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New Approaches to the Study of Brain Function and Dysfunction

Structural Learning in Motor Control

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When we learn a new skill, from riding a racing bicycle to writing on a piece of paper, the motor system adjusts its control parameters so as to achieve the task. However, once we have learned such skills we can rapidly generalize to riding a mountain bike or writing on a blackboard. This ability could arise through two distinct mechanisms. The controller could start from the control parameters of the first task and search for parameters appropriate for the new task. In such parametric learning the generalization relies on the closeness of the starting and final settings of the parameters. Alternatively, the controller could learn the structure of the task that is how the parameters co-vary. Generalization in such structural learning relies on preferential exploration in the restricted parameter space defined by the task structure. To test between these two classes of learning, we conducted a set of sensorimotor learning experiments. The basic idea is to expose human subjects to parametrically unlearnable tasks of the same structure as compared to subjects that are exposed to a different structure. This means that parameters of the task are modified randomly, making it impossible to learn them, while the structure of the task remains unchanged. Although subjects learned nothing on average, we show that when subsequently presented with a novel task, subjects exhibit three key features of structural learning: First, a facilitation of learning for tasks belonging to the same structure (structure-related facilitation). Second, when switching between tasks which require opposite control strategies but belong to the same structure we found only a very weak interference effect in contrast to the normally persisting interference effect reported in the literature (structure-releated interference reduction). Third, we demonstrate that subjects preferentially explored along the learned structure, thus learning occurred on a lower-dimensional submanifold of the sensorimotor space (structure-related exploration). Taken together our results suggest that structural leaning plays a cardinal role in the acquisition of movement skills. The dimensionality reduction afforded by structural learning might provide a solution to the venerable “curse of dimensionality” that is omnipresent in computational motor control. Moreover, structural learning of abstract “motor concepts" might even provide a key to understand concept learning, thus bridging motor control and cognitive neuroscience.

Short term changes in bilateral hippocampal coherence during the initiation phase of epileptiform events

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The mesial temporal lobe epilepsy syndrome (MTLE) is among the most common forms of focal epilepsies. It responds very poorly to pharmacological therapy and treatment is limited to surgical resection of temporal brain areas. For finding less invasive therapies further knowledge of the network structures and dynamics involved in seizure generation is required. Early detection of pre-epileptic states is often performed in EEG recordings, however, further investigation of the time interval immediately preceding seizure onset would much help in understanding the initiation mechanisms of the seizure proper and, thereby, possibly allow acute intervention. Here, we employed the in vivo intrahippocampal kainate model in mice (N=8), which is characterized by unilateral histological changes resembling hippocampal sclerosis observed in human MTLE.

There, we studied synchronization processes between the ipsilateral, sclerotic hippocampus and the contralateral hippocampus immediately preceding the onset of epileptiform events (EEs). In these mice, population spikes occurred during EEs in the ipsilateral, histologically changed hippocampus, but also concomitantly in the contralateral, intact hippocampus. We show that coherence between the two hippocampi changes 8 to 12 s before the onset of EEs at high frequencies (> 100 Hz), without changes in power in these bands. This early decoupling of the two hippocampi suggests that initiation processes of the seizure proceed on a time scale that would allow acute intervention.

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Prediction of Movement Trajectories from Epicortical Field Potentials in Humans

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Epicortical field potentials (EFPs), recorded from intra-cranially implanted electrodes on the cortical surface by electrocorticography (ECoG), are already known to provide reliable information about the direction of arm movements. This indicates the potential of these signals to drive a future brain-machine-interface (BMI) for the application in paralyzed patients. However, recent approaches to ECoG-based BMIs either relied on the classification of different discrete movement patterns or on a voluntary modulation of spectral features, like spectral power in a specific frequency band. For continuous multi-dimensional control of a BMI, the possibility to predict complete movement trajectories from neuronal signals is a desirable addition. Although this has been shown for spike data, as well as for local field potentials (LFPs), recorded intra-cortically, it remains to be demonstrated for EFPs, recorded from electrodes that do not penetrate the brain tissue. We examined EFPs from five human subjects with subdurally implanted ECoG-electrodes during continuous two-dimensional arm movements between random target positions. Using a Kalman filter approach, we show that continuous trajectories of hand position can be predicted from the EFP recorded from hand/arm areas of the motor cortex. This strongly suggests that EFP, related to body movements, can directly be transferred to equivalent controls of an external effector for continuous BMI control.

Adaptive Classifiers for the use in Brain Computer Interfaces

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The performance of a new adaptive classifier for the use within a Brain Computer-Interface (BCI) will be evaluated.This classifier can either be adaptive in a completely unsupervised manner or use unsupervised adaptation in conjunction with a neuronal evaluation signal to improve adaptation. The first variant, named Adaptive Linear Discriminant Analysis (ALDA), updates mean values as well as covariances of the class distributions continuously in time. In simulated as well as experimental data ALDA substantially outperforms the non-adaptive LDA. The second variant, termed Adaptive Linear Discriminant Analysis with Error Correction (ALDEC), extends the unsupervised algorithm with an additional independent neuronal evaluation signal. Such a signal could be an error related potential which

indicates when the decoder did not classify correctly. When the mean values of the class distributions circle around each other or even cross their way, ALDEC can yield a substantially better adaptation than ALDA depending on the reliability of the error signal. Given the non-stationarity of EEG signals during BCI control our approach might strongly improve the precision and the time needed to gain accurate control in future BCI applications.

High frequency components in local field potentials during hippocampal kindling in rats

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Purpose: To assess the evolution of high frequency (HF) content in afterdischarges (ADs) during kindling. Methods: We recorded ADs evoked by short stimulus trains delivered to the right hippocampus of 10 Wistar rats. The recording electrodes were placed bilaterally in hippocampi and frontal neocortices (4 in the right dorsal hippocampus, 2 in the left dorsal hippocampus and 1 in right and left frontal neocortex each). A common reference electrode was placed above the cerebellum. The stimulus consisted of a 60 Hz train of biphasic rectangular pulses lasting 1.6 s. Each biphasic pulse lasted 0.4 ms with an amplitude of ± 0.5 mA. The stimulation was performed daily in each rat over a period of 5-20 days. EEG was recorded at 10.4 kHz sampling rate and signals

were split into physiologically meaningful periods, e.g., control period before stimulus and various AD periods with different waveforms. For each period, spectra and spectrograms were computed to assess the HF content. Results: After the stimulus we recorded an AD at all recording sites. On the first day the AD started with a series of slow spikes. In the subsequent days, HF ripples (100-400 Hz) were superimposed to these slow waves, the total duration of the AD increased, and the HF ripples extended to the contralateral hippocampus. During the AD a behavioral seizure was observed in some cases after the tenth day of stimulation. The HF content of the EEG (consisting of ripples superimposed on slow waves of high amplitude) was observed before and during the first moments of the seizure, and the frequency decreased during the seizure. Conclusions: During the kindling process, afterdischarges occurred from the 1st day on. They were not limited to the site of stimulation but appeared in both, ipsilateral and contralateral hippocampus and neocortical areas. HF discharges developed over subsequent days, and they were not limited to the kindling site but also extended to the contralateral hippocampus.

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Representation of arm movement parameters in the EEG

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Local and epicortical field potentials (LFP & EFP) carry information about parameters of voluntary arm movement. Recently, these intracranial measurements have spurred the quest for the optimal signal in brain-machine-interfacing (BMI). The time and frequency domains modulated by arm movement parameters include slow potentials and gamma range spectral power. Here we used electroencephalographic (EEG) recordings to non-invasively investigate the representation of arm movement parameters.

Methodology/Principal Findings: Eight healthy subjects performed a self-paced centre-out and centre-in right arm reaching task in four directions. There were no external sensory cues, movement direction of the centre-out movements was trial-by-trial self-chosen by the

subjects. We recorded EEG activity from 58 scalp surface positions equally distributed over both hemispheres. Movement-related potentials (MRPs) comprised the classical Bereitschafts-potential and a phasic response occurring during movement execution. Starting with the onset of the phasic response, a cluster of central and centroparietal electrodes on the convexity contralateral to the moving arm recorded MRPs that were modulated by the movement type. We inferred arm movements from the low-pass (<4Hz) filtered signal and movement type separability was reflected by the separability of right arm muscle activations. We could increase decoded information upon pooling movement types with low separability. As of yet, we were not able to infer arm movements from spectral components. We could, however, draw parallels between the gamma range spectral components of EEG signals and EFP by comparing their time course in our EEG recordings with subdural EFP obtained from two epilepsy patients performing an almost identical task. Gamma range spectral power transiently increased both at movement onset, i.e. button release, and movement end, i.e. button reaching. Conclusions/Significance: Here we show that centre-out and centre-in arm reaching movements can be inferred from EEG single trials. Our results indicate that the neuronal mass signal contralateral to the moving arm reflects differential arm muscle activations. In the view of potential new neuroprosthetic applications, we propose to choose arm movements with high electromyogram (EMG) discriminability and to eventually pool movement types for initial training phases. Further on, our findings show a high degree of similarity in the time course of gamma range spectral power changes in EEG recordings from healthy human subjects and intracranial recordings from epilepsy patients. We conclude that gamma range spectral power increase is closely related both to leaving and reaching targets. Keywords: EEG, BMI, gamma.

Characterizing the Specific Behavior of Dynamic Causal Modeling Applied to fMRI Signals

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Recently, investigations using functional magnetic resonance imaging signals have gained particular interest in the analysis of the normal behavior of the brain or its malfunction. To estimate functional interactions between certain brain regions providing deeper insights into the behavior of the brain, dynamic causal modeling has been suggested and is nowadays widely used. Roughly, dynamic causal modeling is based on a Bayesian approach to quantify the strength of interactions between processes. A priori all connections are assumed to be absent. To assess the characteristic behavior of dynamic causal modeling when applied to "real-world" data, we applied dynamic causal modeling to simulated data in the first place. Knowledge of the true parameters used for the simulations allow investigation of the robustness of dynamic causal modeling. Moreover, we have tested whether certain models describing the interaction structure among brain regions can be identified dependent on variations in the prior knowledge of interactions and different signal-to-noise ratios. It turned out that dynamic causal modeling works rather robust even at poor signal-to-noise ratios. Astonishingly high signal-to-noise ratios did not guarantee superior estimates for the interactions. Comparing models with similar interaction structures has demonstrated that although a single comparison often favors one model significantly averaging over many realizations revealed that this decision was actually impossible. These results will be discussed in our contribution. This way, we will characterize abilities and pitfalls of dynamic causal modeling.

Predicting epileptic seizures: Evaluation of a combination of prediction methods

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Concerning the assessment of the predictability of epileptic seizures, a continuous and reliable analysis of neurophysiological recordings of epilepsy patients is necessary. Recent work has indicated that methods from non-linear dynamics can detect significant preseizure changes in the EEG at least for some patients. As a means to increase seizure prediction performance we tested whether or not two different kinds of combination of seizure prediction methods yield superior prediction results. A bivariate phase synchronization index (PSI) and the univariate “Dynamical Similarity Index” (SIM) were adapted for seizure prediction. The analysis of these prediction methods was based on long-term intracranial

EEG data with continuous recordings of 8 patients for 7-11 days including 124 seizures. Two approaches to combine predictions methods were applied, following a logical “and” or a logical “or”. For the “and” combination, an alarm was given if both methods raised an alarm within a certain time window which was set to 20-40 min. For the “or” combination, an alarm was given for each alarm of the individual methods. All results have been validated by a statistical test procedure (Schelter et al, Chaos 2006; 16: 013108). For a fixed set of parameters, significant prediction results could be observed for five (PSI) and four (SIM) patients by evaluating each method individually, with average sensitivities of 51% (PSI) and 49% (SIM). If the same maximal rate of false predictions was permitted, a combination of both methods using a logical “and” showed an increase in sensitivity of about 25%, whereas for a combination following a logical “or” no such improvement could be observed. Hence the use of an “and” combination of seizure prediction methods represents a promising step towards clinical applications.

Lithium induces Cajal-Retzius Cell Neurite Retraction in Hippocampal Slice Cultures

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Hippocampal slice cultures are an excellent model to gain insight in the mechanisms that govern the development of hippocampal cell and fiber layers (reviewed in Förster et al., 2006a). Most hippocampal dentate granule cells are born early postnatally, and thus migrate postnatally to their final positions. This migration process is controlled by Reelin, a protein which is secreted by Cajal-Retzius cells in the marginal zone of the dentate gyrus. An identified component of the Reelin signalling cascade is the enzyme glycogen synthase kinase (GSK)3 beta which has been shown to act on the cytoskeleton by modulating tau phosphorylation. Activity of Gsk3ß is downregulated by application of pharmacological inhibitors, such as Lithium Chloride (LiCl). LiCl is also known as a drug for treatment of schizophrenia, a neurological disorder that is thought to be causally related to developmental neuronal migration defects. Here, we were interested in the question whether LiCl may interfere with developmental processes in hippocampal slice cultures, known to be regulated by Reelin signalling. Different concentrations of LiCl were added to the incubation medium and the morphology of slice cultures was analyzed after 4-5 days in vitro. After treatment with high concentrations of LiCl, we observed a loss of the proper arrangement of the dentate granule cell layer, suggesting that Lithium interfered with proper positioning of dentate granule cells, a process that is known to be regulated by Reelin. Next, we studied the effect of Lithium on the morphology of Reelin secreting Cajal-Retzius cells by immunostaining with an antibody against Calretinin. We found that LiCl induced neurite retraction of Cajal-Retzius cells in a dose dependent manner. These initial observations suggest that Lithium may interfere with hippocampal development by directly acting on Reelin secreting Cajal-Retzius cells. The results also raise the interesting question as to whether Lithium treatment might similarly affect persisting hippocampal Cajal-Retzius cells in the adult hippocampus.

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Structure and dynamics in neuronal networks *in vitro*

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The relation between structure and function in neuronal circuits is not well understood. While discussions on such relations mostly focus on cortical tissue with its prominent layered structure, its complexity limits theoretical and experimental analyses as well as control over structural and/or functional aspects of the underlying neuronal circuits. Simpler and generalized neuronal networks allow such manipulations and enable the verification of theoretical assumptions.
Networks in dissociated cortical cultures are such generic networks. They do not develop predefined anatomical structure or predictable connectivity in first place. Moreover, photolithographic engineering techniques enable the design of patterned cell culture substrates with cell-adhesive and cell-repellent areas. On such substrates, the adhesion of

neurons can be restricted and the outgrowth of neurites can be influenced. If cultured on microelectrode arrays (MEA), the activity dynamics in these networks can be monitored continuously.
In our work, we use this approach to modulate the connectivity statistics of networks in culture to identify general principles of structure-function relations. Tissue from the prefrontal cortex of neonatal rats was dissociated and cultured on 60-site MEAs and glass coverslips. The substrate surfaces were patterned with the covalently linked polymers polyethylene imine and polydimethyl acrylamide. On such patterns, cell somata and neurite outgrowth can be restricted to the adhesive polyethylene imine patterns. The activity dynamics of our networks were recorded with MEA recordings and – on a single cell or cell pair level – with patch-clamp recordings in whole-cell configuration. Structural aspects of the networks were analyzed based on immunohistochemical imaging or single cell staining.
In conclusion, this approach enables the investigation of the principles of structure-function dependencies in very basic but structured neuronal circuits.

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Capillary Pattern in Reeler Hippocampus Differs from Wildtype Layer Specific Pattern

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Early development of the blood capillary network in the cerebral cortex follows stereotyped rules. Thus, first capillaries grow from the pial surface centripetally towards the ventricles. In the reeler mouse, a mutant that is well-known for its characteristic malpositioning of cortical neurons, capillaries no longer invade the developing cortex perpendicular to the pia, but are misrouted into various directions. Among the cues involved in shaping the capillary pattern, factors secreted by cortical neurons are thought to play an important role. Here, we used the reeler mutant as a model to study the relation between neuronal positioning and the development of the capillary network in the hippocampus. Prominent differences in the formation of the capillary network between reeler and wildtype dentate gyrus emerge between postnatal day 6 and 10. At this time point, a compact granule cell layer has already formed in wildtype, whereas in the reeler mutant granule cells remain scattered in the hilar region. The architecture of the wildtype capillary network is characterized by layer specific differences, such as highly branched capillaries in the subgranular zone but few, poorly branched capillaries that cross the granule cell layer perpendicularly. In contrast, in the fascia dentata of the reeler mutant the capillary architecture develops without layer specific differences. Capillaries are rather uniformely distributed, thereby paralleling the uniform distribution of granule cells in the fascia dentata. In addition, first quantification of branching suggests that overall branching of capillaries in the reeler fascia dentata is reduced when compared to wildtype. Since hippocampal stem cells have been reported to be located in capillary associated niches in the subgranular zone, the malformed capillary network in reeler could go along with a reduced number of stem cell niches in the dentate gyrus. This interpretation is supported by the observation of decreased neurogenesis in the adult reeler hippocampus when compared to wildtype (Zhao et al., 2007). The present findings also raise the question as to whether granule cell dispersion linked to temporal lobe epilepsy in humans could go along with similar changes in the architecture of the capillary network.

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FIND - Finding Information in Neuronal Data. An open-source approach to unify access and analysis for multiple-neuron recordings and network simulations

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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 large data flow from 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, in-house) 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 both data stored in different formats and various analysis tools.The FIND-toolbox, standing for Finding Information in Neuronal Data, will be shared to the community as an open-source analysis toolbox for electrophysiological recordings and network

simulation environments. This platform-independent, matlab based, 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. Currently the FIND-Toolbox accommodates import of multiple proprietary data formats, based on the Neuroshare Project (http://neuroshare.sourceforge.net).
This allows direct access to data recorded and stored by recroding systems from Alpha Omega, Cambridge Electronic Design, Multi Channel Systems GmbH, NeuroExplorer, Plexon Inc., R.C. Electronics Inc., Tucker-Davis Technologies and Cyberkinetics Inc. Furthermore, data from network simulations environments (e.g. NEST, www.nest-initiative.org) can now be compared using identical analysis methods as for the recorded data. This allows verifying of both results across experiments and laboratories as well as direct comparison of simulation results and electrophysiological recordings. We expect that the open source approach of the FIND-Toolbox 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 or to join the developers team.

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Investigations on the Functional Organization of the Anterior Insula

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Learning to play a musical piece is a prime example of complex sensorimotor learning in humans. Recent studies using electroencephalography (EEG) and transcranial magnetic stimulation (TMS) indicate that passive listening to melodies previously rehearsed by subjects on a musical instrument evokes differential brain activation as compared with unrehearsed melodies. These changes were already evident after 20–30 minutes of training. The exact brain regions involved in these differential brain responses have not yet been delineated. Using functional MRI (fMRI), we investigated subjects who passively listened to simple piano melodies from two conditions: In the ‘actively learned melodies’ condition subjects learned to play a piece on the piano during a short training session of a maximum of 30 minutes before the fMRI experiment, and in the ‘passively learned melodies’ condition subjects listened passively to and were thus familiarized with the piece. We found increased fMRI responses to actively compared with passively learned melodies in the left anterior insula. The area of significant activation overlapped the insular sensorimotor hand area as determined by our meta-analysis of previous functional imaging studies. Our results provide evidence for differential brain responses during listening to action-related sounds after short periods of learning in the human insular cortex. As the hand sensorimotor area of the insular cortex appears to be involved in these responses, re-activation of movement representations stored in the insular sensorimotor cortex may have contributed to the observed effect. The insular cortex may therefore play a role in the initial learning phase of action-perception associations.

Dynamic encoding of movement direction in motor cortical neurons

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Prior information about movement direction is known to strongly affect the neuronal representation of movement direction. We studied the time-dependent neuronal encoding of movement direction during preparation and execution of arm movements, and how it is modulated by the amount of prior information about the movement direction. The experimental paradigm was a delayed center-out hand reaching task with different degrees of prior information: either 1, 2 or 3 adjacent targets from a total of 6 targets arranged on a circle lit up in green, serving as a preparatory signal. After one second one of them turned red, serving as the reaction

signal and the target to reach out to. The tuning properties and the probability to correctly decode movement direction from single-trial firing rates of a total of 222 motor cortical neurons recorded from 2 trained monkeys were analyzed. Our results demonstrate that the encoding of movement direction in individual neurons is dynamic with respect to time and prior information, during both movement preparation and execution: The temporal episodes when a neuron exhibits tuning differ from neuron to neuron, and each neuron is characterized by a unique time-dependent tuning profile. Additionally, because each neuron dynamically adapts its directional tuning to the different levels of prior information, the tuning profile changes with prior information. For example, movements performed under conditions with complete prior information generally lead to decreased tuning during movement execution. Our finding, that during the same movement different neuronal processing takes place dependent on prior information, is incompatible with a view of the motor cortex having a one-to-one representation of movements. Instead, it suggests that the motor cortex dynamically adapts or changes its representation, influenced also by the cognitive context. We also investigated how this dynamic behavior affects the encoding of movement direction on the population level: First, our analysis shows that, at any time during movement preparation or execution, the decoding accuracy exhausts the maximally available information for larger populations (50-100 neurons). Thus, with complete prior information a precise prediction of movement direction was possible already during movement preparation, up to one second before movement execution. Second, we found that the prior information dependent change of neuronal tuning profiles leads to decreased decoding accuracy, if the decoder is ignorant of the prior information condition. This suggests that, for optimal performance during less constrained behavior, algorithms for movement decoding should be trained under different behavioral contexts.

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Detection of Coupling Directions in Multivariate Dynamical Systems with Applications to Tremor-correlated Spike Activity in Parkinson's Disease

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Tremor in Parkinson's disease is a neurological disorder that manifests itself in involuntary oscillations of the upper limbs at a frequency of approximately 5 Hz. The aim of this study was to investigate the relation between tremor and spike activity in the subthalamic nucleus (STN) of patients with Parkinson's disease. Data were obtained during stereotactic surgery on patients with Parkinson tremor. Muscular and neuronal spike activity was recorded simultaneously. Multivariate analysis techniques were applied to infer the underlying interdependence structure with particular emphasis on distinguishing direct and indirect interdependencies as well as the direction of the information flow. The techniques

were successfully applied and our results support the hypothesis that synchronous neuronal activity in the STN contributes to the pathogenesis of Parkinsonian tremor.

Cortical networks with long-range patchy connections

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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'. 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 various other types of distant connections, e.g. patchy projections. We employed stochastic graph theory to define network properties that characterize our models. 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. In particular, we assessed the mutual overlap of presynaptic and/or postsynaptic populations for individual neurons in the network.

Decoding of Hand Movement Directions from Human MEG-Signals

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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 invasive and non-invasive recording techniques. We found significant power variation between rest and movement for sensors located above motor areas in three frequency bands: an increase for ≤7Hz and 62-87Hz, a decrease for 10-30Hz. Using MEG activity ≤3Hz exclusively of motor area sensors (bilateral), on average significant DP was obtained as early as 200ms before movement onset and increased to 67% around 400ms 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.

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