their number grows exponentially with the number of recorded neurons [3,4]. As a consequence, most attempts to detect active cell assemblies resort to pairwise correlations. Such pairwise correlations, however, do not reflect potential HOCs and are insensitive for sparse synchronous events [5]. As massively parallel extracellular recordings are becoming more and more available, the limited experimental evidence in favor of the cell assembly hypothesis has to a large extent be assigned to a lack of suitable analysis tools [6].

Here we present a novel procedure to detect HOCs in massively parallel spike trains. Based on estimates of only a few low-order cumulants of the summed activity across all neurons (the 'population histogram') we devise a statistical test for the presence of HOCs among the recorded spike trains. The test exploits the fact that absence of HOCs in a neuronal population also imposes constraints on (population-average) correlations of lower order. The latter can, however, be estimated via the respective cumulants of the the distribution of the entries in the population histogram. Under a compound Poisson assumption, where correlations of various orders are induced by 'inserting' appropriate patterns of near-synchronous spikes [7], the upper bounds for these lower order cumulants in the absence of HOCs can be derived analytically, together with the necessary confidence intervals of the respective k-statistics. This makes the test computationaly very modest and hence applicable to large amounts of data without the need for time consuming bootstrap approaches. Furthermore, the inference of HOCs from cumulants of lower order circumvents the need to estimate large numbers of higher-order parameters, making the test less susceptible to the limited sample sizes typical for in vivo recordings than previous approaches [3,4]. We illustrate the test on data which was simulated using a compound Poisson model, and find that cumulants of third order are already surprisingly sensitive for present HOCs. Furthermore, the proposed test detects HOCs even if their effects on pairwise correlation coefficients c are very small (in the range of c $\tilde{0}$.01, compare [5]).

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Epileptic seizure generation requires interaction of sclerotic and intact networks

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Abstract Network structures and dynamics initiating epileptic seizures in mesial temporal lobe epilepsy (MTLE) are still not fully understood. MTLE is accompanied by severe changes of the hippocampal histology, especially cell loss in CA1 and the hilus, granule cell dispersion and mossy fiber sprouting. Excision of those sclerotic areas is necessary to alleviate epileptic seizures and the development of less invasive therapy options requires the knowledge of brain areas participating in seizure generation processes. To determine, whether seizures are initiated by the sclerotic hippocampal areas or if a larger network participates in those processes, we used a model for MTLE in mice. A single unilateral injection of kainate into the dorsal hippocampus induced histological changes comparable to hippocampal sclerosis. Recordings of epileptiform events (EE) in-vivo indicated that hypersynchronous spiking involved not only the sclerotic areas of the injected hippocampus but also the temporal hippocampus, although histologically unchanged. To investigate whether initiation of EEs occurred in those sclerotic areas, we recorded slices from this region on multielectrode arrays. Surprisingly, it was impossible to induce EEs in those slices. In contrast, in slices from the temporal hippocampus without obvious histological damage we could induce EEs (bicuculline) with the same rate of recurrence as in controls. Analysis of the coherence between MEA electrodes revealed, however, that slices from epileptic mice showed a less synchronous activity structure within the dentate gyrus. This decreased synchronization turned out to be due to alterations in gap junction function. Although apparently structurally intact, the network dynamics in these slices thus differed. EE initiation therefore likely requires subnetworks with various degrees of degeneration.

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Embedding single neuron activity in population bursts in vitro

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Abstract The impact of morphology on the computational properties in neuronal circuits is not well understood. Native cortical tissue with its specialized layered organization limits the analysis of fundamentals of neuronal computation with relation to structure. Moreover, an experimental control over structural features of the underlying circuitry is technically constricted. Generic neuronal networks of dissociated cortical cells, however, allow such structural manipulations. Although lacking the complex structure of the native tissue, essential local features of neuronal networks remain conserved. In this respect, such networks closely resemble common random networks studied in computational approaches - in terms of size, complexity, 'randomness' of connectivity, etc. Dissociated networks can therefore be tested to verify predictions of such models on the one hand, and to reveal principles of neuronal computation on the other hand. In the present work, we introduce defined structures into dissociated neuronal cultures by means of microengineering techniques such as photolithography and microcontact printing. We create stable adhesive and restrictive polymer surfaces to shape cell-adhesive patterns and influence network formation. In patterned networks, the connection probability of neurons is restricted or can even be directed in arbitrary ways. In addition, we record the spontaneous activity of networks with random-like connectivity extracellularly with 60-site microelectrode arrays (MEA) in combination with intracellular patch-clamp measurements of individual neurons in whole-cell configuration. We show that individual neurons display a characteristic behavior of participating in the network activity which may tend to explain differing patterns observed extracellularly among subpopulations in the networks. In a broader context, this study adds to understanding structure-function relations in networks with random-like and constraint connectivity, offering the opportunity to closely interlink and test experiment and theory in the near future. This study is supported by the German Federal Ministry of Education and Research (BMBF grant 01GQ0420) and EU-NEST/NEURO.

Correlations in cortical networks

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Abstract The function of cortical networks depends on the collective interplay between neurons and neuronal populations, which is reflected in the correlation of signals that can be recorded at different levels. To correctly interpret these observations, it is important to understand the origin of neuronal correlations. Here we study how cells in large recurrent networks of excitatory and inhibitory neurons interact, and how the associated correlations affect its dynamic state. Our main result is that the underlying recurrent structure of the network induces considerable correlations between synaptic currents, as well as between subthreshold membrane potentials. Although correlations are strongly attenuated when going to action potentials, the residual weak correlations in the spike output of the neurons nevertheless cause substantial fluctuations in the population activity. This is the case even for highly diluted networks and 'asynchronous-irregular' states, which are distinguished by relatively asynchronous population activity and irregular firing of individual neurons. We show that these strong fluctuations arise from the functional segregation of excitation and inhibition, sometimes referred to as Dale's principle. The fluctuations are already prominent in random networks, a topology that is considered as a reasonable model for local cortical networks. Here we examine their impact also in more complex large-scale models of cortex, including networks with patchy connectivity as observed in layer 2/3 of V1 in cats. A statistical analysis of membrane potential and spike correlations can help to unravel structural properties of networks, as we demonstrate by comparing different model networks. Finally, we emphasize the important role of the functional segregation of inhibition and excitation by studying the effect of hybrid networks, where neurons can be excitatory and inhibitory at the same time. The activity dynamics in such networks is only weakly affected by structural features; they behave like random networks with a very narrow dynamical repertoire.

FIND - Finding Information in Neuronal Data: An open-source analysis toolbox for multiple-neuron recordings and network simulations

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Abstract In parallel to the tremendous technical progress in data acquisition (e.g. large number of simultaneous electrode recordings), there is a growing need for new computational tools to analyze and interpret the resulting data from both, experiments and simulations. While there is undeniable progress in novel analysis methods, implementations are difficult to reproduce based on literature or are hidden in (ill-documented and eventually "in-house only") software collections.

We are developing the "FIND-Toolbox" (http://find.bccn.uni-freiburg.de) to address the urgent need of an unified, well-documented interface to process the huge variety of electrophysiological data formats with state of the art analysis tools.

FIND - stands for Finding Information in Neuronal Data and will be shared to the community as an open-source analysis toolbox for electrophysiological recordings and network simulation environments. This platform-independent toolbox can be used to analyze neurophysiological data from single- and multiple-electrode recordings by providing a set of standard and more advanced analysis and visualization methods.

The FIND-Toolbox accommodates import of multiple proprietary data formats, based on the Neuroshare Project. Physiological data from different acquisition systems (Alpha Omega, Cambridge Electronic Design, Multi Channel Systems GmbH, NeuroExplorer, Plexon Inc., R.C. Electronics Inc., Tucker-Davis Technologies, Cyberkinetics Inc.) and data from Network simulations Environments (e.g. NEST, www.nest-initiative.org) can now be loaded and processed based on an unified representation. This allows verifying of both results across experiments and laboratories as well as direct comparison of simulation results and electrophysiological recordings.

To enable the incorporation of new algorithms - a weakness of most commercial toolboxes - FIND will be open source, providing the possibility to extend the collection of algorithms and data formats with new ones. We expect that this will facilitate the development and distribution of new techniques among the scientific community.

Please visit http://find.bccn.uni-freiburg.de to see announcements for new features, release versions, tutorials and training workshops.

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Bursting dependence on AMPA and NMDA -channel mediated glutamatergic transmission in cultured cortical networks

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Abstract Cortical neurons cultured on microelectrode arrays provide a simplified, yet feasible, platform to explore general information processing properties and plastic interactions in the nervous system. After four weeks in vitro, cultured neurons have formed a mature network, where 90% of the spikes reside in bursts. The bursts may bear relevance to plasticity and reliable information transfer within the neuronal network, but the mechanisms behind bursting are not fully known. Bursting has been reported to depend on NMDA -channel activation, while AMPA -channel activation has been linked to asynchronous firing. We report that both channel types affect bursting and that the blockade of neither of the channels alone is able to prevent bursting. We investigated the roles of AMPA and NMDA sensitive glutamate channels in producing and shaping bursts in cortical networks grown on microelectrode arrays by applying channel-specific antagonists (NBQX and APV, respectively). We analyzed antagonist induced changes in single channel bursts and synchronous network-wide bursts. AMPA -channel blockage resulted in a binomial distribution of the number of spikes in a burst (<40 and >200 spikes) and the inter-burst intervals (<2 and >40 sec). The network-wide burst intervals were also binomial but the median (3 sec, range 1-80 sec) of the intervals was not affected. When NMDA -channels were blocked, the bursts had less than 100 spikes, the inter-burst intervals were up to 20 sec, and the median of the network-wide burst intervals was 8 sec (range 2-20 sec). Our results suggest that NMDA -channel activation facilitates the formation of clusters of network-wide bursts, whereas AMPA -channel activation plays a role in recurrent, steady bursting, but cannot maintain the rhythmicity required for the network-wide bursts.

There and back again: Influence of visuomotor rotation learning on backward movements

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Abstract Previous studies have shown that in center-out movements, visuomotor rotations are learned strictly locally. More specifically, learning is restricted to movements starting from the same origin and pointing into similar directions as the trained movement. It is not known, whether this also holds for movements starting at different orgins. Especially, it is unknown whether the backward movements from the trained target are affected during learning. This study addresses this question and examines the influence of visual and proprioceptive information.

Our experiments show that no learning occurs in backward movements if visual feedback is only available in the center-out-, but not in the backward movement. The discrepancy between visual and proprioceptive information that is induced by the transformation induces backward movements whose direction is determined by the average between the two information channels. If, after rotation learning in the forward direction, forward movements are only imagined (supported by visually presented movements), backward movements are solely governed by (the) visual information (channel).

Our study provides valuable hints at the integration of proprioceptive and visual information in the control of arm movements. Furthermore, it also shows that generalisation in visuomotor rotation learning is not only lacking in movements starting from the same origin, but also in backward movements starting in the end position of the learned movement.

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Dendrite Structure and Activity Dynamics in Neuronal Networks

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Dendrite Structure and Activity Dynamics in Neuronal Networks

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In neuronal systems, morphogenesis of individual neurons, network formation and activity dynamics strongly depend on one another. These interdependencies can be studied in primary cell cultures of dissociated neuronal tissue, in which initially isolated cells form complex random networks, based on their intrinsic properties and their microenvironment. This work focuses on implications of dendritic architecture on connectivity and activity dynamics in cortical cell cultures grown on micro-electrode-arrays. The approach includes the pharmacological manipulation of the Protein kinase C (PKC), which comprises a key target for the modulation of neuronal morphology, since it is involved in processes that guide initial outgrowth and activity dependent ongoing reorganisation of neurites and synapses. Cultures were chronically treated with PKC inhibitors to alter neurite outgrowth and thus connectivity in the mature state. Electrophysiological recordings and morphological characterisations were carried out to study structure-function dependencies in the developing networks. A modified Scholl profiling method was developed to describe the radial dendritic field density of neurons in immunohistochemically stained networks. With this method a significantly enhanced dendritic arborisation (of approximately 30%) was determined for neurons in the PKC inhibited cultures. Additional staining against the presynaptic protein synaptophysin furthermore indicated an increased synapse density. Conversely, no significant changes were found in the preliminary electrophysiological analysis, which was, however, limited to basic activity parameters such as the global level of activity, firing rate of single neurons or regularity of spiking. Functional changes that may result from increased connectivity therefore still have to be analysed. In summary, this work shows that chronic inhibition of the PKC increases the dendritic fields of neurons and therefore provides a tool to study dependencies of dendrite structure and activity dynamics in cortical cell cultures.

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Propagation of synchronized spiking and firing rates in locally connected random networks

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Abstract Isolated feedforward networks (FFN) of spiking neurons have been extensively studied for the propagation of firing rates and transient synchrony, in the presence of activity independent synaptic noise (Diesmann et al. 1999, Van Rossum et al. 2002). In a biologically realistic scenario, however, the FFN should be embedded in a recurrent network, such that the background noise, in turn, depends on the activity in the FFN. Adopting this approach, Mehring et al. (2003) reported that the transient synchrony and non-random architecture of the FFN destabilizes the dynamics of the embedding network.

Here we show that by modeling the synapses in the network as conductance transients, rather than as current sources, it becomes possible to embed and propagate transient synchrony in the FFN, without destabilizing the background activity in the embedding, locally connected random network. The stable propagation of transient synchrony depended on background activity statistics: high synchrony and high firing rates in the background always annihilated the synchronous activity in the FFN, whereas low background firing rates and low synchrony supported the traveling synchrony and allowed for increasing precision along the groups of FFN.

We also investigated the propagation of firing rates in the FFN (Vogels and Abbott 2005). We found that synchronous activity states in the network supported neither propagation of firing rates nor synfire activity, whereas asynchronous activity in the background admitted the propagation of both synchronized spiking and low firing rates. However, the propagated firing rate rapidly synchonizes and turns into a rate of propagating synchronous events (Litvak et al. 2003). Our results suggest that for a wide range of parameters, asynchronous activity in cortical networks provides a good substrate for temporal coding relying on the propagation of transient synchrony.

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Precise spike synchronization in monkey motor cortex: from time estimation processes to the selection of movement direction

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Abstract It is commonly accepted that perceptually and behaviourally relevant events are reflected in changes in firing rate in widely distributed populations of neurons. Another concept, the temporal coding hypothesis, suggests that not only changes in firing rate but also precise spike timing constitutes an important part of the representational substrate for perception and action, such as spike synchronization or other precise spatio-temporal patterns of spike occurrences among neurons organized in functional groups, commonly called cell assemblies. The accurate estimation of time intervals or the temporal prediction of forthcoming events is essential for optimizing motor performance. During preparation and execution of a planned movement, motor cortical neurons change their activity not only in relation to the features of the forthcoming movement (such as its direction) but also in relation to higher cognitive events linked to time estimation processes, e.g. signal expectancy (SE). Using a delayed pointing task, it as been shown that, at the moment when a GO signal was expected but did not appear, some neurons changed phasically their activity, transient synchronization among two or more neurons occurred and also the correlation between local field potentials increased. To explore spike synchronization patterns in pairs of neurons in relation to SE and/or to prior information about movement direction, we recorded simultaneously the activities of multiple neurons in monkey primary motor cortex during the performance of a choice reaction time task requiring correct time estimation. In this task, which involved different degrees of spatial and temporal uncertainty, the choice of movement direction was a function of time. To investigate the dynamics of spike synchrony, the unitary events method and the classical tool of cross correlation analysis were used. We found (i) consistent patterns of spike synchronizations linked to SE, and thus to time estimation processes. Surprisingly, we observed (ii) an effect of learning new durations, with a shift in time of the transient occurrence of synchrony from the old expected signal to a new one. And finally, we found (iii) directionally selective patterns of spike synchronizations during movement preparation which presented reciprocal patterns related to the two opposite movement directions.

Cortical networks with long-range patchy connections

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Abstract Most current modeling studies of cortical network dynamics assume random wiring, a practical but presumably too simplistic approach. In reality, cortex has a delicate horizontal structure, composed of both local and long-range connections, the latter featuring a special projection pattern called 'patches'. Here we investigated several alternative scenarios to account for specific horizontal structures, pursuing the aim to develop improved models of cortical network architecture. We assumed an embedding of all neurons in space. Their wiring comprised neighborhood coupling and - depending on the model - other types of distant connections, e.g. patchy projections. We employed stochastic graph theory to define network properties that characterize our models. In particular, we assessed the mutual overlap of presynaptic and/or postsynaptic populations for individual neurons in the network. This allowed us to study the impact of particular features of long-range connections for global network properties and to speculate about their functional implications.

Stimulation-efficacies in neuronal networks in vitro

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Abstract Processing and storage of information are fundamental features of neuronal systems. Complex neuronal interactions on a wide range of spatial and temporal scales are underlying those features, but is unclear by which processes they are governed and how they depend on a specific neuronal environment and network architecture. The goal of our work is to identify means to interact with small neuronal networks in vitro and analyze their capacity to process and store information imposed by electrical stimulation patterns. Cortical cell cultures grown on microelectrode arrays (MEAs) can be accessed for recording and stimulation via 60 electrodes. These networks form numerous functional connections from the first few days in vitro (DIV) on that are modulated by intrinsic activity: The network's activity undergoes a change from unit spiking uncorrelated across recording sites to synchronized bursting activity. This inherent synchronized bursting may play a major role in synaptic plasticity and further modulates the functional connections towards more complex burst patterns as the network matures. Stimulation-response pairings in the network interact with this bursting activity and would hence confound the analysis due to an interplay of the induced and spontaneous dynamics. We therefore characterize the activity-dependent stimulation-response relationships by applying stimulation at defined network states. In our results, we report on the activity characteristics of in vitro neuronal cell cultures with their intrinsic burst patterns and bursting periods. Stimulation experiments under various conditions and paradigms were conducted, e.g. single and multi-site stimulation or stimulation that is locked to a specific phase of the network's activity and stimulation during random activity phases. Evidence that periods of increased bursting activity, so-called superbursts, can act as a reset mechanism to the network's stimulation sensitivity and overall stability is presented. We also show that temporal and spatial aspects have to be considered when the efficacy of electrical stimulation is evaluated. Finally, a possible way to interfere with the bursting activity by electrical stimulation is exemplified.

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