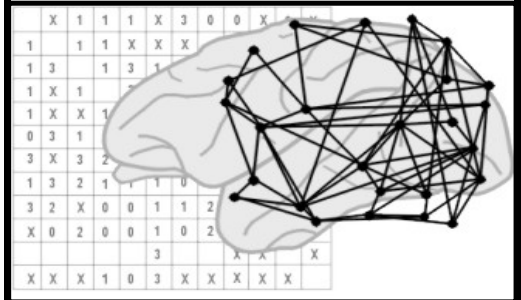
Functional Brain Connectivity

	Thursday 4 April 2002	Friday 5 April 2002	Saturday 6 April 2002
8:45		open doors	open doors
9:00	Schloss Mickeln Düsseldorf **Programme** 	Animal models 2nd Session 1st talk **Schubert**	Inferences 4th Session 1st talk **Stone**
9:55		small break	small break
10:00		2nd talk **Buzás**	2nd talk **Friston**
10:55		large coffee break	large coffee break
11:15		3rd talk **Hübener**	3rd talk **Bullmore**
12:10		optional discussion	optional discussion
12:30		break	break
13:00		lunch	lunch
14:00	open doors	break	break
14:30	Welcome + Introduction		
15:00	Ground work 1st Session 1st talk **Vanduffel**	Multi-modality 3rd Session 1st talk **Paus**	Computations 5th Session 1st talk **Sporns**
15:55	small break	small break	small break
16:00	2nd talk **Goebel**	2nd talk **Koch**	2nd talk **Horwitz**
16:55	large coffee break	large coffee break	large coffee break
17:15	3rd talk **Zilles**	3rd talk **Schiff**	3rd talk **McIntosh**
18:10	optional discussion	optional discussion	optional discussion
18:30	end	end	end
19:00			transfer to Rheinturm for invited guests

List of contributions

Significance of connectivity differences between groups of FMRI data

Ed Bullmore
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What should we do if we have fMRI data on more than one group and we wish to say something about possible between-group differences in connectivity? I have sometimes approached this problem by averaging or concatenating time series over subjects in each group, effectively eliminating individual variability, to construct a group mean connectivity matrix. There are then various ways of testing for a difference between two or more such generic connectivity matrices – including path analysis and a resampling method based on generalised Procrustes analysis. I will briefly describe a couple of alternative approaches, which have in common a greater respect for individual variability in integrative brain function! Three-way multidimensional scaling, also known as individual differences scaling, is an established multivariate method that defines a generic configuration of regions in low dimensional functional space as well as the "weirdness" or deviation of each individual from the generic form. Also, correlation and path coefficients estimated in each individual subject can be used as dependent variables in a second-level linear mixed effects analysis, formally identical to models already widely used to assess between group differences in univariate activation statistics. The issues are illustrated using groups of data from a case-control study of schizophrenia and a study of dopaminergic drug effects.

Fine structure of cortical connections - fine structure of cortical maps

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The talk will address the question of lateral connectivity rules in the primary visual cortex. More specifically: how to measure them experimentally and how to interpret the measurements as seen on examples from areas 17 and 18 of the cat. Horizontal connections are formed by axons of both excitatory neurones (pyramidal and spiny stellate cells) and inhibitory ones (basket cells). Extracellular tracer injections allow a look at the global morphology of these connections and a few general rules become evident: excitatory connections are longer (up to 3.5 mm radius) and patchy while inhibitory connections are somewhat shorter (up to 1.5 mm radius) and not patchy. We can come closer to the functional specificity of these connections by projecting them onto cortical maps obtained by optical imaging. When using the orientation map in this comparison (Kisvárday et al., 1997), the long-range axons (those extending beyond the parent functional column) appear to target sites possessing a wide range of orientation selectivity with some prevalence of iso-orientations in the excitatory patches. Looking at single cell axons, there is a large morphological variability: the axon arbours differ in the amount of local and long-range connections, the radial arrangement and symmetry of the axon branches around the soma, the termination pattern in the different cortical laminae etc. Combining this anatomical picture with the orientation map (Kisvárday et al., 1994; Buzás et al., 1998) reveals an individual variability under the "envelope" of the orientation topography of the population. In addition, each target cell represents a multitude of stimulus features, some of which form functional maps (e.g. direction and ocular dominance maps). Our analysis of single neurones (Buzás et al., 2001) shows that the relationship between axons and the "polymap" (Landau & Schwartz, 1992) can vary even within the same morphological cell type and it obeys most probably multiple connection rules.

References and further reading:

- P. Landau and E. Schwartz. Computer simulation of cortical polymaps: a proto-column algorithm. *Neural Networks* 5:187-206, 1992.
- Z. F. Kisvárday, D. S. Kim, U. T. Eysel, and T. Bonhoeffer. Relationship between lateral inhibitory connections and the topography of the orientation map in cat visual cortex. *Eur J Neurosci* 6:1619-1632, 1994.
- Z. F. Kisvárday, T. Bonhoeffer, D. S. Kim, and U. T. Eysel. Functional topography of horizontal neuronal networks in cat visual cortex (area 18). In: *Brain theory - biological basis and computational principles.*, edited by A. Aertsen and V. Braitenberg, Amsterdam:Elsevier, 1996, p. 97-122.
- Z. F. Kisvárday, É Tóth, M. Rausch, and U. T. Eysel. Orientation-specific relationship between populations of excitatory and inhibitory lateral connections in the visual cortex of the cat. *Cereb.Cortex.* 7:605-618, 1997.
- P. Buzás, U. T. Eysel, and Z. F. Kisvárday. Functional topography of single cortical cells: an intracellular approach combined with optical imaging. *Brain Res.Brain Res.Protoc.* 3 (2):199-208, 1998.
- P. Buzás, U. T. Eysel, P. Adorján, and Z. F. Kisvárday. Axonal topography of cortical basket cells in relation to orientation, direction, and ocular dominance maps. *J Comp Neurol* 437 (3):259-285, 2001.

Dynamic Causal Modeling

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With the current quality of fMRI data, and a growing understanding of the dynamical systems that model the translation of neuronal activity into hemodynamic responses, nonlinear system identification techniques are becoming tenable in fMRI data analysis. This enables a causal modelling approach to fMRI time-series that is explicitly dynamical. It rests upon a description of the system in terms of differential equations whose parameters reflect the coupling among brain regions and the relationship between neuronal activity (hidden state variables) and the measured fMRI response (output). In principle this approach could provide a comprehensive and biologically plausible characterization of functional coupling in the brain and represents a dynamical alternative to models based on stochastic models used so far (e.g. structural equation modelling).

Combining fMRI and DTI: Constraints for functional connectivity analysis

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In vivo visualization of the brain's functional architecture using fMRI is ubiquitous these days. However, in order to understand the "how" of the brain's information processing, it is of central importance to map the pattern of the neuronal connectivity in the same non-invasive manner. We present work-in-progress using fMRI and Diffusion Tensor Imaging (DTI) to reveal functional activity and connectivity patterns from the same animals. Investigating animals is important to validate reconstructed fibers based on the local DTI data. Cats were anesthetized using standard protocols. Subsequently, ultra-high field (9.4Tesla) fMRI signals were obtained during visual stimulation. Consecutively, high-resolution DTI scans were conducted. The MR parameters for functional scans were:64x64x64 matrix; FOV=5x5x4cm3, TE/image TR=12ms/1.5s. For DTI, a 3D Spin-EchoEPI sequence was used. The diffusion weighting parameters were: Diffusion time=16 msec, gradient duration=6 msec and gradient strength=17gauss/cm. At each session, 7 data sets were acquired with the gradients applied in 7 different combinations. From the DTI data, fiber tracking algorithms were used to reveal connectivity between activated sites as detected by standard fMRI analysis. The combined fMRI/DTI data may serve as constraints for modelling functional connectivity. A particular approach for estimating effective connectivity ("Granger causality") is described and the results of its application to a dynamic sensory-motor mapping paradigm are presented.

Using simulation modeling to determine the neural correlates of functional connectivity

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The issue of how to relate the concept of functional connectivity, as defined by the hemodynamic-based (HB) methods of PET, fMRI and optical imaging, to its neural substrate is discussed. HB functional connectivity is determined by evaluating the correlation in activity between two regions. What is obtained is information about how the HB activity in one region is related to that in other regions. However, functional connectivity is often discussed in terms of how neural activity in one area is related to neural activity in other areas, but to do this requires having some idea about the neurobiological substrate of our estimate of HB functional connectivity. A way to understand this relationship by means of a large-scale, neurobiologically realistic computational neural model with multiple interconnected brain regions that performs a delayed match-to-sample task is provided. The simulated electrical activities in each region of the model summed synaptic activities match HB activities obtained from human PET and fMRI studies. We demonstrate that the simulated HB functional connectivity between two regions in our model depends on both the strength of the anatomical connection between the two regions, and on the task being performed. We will discuss how simulation modeling can lead to greater clarity in understanding the ways in which measured functional/effective connectivity should be interpreted.

Some General References:

- Tagamets, M.-A. and Horwitz, B.: Integrating electrophysiological and anatomical experimental data to create a large-scale model that simulates a delayed match-to-sample human brain imaging study, Cerebral Cortex 8: 310-320, 1998.
- Horwitz, B., Tagamets, M.-A. and McIntosh, A.R.: Neural modeling, functional brain imaging and cognition, Trends in Cogn. Sci. 3: 91-98, 1999.
- Horwitz, B., Friston, K.J. and Taylor, J.G.: Neural modeling and functional brain imaging: An overview, Neural Networks 13: 829-846, 2000.

Studying connectivity with optical imaging

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Optical imaging of intrinsic signals is a functional brain imaging technique, which is based on activity related reflectance changes of nervous tissue in the visible light and near infrared range. A number of different signal sources contribute to the overall change in light reflectance, the most important ones being changes in the oxy-/deoxyhemoglobin ratio, changes in blood volume, and changes of the light scattering properties of active brain regions. Compared to other brain mapping methods optical imaging of intrinsic signals offers the possibility to map multiple stimulus representations in large regions of the brain with high spatial resolution.

In my talk I will present two experimental strategies, which we use to study the question of connectivity in the visual system with optical imaging. First, optical imaging can be employed to target retrograde or anterograde tracer injections to specific functional domains in order to study their in- and outputs. Employing this technique we could show that in cat visual cortex domains preferring different spatial frequencies receive inputs from distinct populations of input cells in the lateral geniculate nucleus, whose spatial frequency preferences match those of their target regions in the cortex. Thus, this specific response property of visual cortex cells is not generated within the cortex, but rather seems to be based on their thalamic input cells. Second, I will show some preliminary data on how optical imaging can be used to directly study functional connectivity in the cortex. The principle of the approach is straightforward: electrical stimulation of groups of neurons results in synaptic activation of the targets of these neurons, and this activation can be readily visualized with optical imaging. I will demonstrate the feasibility of this approach by showing that it can be used to map the long-range horizontal connections, which link domains of similar orientation preference in the visual cortex.

An investigation of functional and anatomical connectivity using MRI

Martin A. Koch
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In this talk I will describe an experiment that examines functional and anatomical connectivity in healthy human subjects measured with magnetic resonance imaging methods. An estimate of anatomical connectivity in white matter can be obtained from measurements of the diffusion tensor. We used a Monte-Carlo simulation to determine the probability that a virtual particle "diffuses" between two points, with the probability of a jump from a given voxel in a particular direction being based on the local value of the diffusion tensor components. This method may appropriately be termed "statistical fibre tracking".
Functional connectivity between grey matter pixels was assessed without recourse to a specific activation paradigm, by calculating the correlation coefficient between random fluctuations in the blood oxygenation level dependent (BOLD) signal time courses in different pixels. With these methods, we examined the anatomical and functional connectivities between crowns of adjacent gyri. High functional connectivity was found between grey matter pixels, with white matter displaying only very low correlation. A comparison of the measurements of anatomical and functional connectivity found that there is no simple correlation between these measures, except that low values of functional connectivity were not found together with high values of anatomical connectivity. In addition, pairs of regions situated around the central sulcus indicated a dependence of the two connectivity measures on each other. These results are in accordance with an interpretation that regions which are clearly directly linked by white matter fibre tracts should show high functional connectivity, but that the inverse need not be true as functional connectivity may also be indirectly mediated via more distant grey matter regions.

References:

- B.B. Biswal, F.Z. Yetkin, V.M. Haughton, J.S. Hyde: Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar MRI. Magn. Reson. Med. 34, 537 (1995)
- E.V. Golanov, S. Yamamoto, D.J. Reis: Spontaneous waves of cerebral blood flow associated with a pattern of electrocortical activity. Am. J. Physiol. 266, R204 (1994)
- M.A. Koch, D.G. Norris, M. Hund-Georgiadis: An investigation of functional and anatomical connectivity using magnetic resonance imaging. Neuroimage, in press.

Linking cognitive function and brain through neural context

A. Randy McIntosh
Rotman Research Institute - Baycrest, Univ of Toronto, Canada

Identifying the link between mental operations, as considered in cognitive psychology, and the biological operations of the brain has been a perpetual challenge for neuroscientists. There is a growing concensus that cognitive function arises from some combination of localized operations in specific brain areas and distributed interactions among several regions, although these two notions are often treated as mutually exclusive phenomena. What is not yet clear is how to combine these two notions to best describe how the brain translates biological operations into cognition. I will propose that such a translation may be best appreciated under the principle of Neural Context. Systems-level neuroanatomy shows that most parts of the brain receive projections from many areas and send to projections to many others. Neural context emphasizes that the precise pattern of functionally engaged structural connections defines the translation of brain operations into cognitive operations. Consequently, the same region may show identical levels of activity across many different tasks. Because the pattern of interactions with other connected areas differs, the resulting cognitive operations vary, but yet the same region is involved in each task. Stated differently, the neural context within which an area is active embodies the cognitive operation.

Background information for these ideas can be found at:
http://psych.utoronto.ca/~mcintosh/#Pub

Imaging and stimulating the human brain.

Tomáš Paus
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Transcranial magnetic stimulation (TMS) is a powerful tool allowing investigators to affect cortical activity in a non-invasive fashion. When combined with the concurrent measurement of brain activity, using electroencephalography (EEG) or positron emission tomography (PET), one is provided with an opportunity to investigate effective connectivity of the human cerebral cortex. In my presentation, I will talk about the motivations that led to the development of this approach and discuss a few methodological issues involved in setting up combined TMS/PET and TMS/EEG experiments.

- Paus T, Castro-Alamancos MA, Petrides M. Cortico-cortical connectivity of the human mid-dorsolateral frontal cortex and its modulation by repetitive transcranial magnetic stimulation. Eur J Neurosci. 2001 Oct;14(8):1405-11. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11703468&dopt=Abstract
- Paus T, Sipila PK, Strafella AP. Synchronization of neuronal activity in the human primary motor cortex by transcranial magnetic stimulation: an EEG study. J Neurophysiol. 2001 Oct;86(4):1983-90. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11703468&dopt=Abstract
- Paus T. Imaging the brain before, during, and after transcranial magnetic stimulation. Neuropsychologia. 1999 Feb;37(2):219-24. Review. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11703468&dopt=Abstract

Quantitative approaches to system identification in human epilepsies

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Nonlinear and multi-channel time series analysis methods find wide application in the study of human epilepsies. Many such approaches focus on prediction of the onset of seizures or aim to characterize topologically invariant aspects of electroencephalographic (EEG) time series. A parallel application aims to 'fingerprint' characteristic nonlinear temporal interactions generated by underlying neuronal circuits. The features extracted by this approach are not topological invariants, but nevertheless can help to uncover similar physiological mechanisms in human epilepsies. For example, similarities among the clinical features of complex partial temporal lobe seizures and absence (petit mal) seizures suggest shared underlying mechanisms, but dissimilar electrographic features of the two seizure types have cast doubt on common neuronal substrates. Using nonlinear autoregressive analysis, EEG time series from absence seizures reveal a consistent 'fingerprint' of nonlinear temporal interactions in 3/s discharges within and across patients that share features with time series from some complex partial seizures. In junction with a novel multi-channel data analysis method (hierarchical decomposition) these dynamical fingerprints can be further used to examine relationships among underlying generators of the spatio-temporal signal. Physiological interpretations available from these methods can be extended to develop and test hypotheses about mechanisms underlying seizure generation and impaired consciousness seen in both epilepsies. Insights gained from these studies of epilepsy may be applied to the search for underlying simplicities in the normal EEG related to control of on-line continuous behavior and awareness.

Mapping functional connectivity through optical stimulation

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Institutes of Neurophysiology, Anatomy and Brain Research, Heinrich-Heine-Universität, Düsseldorf, Germany

We combine morphological, electrophysiological and computational approaches to map the functional connectivity in slices of rat barrel cortex to specific columns, layers and cell types. Focal optical release of caged transmitters at hundreds of brain sites provides functional input maps for intra- and extracellularly recorded neurons and neuronal populations. While we find clear relations between dendritic morphology, firing patterns and input fields of individual cells, the functional input maps deviate from the known preferences of axonal connections. Strategies for unravelling relations between anatomical and functional connectivity will be discussed.

References:

- Kötter R., Staiger J.F., Zilles K., Luhmann H.J. (1998) Analyzing functional connectivity in brain slices by a combination of infrared videomicroscopy, flash photolysis of caged compounds, and scanning methods. Neuroscience 86: 265-277.
- Staiger J.F., Kötter R., Zilles K., Luhmann H.J. (2000). Laminar characteristics of functional connectivity in rat barrel cortex revealed by stimulation with caged glutamate. Neurosci. Res. 37: 49-58.
- Schubert D., Staiger J.F., Cho N., Kötter R., Zilles K., Luhmann H.J. (2001) Layer specific intra- and transcolumnar functional connectivity of layer V pyramidal cells in rat barrel cortex. J. Neurosci. 21: 3580-3592.
- http://www.hirn.uni-duesseldorf.de/rk/Cx/cx.htm

From neuroanatomy to functional brain connectivity - and back?

Olaf Sporns
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Neural systems exhibit characteristic patterns of temporal correlations that emerge as the result of functional interactions within a structural network. There is mounting evidence that specific patterns of neuronal activation as well as patterns of functional connectivity are possible neural correlates of perceptual and cognitive processes. Which functional connectivity patterns arise depends on the anatomical structure of the underlying network, which in turn is modified by a broad range of activity-dependent processes. Given this intricate relationship between structure and function, the question of how patterns of anatomical connectivity constrain or determine dynamical patterns is of considerable theoretical importance.

In my talk, I will discuss computational tools to analyze networks both in terms of their structural and functional connectivity. Using these tools, different classes of networks can be distinguished, including networks that are characterized by highly complex functional interactions. These highly complex networks have distinct structural characteristics such as clustered connectivity and short wiring length similar to those of large-scale networks of the cerebral cortex.

Independent component analysis: Principles and applications

Jim V. Stone,
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The principles underlying independent component analysis (ICA) and other blind source separation (BSS) methods will be described in simple geometric terms, and a brief overview of applications of ICA will be given.

Links:

- ICA demonstrations and MatLab code can be found on my web page: http://www.shef.ac.uk/~pc1jvs
- Other ICA links are given in the following paper, Stone JV, "Independent Component Analysis: An Introduction", Trends in Cognitive Sciences, 6(2), pp59-64, Feb 2002. which is available from: http://www.shef.ac.uk/~pc1jvs/papers_published.html.

Ground truth for functional connectivity measures

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Cerebral networks are complex sets of connections that resemble a ladder-like web of multiple parallel feedforward, lateral and feedback connections. This static anatomical description has been pivotal in guiding investigations of signal processing within these networks. However, measures on both magnitude and functional significance of connections are limited. Currently, estimates of functional connectivity are being derived from human fMRI experiments. However it remains an open question how such functional connectivity measures can be validated: i.e. what is the ground truth of such functional connectivity measurements. In the past, we compared the anatomic connectional strengths of a set of cerebral pathways emerging from middle level visual cortical areas (in the cat) with measures of the functional impact the same region has over distant sites. The functional impact of the connections was obtained by analyzing the local and distant effects of cortical cooling deactivation on 2-deoxyglucose uptake. Relative to major efferent projections from middle cortical areas that have a strong influence, projections to early visual processing stages have lower functional impact than predicted from the anatomy. For higher processing stages, the converse holds. The problem with these earlier measurements the functional impact of connections is the static nature from a deoxyglucose study: it integrates metabolic activity over an extended period of time (up to 30 minutes). This problem can be solved by combining our newly developed fMRI technique in awake monkeys with a reversible deactivation technique (cooling/pharmacologically). With the awake monkey fMRI technique we will be able to perform virtually identical imaging procedures in human and monkeys (this will be illustrated for 3D-structure-from motion processing). Therefore, this can be used to test 'classical' functional connectivity measurements in 'homologous' functional networks of humans and monkeys. The additional combination of reversible deactivations with awake monkey fMRI might become the ground truth to validate functional connectivity measurements in humans.

The contribution of postmortem studies to functional and diffusion tensor imaging

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It will be demonstrated that high resolution images of cyto-, myelo- and receptor-architecture and of long myelinated fiber tracts stained in serially sectioned, postmortem human brains provide novel insight into the organization of the cerebral cortex. Additionally, such data can be used for the evaluation of structural and functional imaging results as provided by PET and MRT (including DTI). This is possible, since three-dimensionally registered (using structural MRT) human brains provide a common visualization platform on which the data from different sources can be coregistered. Non-linear transformation procedures were developed to allow the integration of data from greatly differing levels of spatial resolution. The results indicate that architectonical, neurochemical and neuroimaging aspects of the cortex are associated and reveal underlying organizational principles of brain maps.