Helsinki University of Technology
Department of Biomedical Engineering and Computational Science Publications
Teknillisen korkeakoulun Lääketieteellisen tekniikan ja laskennallisen tieteen laitoksen julkaisuja
April, 2010 REPORT A16

DYNAMIC CORRELATIONS IN ONGOING NEURONAL OSCILLATIONS IN HUMANS — PERSPECTIVES ON BRAIN FUNCTION AND ITS DISORDERS

Simo Monto

Doctoral dissertation for the degree of Doctor of Science in Technology to be presented with due permission of the Faculty of Information and Natural Sciences for public examination and debate in Auditorium B at the Aalto University School of Science and Technology (Espoo, Finland) on the 29th of April, 2010, at 12 o'clock noon.

Aalto University
School of Science and Technology
Faculty of Information and Natural Sciences
Department of Biomedical Engineering and Computational Science

Aalto-yliopisto
Teknillinen korkeakoulu
Informaatio- ja luonnontieteiden tiedekunta
Lääketieteellisen tekniikan ja laskennallisen tieteen laitos

Distribution:
Aalto University
School of Science and Technology
Department of Biomedical Engineering and Computational Science
P.O. Box 12200
00076 AALTO
FINLAND

Tel. +358 9 470 23172
Fax +358 9 470 23182
http://www.becs.tkk.fi/en/

E-mail: simo.monto@gmail.com

ISBN 978-952-60-3114-9
ISBN 978-952-60-3115-6 (PDF)
ISSN 1797-3996
URL: http://lib.tkk.fi/Diss/2010/isbn9789526031156/

Picaset Oy
Helsinki 2010

Aalto University

ABSTRACT OF DOCTORAL DISSERTATION	AALTO UNIVERSITY SCHOOL OF SCIENCE AND TECHNOLOGY P.O. BOX 11000, FI-00076 AALTO http://www.aalto.fi

Author Simo Petteri Monto

Name of the dissertation

Dynamic correlations in ongoing neuronal oscillations in humans – perspectives on brain function and its disorders

Manuscript submitted 2009-11-24	Manuscript revised 2010-04-10

Date of the defence 2010-04-29

☐ Monograph ☒ Article dissertation (summary + original articles)

Faculty	Faculty of Information and Natural Sciences
Department	Department of Biomedical Engineering and Computational Science
Field of research	biomedical engineering, brain research
Opponent	Professor Dante Chialvo
Supervisor	Professor Risto Ilmoniemi
Instructors	Professor Juha Voipio, docent J. Matias Palva

Abstract

This Thesis is involved with neuronal oscillations in the human brain and their coordination across time, space and frequency. The aim of the Thesis was to quantify correlations in neuronal oscillations over these dimensions, and to elucidate their significance in cognitive processing and brain disorders.

Magnetoencephalographic (MEG) recordings of major depression patients revealed that long-range temporal correlations (LRTC) were decreased, compared to control subjects, in the 5 Hz oscillations in a manner that was dependent on the degree of the disorder. While studying epileptic patients, on the other hand, it was found that the LRTC in neuronal oscillations recorded intracranially with electroencephalography (EEG) were strengthened in the seizure initiation region.

A novel approach to map spatial correlations between cortical regions was developed. The method is based on parcellating the cortex to patches and estimating phase synchrony between all patches. Mapping synchrony from inverse-modelled MEG / EEG data revealed wide-spread phase synchronization during a visual working memory task. Furthermore, the network architectures of task-related synchrony were found to be segregated over frequency.

Cross-frequency interactions were investigated with analyses of nested brain activity in data recorded with full-bandwidth EEG during a somatosensory detection task. According to these data, the phase of ongoing infra-slow fluctuations (ISF), which were discovered in the frequency band of 0.01-0.1 Hz, was correlated with the amplitude of faster > 1 Hz neuronal oscillations. Strikingly, the behavioral detection performance displayed similar dependency on the ISFs as the > 1 Hz neuronal oscillations.

The studies composing this Thesis showed that correlations in neuronal oscillations are functionally related to brain disorders and cognitive processing. Such correlations are suggested to reveal the coordination of neuronal oscillations across time, space and frequency. The results contribute to system-level understanding of brain function.

Keywords magnetoencephalography, electroencephalography, human brain, neuronal oscillations, epilepsy, cognition

ISBN (printed) 978-952-60-3114-9	ISSN (printed) 1797-3996
ISBN (pdf) 978-952-60-3115-6	ISSN (pdf)
Language English	Number of pages 86 + 84 in appendices

Publisher: Aalto University School of Science and Technology, Dept. of Biomedical Engineering and Computational Science

Print distribution Aalto University, Department of Biomedical Engineering and Computational Science

☒ The dissertation can be read at http://lib.tkk.fi/Diss/2010/isbn9789526031156/

Aalto-yliopisto

VÄITÖSKIRJAN TIIVISTELMÄ	AALTO-YLIOPISTO TEKNILLINEN KORKEAKOULU PL 11000, 00076 AALTO http://www.aalto.fi
Tekijä Simo Petteri Monto	
Väitöskirjan nimi Dynamic correlations in ongoing neuronal oscillations in humans – perspectives on brain function and its disorders	
Käsikirjoituksen päivämäärä 24. 11. 2009	Korjatun käsikirjoituksen päivämäärä 10. 4. 2010
Väitöstilaisuuden ajankohta 29. 4. 2010	
☐ Monografia	☒ Yhdistelmäväitöskirja (yhteenveto + erillisartikkelit)
Tiedekunta Informaatio- ja luonnontieteiden tiedekunta Laitos Lääketieteellisen tekniikan ja laskennallisen tieteen laitos Tutkimusala lääketieteellinen tekniikka, aivotutkimus Vastaväittäjä Professori Dante Chialvo Työn valvoja Professori Risto Ilmoniemi Työn ohjaajat Professori Juha Voipio, dosentti J. Matias Palva	

Tiivistelmä

Tämän väitöskirjan tavoitteena oli tutkia ihmisaivojen tuottamaa paikallista rytmistä toimintaa, erityisesti sen vaillinaisesti tunnettuja tilastollisia riippuvuuksia yli ajan, paikan ja taajuuden. Näitä riippuvuussuhteita sekä niiden vaikutusta aivojen tiedonkäsittelyyn ja toiminnallisiin häiriöihin tutkittiin terveillä koehenkilöillä sekä masennusta tai epilepsiaa sairastavilla potilailla. Sähköistä aivotoimintaa kuvannettiin monikanavaisella aivosähkökäyrällä (elektroenkefalografia, EEG) sekä sen magneettikenttiä luotaavalla vastineella, magnetoenkefalografialla (MEG).

Epilepsiapotilaiden kallonsisäisistä EEG-mittauksista löydettiin pitkäkestoisia ajallisia korrelaatiota, jotka olivat suurentuneita kohtaukset synnyttävän aivoalueen läheisyydessä. Masennuspotilaiden MEG:lla kuvannetun aivotoiminnan puolestaan havaittiin olevan huomattavasti heikommin korreloitunutta ajan yli kuin terveiden koehenkilöiden, ja lisäksi eron verrokkeihin todettiin kasvavan suhteessa masennuksen vakavuusasteeseen. Väitöskirjassa kehitettiin myös uusi lähestymistapa aivojen toiminnallisten yhteyksien kartoittamiseen tutkimalla rytmisen toiminnan vaihekorrelaatioita eri aivoalueiden välillä. Menetelmää sovellettiin tutkittaessa näkömuistitehtävää suorittavia koehenkilöitä MEG:lla ja EEG:lla, jolloin havaittiin rytmisen toiminnan tahdistuvan useiden eri aivoalueiden välillä. Lisäksi huomattiin, että tahdistumisen synnyttämien aivoalueverkkojen ominaisuudet riippuivat tahdistumisen taajuudesta. Väitöskirjassa tehtiin merkittävä löytö myös tutkitttaessa erittäin hitaita, yli kymmenen sekunnin kestoisia aivoaaltoja heikkojen tuntoärsykkeiden havaitsemistehtävän aikana: havaitsemistodennäköisyyden huomattiin kasvavan aaltojen nousuvaiheessa ja pienenevän laskuvaiheessa. Aivotoiminnan nopeammat taajuudet olivat tällöin riippuvaisia hitaista aalloista samalla tavalla kuin koehenkilöiden havaitsemiskyky.

Väitöskirjatyö osoittaa, että hermosoluverkkojen rytmisestä toiminnasta löydetyt korrelaatiot liittyvät sekä aivojen tiedonkäsittelyyn että aivotoimintaan liittyviin häiriöihin, ja että ne voivat paljastaa uusia näkökulmia näiden asioiden tutkimiseen. Löydöt auttavat tutkimaan ja ymmärtämään niitä moniulotteisia ilmiöitä, jotka nousevat esiin tarkasteltaessa rytmistä toimintaa koko aivojen mittakaavassa.

Asiasanat	magnetoenkefalografia, elektroenkefalografia, ihmisaivot, hermostolliset oskillaatiot, epilepsia, kognitio		
ISBN (painettu)	978-952-60-3114-9	ISSN (painettu)	1797-3996
ISBN (pdf)	978-952-60-3115-6	ISSN (pdf)	
Kieli	englanti	Sivumäärä	86 + liitteissä 84

Julkaisija: Aalto-yliopiston teknillinen korkeakoulu, Lääketieteellisen tekniikan ja laskennallisen tieteen laitos

Painetun väitöskirjan jakelu Aalto-yliopisto, Lääketieteellisen tekniikan ja laskennallisen tieteen laitos

☒ Luettavissa verkossa osoitteessa http://lib.tkk.fi/Diss/2010/isbn9789526031156/

Academic Dissertation

Dynamic Correlations in Ongoing Neuronal Oscillations in Humans — Perspectives on Brain Function and Its Disorders

Author

Simo Monto
Neuroscience Center
University of Helsinki;
BioMag Laboratory
Helsinki University Central Hospital, Finland

Supervisor

Professor Risto Ilmoniemi
Department of Biomedical Engineering
and Computational Science
Aalto University, School of Science and Technology, Finland

Instructors

Professor Juha Voipio
Department of Biosciences
University of Helsinki, Finland

Docent J. Matias Palva
Neuroscience Center
University of Helsinki, Finland

Reviewers

Dr. Vadim Nikulin
Department of Neurology and Clinical Neurophysiology
Charité - University Medicine Berlin, Germany

Docent Jan Wikgren
Department of Psychology
University of Jyväskylä, Finland

Opponent

Professor Dante Chialvo
Department of Physiology, Feinberg School of Medicine
Northwestern University, Chicago, U.S.A.

Contents

ACKNOWLEDGEMENTS **ix**

LIST OF PUBLICATIONS **xi**

LIST OF ABBREVIATIONS **xii**

INTRODUCTION **1**

BACKGROUND **3**

NEURONAL OSCILLATIONS 3
STRUCTURE OF NEURONAL NETWORKS 7
DYNAMICAL SYSTEMS THEORY 11

EXPERIMENTAL STUDIES **15**

EXPERIMENTS 15
DATA ACQUISITION 18
DATA PROCESSING 20
MAIN RESULTS 25

DISCUSSION **31**

VIEWS ON BRAIN MECHANISMS OF COGNITION 31
CLINICAL PROSPECTS OF NEURONAL OSCILLATIONS 33
METHODOLOGICAL CONSIDERATIONS 36
OSCILLATORY CORRELATIONS AND ORGANIZATION OF BEHAVIOR 40
ON STRUCTURE–FUNCTION RELATIONSHIPS 42
SYSTEMS VIEW ON NEURONAL CORRELATIONS 46
SUMMARY AND CONCLUSIONS 52

REFERENCES **55**

Acknowledgements

This work was carried out in the BioMag Laboratory and in the Neuroscience Center of the University of Helsinki. I'm grateful to Risto Ilmoniemi for first welcoming me to BioMag and then supervising my work, jointly with Toivo Katila. Risto's uncompromising attitude and resourcefulness have had a great impact on me. My instructor and closest collaborator J. Matias Palva must be accredited with initiating this Thesis project and, above all, helping finish it. His all-embracing but detail-minded approach to science together with the enthusiasm in sharing it make him an indispensable tutor. I'm also thankful to my other instructor Juha Voipio for bringing his scientific expertise to my work and for initiating me to the foundations of neuroscience. His helpfulness in the early stages of this project initially made it possible. My thanks also go to the preliminary reviewers, Vadim Nikulin and Jan Wikgren, for their kind comments on my work, and to Christopher Bailey for the quick and thoughtful proofreading and for the many years of (e-)friendship.

My co-authors have naturally played an important role in completing my studies. I was lucky to learn from Klaus Linkenkaer-Hansen in the beginning of my research career. Klaus was always ready to share his views and time, and patiently instructed me in the very basics of making science. From Seppo Kähkönen I learned a lot about psychiatry and psychoactive substances, but in particular about music, food, distant corners of the world and other as important things. Sampsa Vanhatalo guided me to the wonderful world of intracranial and direct current EEG studies and to the sometimes deviant ways clinical doctors think of brain research. He was also heavily involved in reviewing and soliciting the numerous grant applications that kept this project alive. Yet, I want to thank Satu Palva for sharing her knowledge of the cognitive side of neuroscience and amusing me with her critical summaries of the numerous papers she keeps on reading. And even more than about scientific life, I have enjoyed our discussions about the complexities of combining family life to it.

It has always been a pleasure to work in the BioMag Laboratory. I thank the current staff, Jyrki Mäkelä, Juha Montonen, Suvi Heikkilä and Pirjo Kari for making it easy for us researchers. The considerable cross-subject variability among research fellows has made the lab a great place to see brain research from different perspectives. I have cheerful memories from the various social events and plain ordinary working days, not to forget the B-class lunch discussions, with you all. To mention but a few, I'm grateful to my long-standing room mates, Ville Mäkinen, Juha Heiskala, Jussi Nurminen and Ville Mäntynen for their funny, inspiring, refreshing and often extremely warming presence. I also thank Elina Pihko, Leena Lauronen, Päivi Nevalainen, Pantelis Lioumis, Dubravko Kicic and Katja Airaksinen for their company both in the lab and outside of it. In the Neuroscience Center, I've received valuable assistance from the can-do guys in our group, Tomi Maila, Shrikanth Kulashekhar and Santeri Rouhinen.

Grants from several private institutions have made it possible for me to work on this project and still continue a relatively normal life. I am grateful to the Jenny and Antti Wihuri Foundation, the KAUTE Foundation, the Emil Aaltonen Foundation, the Instrumentarium Science Foundation, the Finnish Foundation for Technology Promotion, the Orion-Farmos Research Foundation, the University of Helsinki Research Funds, and Biomedicum Helsinki for generous financial support.

I want to sincerely thank my parents Helena and Tapio for always giving me what I needed and for never putting my choices in life under question. I'm as thankful to my sister Hanna for always encouraging me and showing the importance of hard work in becoming really good.

Finally, few words can express my gratitude to Elina for her love and support, even at the times it was unclear when, how and if this project was going to end, and my dear sons Nuutti and Kaapo for just existing. Rakastan teitä.

At home, April 13th, 2010

Simo

List of Publications

This Thesis is based on the following five publications, which are referred to in the text by the Roman numerals I – V.

I Linkenkaer-Hansen K, Monto S, Rytsälä H, Suominen K, Isometsä E, Kähkönen S (2005) Breakdown of long-range temporal correlations in theta oscillations in patients with major depressive disorder, *Journal of Neuroscience* 25(44):10131–10137

II Monto S, Vanhatalo S, Holmes MD, Palva JM (2007) Epileptogenic neocortical networks are revealed by abnormal temporal dynamics in seizure-free subdural EEG, *Cerebral Cortex* 17(6):1386–1393

III Monto S, Palva S, Voipio J, Palva JM (2008) Very slow EEG fluctuations predict the dynamics of stimulus detection and oscillation amplitudes in humans, *Journal of Neuroscience* 28(33):8268–8272

IV Monto S, Palva S, Kulashekhar S, Palva JM. Mapping brain-wide neuronal interactions with MEG / EEG recordings using cortical parcellations, *Department of Biomedical Engineering and Computational Science Publications, Report A14*, 30 pages

V Palva S, Monto S, Palva JM (2010) Graph properties of synchronized cortical networks during visual working memory maintenance, *NeuroImage* 49(4):3257–3268

Author's Contribution

All the studies included in this Thesis were results of group effort. Below, the contributions of the author of this Thesis in each Study are delineated.

In Study I, the candidate performed the initial data analysis, contributed methods, and wrote the manuscript together with the first author. The candidate initiated Study II together with the second author, performed the data analysis, and wrote the manuscript. In Study III, the author performed the measurements and data analysis, and wrote the manuscript together with the co-authors. In Study IV, he developed the methods and implemented them together with the co-authors, and wrote the manuscript. For Study V, the author contributed methods and participated in writing the manuscript.

List of Abbreviations

BOLD	blood oxygenation level dependent
CBF	cerebral blood flow
DFA	detrended fluctuation analysis
ECoG	electrocorticography
(Fb)EEG	(full-band) electroencephalography
(f)MRI	(functional) magnetic resonance imaging
ICA	independent component analysis
ISF	infra-slow fluctuation
LFP	local field potential
LRTC	long-range temporal correlations
MEG	magnetoencephalography
MNE	minimum-norm estimate
PLV	phase-locking value
PSD	power spectral density
ROI	region of interest
SOC	self-organized critical(ity)
VWM	visual working memory

Introduction

A commonly acknowledged paradox in brain research exists between how much we know and how little we understand. Although we strive for increasingly detailed information on neuronal structure and function, the lack of integrated understanding accentuates the need for studies that inspect the brain as a systemic whole. For the researcher, the shift from reduction to synthesis requires not only a change in mentality, but also the development of new tools and concepts. By using various experimental approaches and scales of inspection we may gradually approach a system-level model of brain function. This model should be rooted in the low-level neurobiological facts and yet explain the higher-level observations of emerging behavior. A natural requirement for such a model is that it be founded in a modern understanding of physics. The methods of statistical physics, in particular, are suitable for treating and understanding the behavior of systems composed of large numbers of elements – in this case, neuronal cells. The data analyses applied in this Thesis are to a large extent influenced by methods in statistical physics.

Whereas the basic structural unit of the brain is the neuron, the basic unit of information transmission is an action potential, which is elicited in the cell and transmitted to other cells through synapses. And, as the cells do not live in solitude but are locally knit into densely interwoven cell groups by the synaptic connections, the cells also have inherent group dynamics: they commonly fire rhythmically in unison, giving rise to local neuronal oscillations. Oscillations seem to be related to an evolutionarily conserved computational implementation of information processing in neuronal networks [1]. While we do not yet have a full account of the merits of this implementation compared to other possibilities, we have some neurophysiological understanding of how activity in single neurons and population oscillations are interlinked. The main target of study in this Thesis are the ongoing neuronal oscillations, which are recorded using electrophysiological methods.

Localized oscillatory activity is dispersed over the spatial, temporal and spectral dimensions. However, our experience and behavior is unified, so distributed processing must be somehow brought together across these dimensions. Non-random relationships in network oscillations can be estimated from electrophysiological data to reveal multi-dimensional neuronal integration. Tight integration is also suggested by the short synaptic distances between neurons in the human cerebral cortex: all of the roughly 10^{10} neurons are estimated to be interconnected through as few as 6 synapses [1]. This surprisingly short distance becomes understandable in the light of recent findings in graph theory, which has been developed to investigate properties of large networks [2]. Co-operation between brain regions is thought to be central for brain function, and graph theory is well suited to study the networks of inter-regional connections. Neuronal connections are in the first place structural, but on this structure resides a fluctuating pattern of functional connections supporting our everchanging perception and actions. This Thesis advocates the interaction-centered view of brain activity and contributes to methods that can be used in studying them.

A complementary view on correlations between spatially separated brain regions is offered by the theory of self-organized criticality (SOC), which was originally conceived in physics as a general mechanism to explain a wide array of phenomena that operate without a specific spatial

or temporal scale [4]. The proposed generative principles of the SOC state fit well to elementary models of neuronal networks, as both are composed of large arrays of interacting threshold-activated elements. SOC offers a convenient solution to the old debate on the choice of the correct scale of inspection to study brain function by suggesting that no scale of inspection is more informative than the others. What is more, criticality predicts that extended spatial and temporal correlations are present in the self-organized dynamics. Hence, not only the spatial correlations already considered above, but also correlations over time in neuronal activity should be investigated. While the presence of SOC in neuronal systems has already been demonstrated *in vivo* and *in vitro*, we largely lack the understanding of the functional consequences of considering the brain as SOC. In this Thesis, we shed light on this issue by contrasting analyses motivated by SOC with behavioral changes during cognitive experiments and, on the other hand, with data from brain disorder patients.

This Thesis is involved with the estimation of correlations in neuronal oscillations across the dimensions of time, space and frequency [1]. Neuronal oscillations are recorded using magnetoencephalography (MEG) and electroencephalography (EEG). In the individual studies of this Thesis, I, together with the co-authors, quantify long-range temporal correlations (LRTC) to develop a biomarker that could have diagnostic potential as a neuronal correlate of affective disorders (Study I). In addition, we apply LRTC in patient recordings to locate the epileptogenic region, aiming at therapeutic advances in surgical treatment of epilepsy (Study II). Very slow brain activity, recorded with the emerging method of full-band electroencephalography (FbEEG) in the frequency band starting from 0.01 Hz, is investigated to study the role of infra-slow brain activity, which is here taken as brain activity in frequencies < 0.2 Hz, during a somatosensory stimulus detection task (Study III). To study ongoing oscillations across the spectral dimension, we investigate cross-frequency nested relations between infra-slow activity and higher-frequency neuronal oscillations, as well as correlations between infra-slow activity and behavioral performance. By studying spatial correlations we aim at revealing how neuronal oscillations may enable brain-wide information processing. We quantify spatial correlations using phase synchrony, *i.e.*, correlation among the phases of oscillations [3]. We develop an approach to assess oscillatory phase synchrony in the extent of the whole cerebral cortex (Study IV). Then, we use the novel approach to assess the topology to which the synchronous networks self-organize during visual working memory (Study V). Taken together, I search for spatial, temporal and spectral correlations that reveal organization of oscillatory neuronal activity. I hypothesize that these dependencies define system-wide neuronal states that characterize behavior in normal subjects and pathological brain activity in patients with brain disorders.

In this summary part of the Thesis, a literature overview of the central neurobiological and systems-level concepts are first presented. Emphasis is put on the generation and significance of neuronal network oscillations in the complex structural networks of the brain. The working hypotheses for the individual studies, their experimental setups and the methods applied in data acquisition and analysis are covered next, followed by the main results from each Study. The significance of the results are then discussed in detail along with aspects of the experimental approaches. Finally, prospects based on these studies and other developments in the field are integrated to consider future studies of normal cognition and neuronal disorders in the context of the Thesis.

Background

Neuronal oscillations

The main interest in this Thesis are the seemingly ubiquitous neuronal oscillations [5]. As noted by Caton already in 1875, high-amplitude rhythmic activity is immediately visible when a mammalian brain is coupled to a device recording electric signals. Because the oscillations are prominent and easily measurable, they have been studied widely ever since their discovery. An important early observation, made by Hans Berger, was that closing the eyelids causes an increase in the amplitude of the oscillations in the 10 Hz frequency band [6]. Later, it was learnt that alterations in EEG patterns in patients corresponded to various clinically relevant changes in the patients' state. These findings opened up the intriguing possibility of studying the basis of human mental functions and behavior by measuring the rhythmic electric activity emanating from the brain.

Oscillations from coordinated population activity

To study neuronal oscillations on the macroscopic level, it is useful to have an idea of the cellular level activities underlying this signal. After all, the elementary processes of brain function take place in individual cells and the synapses connecting them. It is known that the firing of action potentials, the primary means of communication between neurons, can be rhythmic even in single neuronal cells. Cells that fire rapid bursts of spikes at a relatively constant frequency are considered to be central to rhythm generation in populations of cells [7]. Furthermore, single cells often have a characteristic resonance frequency, which might have an impact on their responsiveness to external stimuli or on their capability to participate in rhythmic network activities [8–10].

The currently imperfectly understood relationship between neuronal activity and information processing is often referred to as the neuronal code. Two views have dominated the discussion on information coding in the spike trains of neurons. Conventionally, cells were thought to increase their firing rate when they are transmitting information [11, 12]. A more contemporary view states that the timing of the spikes is also of high importance, and especially the timing in relation to spikes in other neurons [11, 13, 14]. The relative importance or generality of these two coding strategies is not completely understood. However, an interesting series of experiments with odor recognition in insects showed that interfering with the population coding by altering the simultaneity between neuronal spiking activities impaired odor recognition [15]. Moreover, the information content that can be encoded by a neuronal population is increased when temporal relations between the spikes of cells are taken into account [16, 17].

The population coding scheme is also interesting when considering oscillatory activity. If a neuronal group spiking in unison does so at regular intervals, we will observe oscillatory

activity at the population level. Indeed, it is known that the response to a stimulus representation often involves repetitive volleys of spikes [18–20]. In addition, the correlations among responding cells are evident in average measures of larger scale neuronal activity. By averaging over multiple single spikes, they have been found to be associated with similar time courses of the local field potential, which is recorded extracellularly and reflects the summed currents from close-by neurons [21]. Moreover, repeating spatial patterns of neuronal correlations have been observed with voltage-dependent cortical imaging [22]. Finally, an interesting connection between neuronal oscillations and the spike coding scheme has been found, where the phase of a spike relative to an ongoing oscillation conveys information [23–25].

The strongly correlated nature of neuronal activity evident in population coding and neuronal oscillations seems to be at odds with the understanding from information theory, according to which it is entropy, not correlatedness, that conveys the maximum amount of information [26]. However, neuronal systems are strongly based on transmission of information that takes place through neuronal interactions. The importance of correlations is reflected in the fact that maximally entropic, or random, neuronal activity has little effect on the target neurons, compared to the effect of spatially and temporally correlated activity. The two different coding schemes correspond to established mechanisms in neurons that are in the receiving end of neuronal communication. Neurons that are sensitive to the rate code are conceptualized as integrate-and-fire neurons, which sum their input over time until the firing threshold is exceeded [27, 28]. On the other hand, neurons sensitive to the simultaneity of spikes from a population of broadcasting neurons function as coincidende detectors [29]. The current view on the importance of population coding is that neurons are sensitive to specific spatio-temporal patterns of input, enabling considerable sparsening of neuronal activity and consequential expansion of the coding space [13, 20, 30].

Thus, timing of spikes and their mutual correlations seem to play an important role in neuronal processing and generation of oscillatory activity. At higher levels of neuronal organization, more macroscopic rhythmic activity takes place in neuronal networks. Theoretically, such network oscillations promote neuronal synchrony between the oscillatory populations and provide time frames for neuronal communication [31]. The prevalent view on the generation of network oscillations is that they emerge as a result from the interactions between inhibitory and excitatory cells of the network, instead of central rhythm generators [32, 33]. Then, the population of principal neurons, *i.e.*, large pyramidal neurons, recovers simultaneously from the refractory period caused by the inhibitory influence of synchronized pre-synaptic interneurons [32–35]. Interneuronal activity might give rise to several distinct oscillatory networks, dictated by their network structures and interneuronal subtypes [36–38]. However, also excitatory principal neurons can work as pacemakers in neuronal networks [32, 39]. These active network-level rhythm-generation mechanisms in the two most abundant neuronal cells of the neocortex, pyramidal neurons and interneurons, further suggest a central position for oscillations in neuronal computations. These local oscillations arising at the network level are the main subject of this Thesis.

Putative significance of oscillations in neuronal information processing

Despite the fact that oscillations are observed in the brain, as reviewed above, does not attach them any role in neuronal information processing or mean that they are functionally significant. In a complex dynamical system such as the brain oscillations may simply emerge as an irrelevant side effect, and in several engineering applications like control theory they are a sign of non-functional dynamical regime. However, it was recently discovered that rhythmic activity in the specific frequency band of 30–80 Hz, the so-called gamma oscillations, directly enhances the flow of information in the cortex [40]. This finding complements earlier reports of gamma oscillations as a network response to stimuli that are optimal at evoking activity in a local population of neurons [19]. The period length in this frequency band fits the time scales of pyramidal cell membrane relaxation and synaptic plasticity, and can therefore be considered a natural frequency of cortical networks.

In human studies, the amplitudes of oscillations at various frequencies recorded with EEG, MEG and intracranial EEG, in several locations, have been found to be affected by stimulus properties and concurrent tasks [41]. Generally speaking, gamma oscillations are correlated with perception of sensory stimuli and attended stimulus processing [42–46]. Activity in other frequency bands is related to many other functions, such as the link of 4–8 Hz theta and 8–13 Hz alpha oscillations to working memory [47, 48]. Although oscillations are consistently related to neuronal processing, it is sometimes difficult to assess the exact correlates of oscillations, as they sometimes react differently to the same stimulus under even subtly different task conditions [49]. More evidence for a functional significance of rhythmic activity comes from altered oscillatory profiles in several types of pathophysiological cases [50, 51].

In the preceding discussion, it was argued that cortical activity is largely characterized by oscillations. Are oscillations the only type of network response elicited by external stimuli, or are there other mechanisms that code for stimulus properties as well? By averaging recorded activity over several epochs with respect to a stimulus onset, a stereotypic wide-band response is typically observed at latencies of ~ 20 – 300 ms [52]. However, if the results from averaging are inspected in the frequency domain, rather than the time domain, a complementary picture emerges. Oscillatory amplitudes react to sensory stimulation, but the latency is often increased and is incompatible with fast stimulus recognition that is observed behaviorally [53, 54]. Conversely, the phases of the oscillations are partially reset by stimulus presentation, suggesting that the stereotypic wide-band evoked responses are affected by overlapping oscillatory responses and the resetting of their phases [55–57]. Another mechanism that affects stimulus-evoked responses has also been proposed, where the asymmetry of oscillatory activity with regard to the long-term signal average generates the responses as baseline shifts related to the oscillatory amplitude modulation [58].

Correlations in oscillatory activity

In the preceding review, the mechanisms and significance of correlations in the activity of local neuronal populations were reviewed. However, as neurons are coupled synaptically over significant distances, their activities could also become coupled at a long range, via one or

consecutive synaptic connections [59]. Indeed, measurements of visual evoked activity in cats revealed that two oscillatory neuronal groups can become synchronized across hemispheres via a cortico-cortical connection through the *corpus callosum* [60]. This happens specifically if the visual information suggests that the stimuli the two regions in opposite hemispheres are responding to are related. Thus, two oscillatory neuronal populations can be long-range synchronized to signal their relatedness, a general property of neural systems predicted by the correlation hypothesis [61]. On the other hand, apparent synchrony without a functional role can be generated simply by common afferent signals or overlap in receptive fields [13]. Apart from cortical mechanisms, another strong candidate to mediate cross-region synchrony are cortico-thalamic interactions [59, 62–64]. Note that there are commonly ambiguities in the terminology with respect to local and long-range synchronization, or oscillatory synchrony and synchronous oscillations [13]. In the framework of this Thesis, we refer to an oscillation when the oscillating neuronal population that is seen with the data acquisition method is spatially continuous, and to synchrony only when the oscillatory populations are spatially distinct so that two distinct oscillatory networks can be seen with the recordings. Thus, these definitions may be affected by the applied data acquisition and processing methods.

In addition to signaling relatedness of two objects or features that are present simultaneously, it is conceivable that relatedness should also be bound across time. For instance, short-term memory, goal-directed behavior, or complex motor activities require integrating neuronal information across time, giving rise to a binding problem not unlike that debated in cognitive neuroscience for decades [65]. In short, brain activity should be organized by correlations over time just as it is hypothesized to be organized by oscillations and synchrony over space. To clarify this dichotomy, the latter one will be referred to as spatial correlations, and integration or coordination over the time dimension will be called temporal correlations.

Data lending functional relevance to correlations between two spatially separated regions include behaviorally modulated zero-time lag correlations between motor and parietal cortex during coordination and a visual discrimination task, as well as attention induced synchrony between areas along the visual processing hierarchy [21, 66–68]. In humans, synchrony between EEG electrode signals has been found to correlate with perception and associative learning [69, 70]. Abnormalities in spatial correlation structure have been linked to several cognitive dysfunctions and brain disorders [71].

Experimental data on correlations extending across time in signals that were recorded in single brain regions are more scarse and indecisive than the data on correlations over the spatial dimension. However, synaptic strength is known to be modulated across time in an activity-dependent manner, which gives rise to dependency on past activity [72]. This kind of plasticity is evident in memory traces imprinted in synaptic networks by preceding activity, which in turn affects the responses to upcoming stimuli and can thus be considered as a form of short-term memory [73]. Strikingly, neuronal activity patterns can be repeated even after minutes with precision in the range of milliseconds, either after stimulation or without associated stimulation [74–76]. This can be interpreted physiologically as memory formation or network consolidation. From an information processing point of view, on the other hand, the interpretation is that network phenomena can be highly repeatable and reliable even when phenomena in individual neurons are not. In search of more straightforward interactions across time, certain neurons in the prefrontal cortex were found to correlate with either past or future performance, but not with

current task performance [77]. These findings show that brain activity is coordinated, or non-randomly fluctuating, over substantial time lags. Neuronal oscillations themselves clearly have strong correlations over time, but not much information may be gathered by inspecting similar oscillation periods over time. Instead, the presence of temporal correlations in amplitude of neuronal oscillations was recently assessed explicitly in the human brain with MEG and EEG recordings. It was found that oscillations display robust long-range temporal correlations lasting up to 300 seconds or more [78]. Thus, we may conclude that neuronal oscillatory activity shows correlations both across space and across time. Moreover, the presence and strength of such correlations may be resolved to allow experimental testing of their functional relevance.

Intrinsic neuronal activity – noise or signal?

The existence of spontaneous, *i.e.*, non-stimulus related, neuronal activity is well established, but its features that are significant for cognitive processing are still largely unclear. This intrinsically generated activity reflects changes in the subject's state, such as from active to resting awake state, transitions between different sleep stages and closing the eyes [6, 79, 80]. It was also found that the variability in neuronal responses can be explained by the variability in spontaneous background activity in single cells and at the neuronal network level [81, 82]. For these reasons, spontaneous activity is understood as more than background noise. Rather, the momentary state of the whole neuronal system needs to be taken into account when determining how the networks are engaged by sensory input and how information is processed and transferred [83].

It is thus established that spontaneous activity reflects intrinsically generated changes in a subject's state and is decisive on how information about upcoming external events are processed and interpreted. In this sense, the ongoing activity clearly forms the context of sensory processing, independent of whether this context is attributable to internal or external origins. Interestingly, it was recently discovered that spontaneously emerging activation states of neuronal networks might be similar to neuronal representations of actual objects in the external world [84]. Yet, the central question of exactly which features of ongoing activity determine the outcome from processing of inbound information stands unresolved. It has been suggested that neuronal oscillations and interactions between them play an essential role in the dynamical regulation of information flow and neuronal processing [13, 31, 85–88]. Studying spontaneous activity as an ongoing brain state is becoming increasingly important at the time when the focus of mainstream brain research is shifting away from the simplistic input-output machine view towards studies of an adaptive, creative and predictive subject. Based on these views and the importance of neuronal interactions in brain function, a prediction arises that the global anatomical connectivity that mediates long-range synchrony between oscillatory networks and the mechanisms regulating these oscillations are essential for the proper operation of the brain.

Structure of neuronal networks

Let us turn the focus from the origins and significance of neuronal oscillations to the underlying anatomical substrate that these phenomena rely on. Neocortical neuronal networks consist of

dozens of different cell types and synapses that densely interconnect them. From these simple building blocks, more and more complex structures develop during evolution, ontogenesis and activity-dependent rewiring [89]. As it turns out, some interesting non-random properties of these network structures can be described and, most importantly, quantified. These considerations are often based on graph theory, a branch of mathematics that is now quickly spreading as an interdisciplinary toolkit for analysis of structures that can be cast to the simple form of nodes connected by edges [1, 90–93].

Descriptive graph theory for neuroscience

Graphs in the context of graph theory comprise of individual agents, which are similar to each other in some respect, and a set of connections between these agents. In applications of graph theory to neuroscience, the agents, or graph nodes, are most often brain regions or restricted neuronal ensembles, and sometimes even individual cells. The connections, also called edges, often stand for anatomical connections, for example bundles of axons forming monosynaptic routes. In addition to structural connectivity, graphs may be constructed from functional data recorded at different scales, from the synaptic level to the system level [93]. In the functional case, the edges correspond either to functional or effective connectivity. The difference between these is that functional connectivity is defined as a statistical interdependence between the nodes: when one is active, the activity (or quiescence) of the other can be predicted with a probability above chance. Instead of a statistical relationship, the definition of effective connectivity enforces a mechanistic rule with a specific direction: the activation of one node leads to activation of the other [94].

The popularity of the graph-theoretical approach probably stems from it being conceptually simple but still versatile in describing very different systems. It also represents large and complicated data sets efficiently and enables their analysis at the systems level. Applications of graph theory to diverse fields of science has revealed surprising commonalities in the structure of networks of entirely different nature and origins, natural or manmade [2, 90, 92, 95–97]. This suggests that the development or construction of these systems may have underlying common principles that are, however, largely unknown at present [96]. These common principles in construction might lead to common principles in function as well [2, 90, 91, 95].

It has been found that many different kinds of systems that can be studied in the graph-theoretical framework belong to a few basic classes of graphs. This universality has lead to extensive studies of these few types of graphs. Naturally, instances of these classes have been found also in neuroscience. In the class of completely regular graphs, often embedded in lattice structures, all the nodes have the same number of connections . They are constructed by a rule such as “connect to n nearest neighbors”, making the graph structure and statistics homogeneous. With this type of rule one obtains graphs that are fully connected in neighborhoods of single nodes, *i.e.*, maximally clustered, but have a large characteristic path length, the average number of steps needed to get from one node to another, which scales as $\sim N$ with a growing number of nodes, N. In the opposite end, random networks are constructed by taking a set of nodes and connecting them at random with a certain number of connections. It has been shown that this class of networks has a short characteristic path length that scales as $\ln(N)$ [91, 95]. Very different graphs may result from restricting the pure randomness in the

construction process; for instance, if connection probability is made proportional to the number of connections d a node already has, called the degree of the node, a scale-free graph emerges [96]. The nodes of a scale-free graph have a degree distibution of the form $\sim d^{-\alpha}$, which has a heavy tail unlike the exponential or Gaussian distributions of the degrees in random graphs. Scale-free graphs often have short path lengths as well. Finally, a commonly encountered type of networks lies in the middle ground of the completely random and regular ones: by taking a clustered lattice and adding some random shortcuts between distant nodes the graph turns into a small-world network [95]. This graph is interesting because it combines the often desirable features of high local clustering and short characteristic path length from regular and random graphs, respectively [90]. The name small-world stems from sociology, where the surprisingly common finding of having mutual friends with a stranger was related to the small-world property of social networks [90]. Other principal properties of graphs determined by the classes include robustness to failures and attacks and efficacy of information transmission. Scale-free graphs are very resistant against random failures, because most of the nodes have low degree and, hence, their loss has a low impact on overall connectivity [97]. However, these networks are vulnerable to targeted attacks on the most connected nodes, called hubs [97]. Efficacy of networks, motivated in terms of information processing systems, has most often been related to the inverse of path lengths, so networks having random connections are considered to be maximally efficient [98, 99].

Local anatomical networks

The human neocortex consists of colums of neurons that are densely connected inside the column, but less connected to other columns further apart [100]. On the cellular scale, the networks are largely defined by the connectivity of interneuron networks [101]. This can be seen as corresponding to a conservation principle of expanding brains during evolution, which states that pre-existing, and thus tested, networks are simply multiplied instead of replaced by new kinds of networks [101, 102]. Many biological networks have a disproportionately large amount of certain elementary building blocks, while other, theoretically just as feasible ones, are virtually absent [103, 104]. Such basic building blocks are called motifs, and repeating structures of them can be found in several neuronal systems in numbers depending on their functional stability [102, 105, 106]. Moreover, local cortical structures are characterized by abundant reciprocal and cyclic connections and low mean wiring length [107, 108]. Finally, local neuronal groups display highly clustered structures [108].

Systems-level structural networks

From the point of view of systems neuroscience the properties of small-world networks are interesting, as they seem to be compatible with the idea of highly parallel processing, which would take place in the local clusters, while still offering efficient system-wide connectivity via the shortcuts [95, 107]. In addition, material and space costs of wiring are minimized because of the small number of long-range connections needed [94, 109]. Whereas neuronal structures have been elucidated using staining methods of mostly animal brain slices for a century, the long-sought-after large-scale neuronal structure of living human brains has become accessible only recently, with the advent of water diffusion-weighted techniques in magnetic resonance imaging

(MRI) of brain anatomy making high-resolution neuronal pathway data available [110–113]. Evidence for small-world-like organization was found in several studies [112, 114–116], often with exponentially truncated power-law degree distributions [112, 114–116]. Central hubs and a central connectivity backbone were discovered mainly in medial and posterior cortical regions but also in parts of the parietal and frontal cortices [114–117]. Moreover, the structural networks were found to be composed of modular subcomponents, which were more densely connected within the module than to nodes outside the module [117, 118].

The presence of hierarchical relationships at multiple levels has been thought to be an essential organizational principle of cortical connections [119]. However, the hierarchical relationships in the neuronal structure are so complex that defining them in an unambigous way seems next to impossible [120]. With solid data on connectivity and emerging computational methods, a definite hierarchical organization might be resolved in the future. However, it has already been found that the primate visual cortex is, indeed, highly hierarchical and clustered [121]. Together, these features suggest a nested modular structure, where modules are composed of smaller modules at a lower hierarchical level [93, 122, 123]. Such fractal-like organization has already been found in many biological networks that are scale-free, modular and hierarchical [123].

Network structure and neuronal activity

Like all structures with any functional role that have been evolved in nature, the form and function of the human central nervous system are strongly interrelated. It is clear that neuronal activity depends on the structure of the underlying neuronal substrate, and the Hebbian principle formulates an explicit interdependence between the two by stating that a persistently effective connection will increase in strength. Low-level information processing can be performed by simple network motifs, some of which can be associated with elementary computations [102–105]. For example, a motif with positive feedback could implement signal detection by transforming a graded signal to an all-or-none response. Furthermore, the difference between brain regions underlying different functionalities lies not in the regions themselves being affiliated with the processing tasks, but in their connections to other regions [124].

At the systems level, each part of the brain is connected to all the other parts. Furthermore, according to the small-world property the connection between any two regions is short. It has been estimated that each neuron in the human brain is connected to each other neuron via as few as six synapses [1]. A central principle of human brain operation, the simultaneous segregation and integration of information, may be brought about by corresponding principles in brain structure [93, 107, 125]. Structural modularity has been associated not only with stability in evolution and function, but also with differentiation among motor, perceptual and cognitive functions and, accordingly, experimental work has shown that brain regions in the same structural module are functionally related [93, 117, 118, 121, 122]. The locations of hub nodes, which are brain regions in a central position for the systems-level anatomical connectivity, have been found to coincide with the conventional association cortices [114, 115, 117]. When considering the roles of structural connections as the substrate of brain function, it is plausible that the functional neuronal interactions are dynamically modulated from the complex structural networks to produce functional networks. Moreover, as the spontaneous neuronal activity is

often wildly fluctuating, it is reasonable to expect that the large-scale functional connectivity, when averaged over long time windows, will be correlated with the underlying structural connectivity [304].

Dynamical systems theory

A language for neuronal dynamics

The activity in the brain, as well as many other physiological systems, are actively investigated at multiple scales in the framework of complexity and dynamical systems [93, 122, 126–130]. This framework is a natural choice for analysis of the dynamics in neuronal networks, as dynamical systems theory provides the concepts required for the description of complex phenomena that are otherwise challenging to grasp [131]. Theoretical developments have rapidly been implemented as new methods for analyzing recorded data [132]. Next, a short digression to the concepts needed to understand the analysis approaches and interpretation of the findings follows.

A central concept in dynamical systems theory is the phase space, with the help of which one can describe the temporal development of the system by plotting the history of an observable. An observable is a dynamic variable that can be measured, at least in principle, as opposed to a hidden variable. Nonlinearity is often attributed to activity in the brain. Mathematically, a dynamical system is nonlinear if the differential equations governing the behavior of the system are not linear. In more practical terms, linear behavior means that the superposition principle is valid and that changes in output are proportional to changes in the system's behavior, which is not always the case for nonlinear systems. The simplest neuroscientific example of nonlinear behavior is a neuron initiating an action potential after crossing the firing threshold. Stationarity means that the statistical expectation values of the system's observables do not change over time. Thus, a harmonic oscillator is stationary, but the alpha oscillations measured occipitally in the human brain are not, because their amplitude and frequency tend to shift in time scales typically used in their observation. Stability, on the other hand, refers to properties of a single dynamic state instead of the system. A dynamical system might set itself into a fixed point, which is stable if the system after a small perturbation returns to the same state. Instead of a point, the state might be described by a limit cycle on any manifold, in which case the system undergoes oscillations. If several stabile states exist, the system is multistable, whereas short-lived stable states are called metastable. A stable limit cycle is called an attractor, as any neighboring phase space trajectories tend to come asymptotically closer to it. The existence of an attractor does not, however, mean that the system's behavior would be predictable. Even if the equations describing the dynamics of the system were deterministic, the behavior of the system might be unpredictable, except in short time scales, like is the case with the three-body problem in mechanics. Furthermore, even in the case that the system is, in fact, deterministic, even minute changes in initial conditions may cause changes in phase space coordinates that grow exponentially in time. The dynamics of this type of a system are called chaotic and it are described by a fractal-dimensional strange attractor. Finally, two dynamic systems might spontaneously coordinate their dynamics, or synchronize – in fact, this is surprisingly common

in nature as only a weak interaction is needed between the systems. The exact type of synchronization depends on the systems [91, 128].

With the huge numbers of neurons and their connections, studying the detailed dynamics of the whole brain is out of the scope of current and foreseeable future research methods. However, because neuronal activity is highly correlated across time and space, the complexity in the dynamics that are visible in the system scale of inspection becomes reduced. Brain activity, measured with electrophysiological methods, could then be potentially understood using the concepts and analysis tools provided by dynamical systems theory. Simplification of the system is welcome when looking for behavioral correlates in neuronal activity, because behavior is often rather simple in dynamical terms, especially in cognitive experiments [133]. The drawback of this approach is that the neuron-level details underlying the observed dynamics are lost. Therefore, one should try to differentiate between understanding the behavior of a system and giving only phenomenological descriptions of it. A classical example is finding an explanation for epileptic seizures from bifurcation, a qualitative change in system dynamics that clearly takes place at seizure onset, without an idea of the causes of such a change. However, combining the idea of searching for dynamical bifurcations to careful neuronal modeling studies can prove a fruitful approach [134]. The dynamical systems view thus offers a language to qualitatively describe the behavior of neuronal systems and tools for quantitative analyses [127, 135].

Self-organized criticality

The complexity of the structure and function in the nervous system has evolved under the pressure of the dynamic complexity and changing requirements in the environment. Therefore, it can be argued that the neuronal dynamics could at least partly be inherited directly from the surroundings. For the opposite to hold, it should be demonstrated that inherent order may be created in the neuronal network dynamics solely by the properties of the interacting non-linear neuronal elements. This is possible by modeling a neuronal system and checking if it spontaneously develops rich dynamics. Indeed, massive computational simulations with realistic models have shown that such systems are able to self-organize from various starting configurations and without external influence or guidance to a sustained coherent state, which resembles that of human brain dynamics in several aspects [136]. Thus, the spatiotemporal complexity in neuronal dynamics is probably created by the properties of the neuronal networks themselves, not by being influenced by the complex dynamics in the environment they have adapted to.

Statistical thermodynamics describes how bulk substances undergo phase transitions. In certain types of phase transitions or close to critical points of the parameter space, correlations extending over the entire system emerge, despite the fact that interactions between parts of the system are strictly local. Interestingly, the correlations scale with regard to the length variable l as a power-law, *i.e.*, $\sim l^{-\beta}$, where β is called the scaling exponent. This relation reveals that correlations are present at all length scales, which hints at a fractal dynamical structure, where no typical length scale to describe the system dynamics is present. However, there is nothing that should separate thermodynamic bulk matter phase transitions from systems with similar adjustable interactions between its components. This gives rise to phase transitions and critical

points in dynamical systems as well. The development of the self-organized critical (SOC) state in dynamical systems was initially explained using a simple model, often referred to as the sand-pile model [4]. Later, analogies were drawn to models of diverse systems in many fields of study, which extended the use of the SOC concept to investigate, *e.g.*, dynamics of forest fires and financial markets [137–139].

The conditions for systems to self-organize into a critical state are rather general and compatible with the developmental principles of the brain [140]: they should be composed of many agents, the system's evolution should be long and the driving dynamics should be slow, the dissipative medium should be structurally modified by the driven perturbations and the behavior of the system should be dominated by local interactions between the agents. The SOC state is insensitive to initial conditions of the system or exact mechanisms of signal propagation. Interestingly, the SOC dynamics are characterized by spatial and temporal correlations, intimately linked to each other, at all scales [137, 141]. This is often considered the hallmark of SOC, but strictly speaking it is not a sufficient condition [142]. Studies of brain function motivated by the SOC model should expect that both spatial and temporal correlations are strong and widespread. Moreover, the SOC approach makes it feasible that order and correlations in brain activity develop spontaneously, but are context-dependent because of the state dependency inherent in the dynamics of the SOC models.

Critical dynamics in brain function

Spatial and temporal correlations in neuronal systems have been studied in search for evidence of SOC. Different methods have been applied, ranging from cellular-level *in vitro* approaches to system-level measurements of behaving humans [78, 143–149]. In analogy with the now famous Bak–Tang–Wiesenfeld sand pile model, neuronal networks spontaneously produce avalanches, discrete cascades of contiguous neuronal activity, which have spatial and temporal correlations described by power-laws both *in vitro* and *in vivo* [4, 137, 144, 146]. Neuronal oscillatory activity has also been analyzed for presence of scale-free avalanches with similar results [147, 150]. In these studies, the power-law decay of long-range temporal correlations (LRTC) in human MEG and EEG oscillations have been interpreted as indicative of SOC [78]. Note, that the perturbations analyzed in these studies may be internally generated, as opposed to the external perturbations in SOC models [4, 137, 142]. The spatial correlations among oscillations are harder to quantify than the temporal ones, as the distance between oscillatory ensembles is not defined with the Euclidean metric but by the graph constructed from the neuronal connections. Despite this, quantifying the strength of phase synchrony against inter-electrode distance in subdural recordings of epileptic patients reveals a dependence of roughly the power-law form (Fig. 1). For robust analyses of this kind, synchrony should be quantified across all brain regions in many scales, not only within an electrode grid, and an additional distance metric should be taken from structural connectivity data.

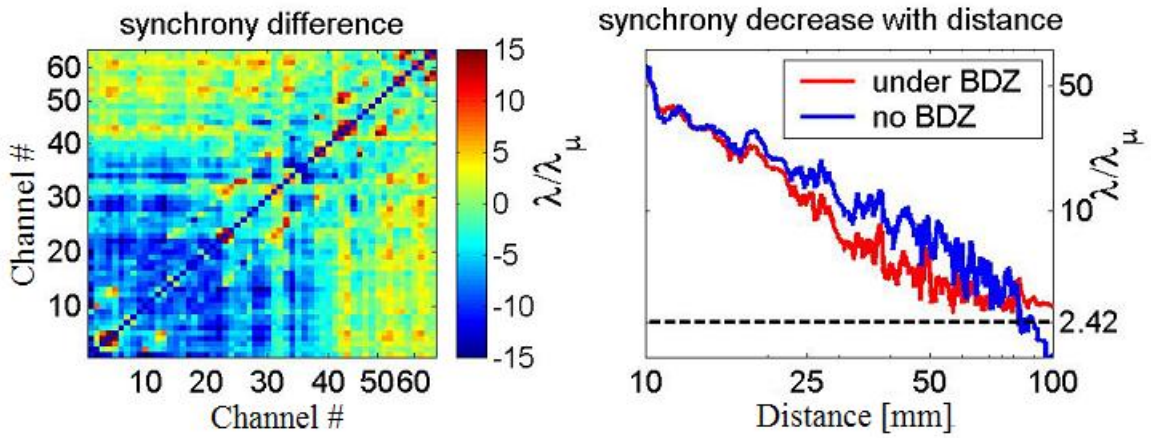

Fig. 1 Intracranial subdural electric recordings show a dissociated effect of the benzodiazepine lorazepam, a GABA-binding promoter, on oscillatory synchrony between electrodes in different cortical regions (left). Synchrony scales roughly like a power-law as a function of distance (right). (Modified from [268])

Experimental Studies

Experiments

Somatosensory detection

Motivation. Human performance in a number of cognitive and coordination tasks has been found to be correlated over consecutive trials [151–161]. As the stimuli used in such experiments were invariant over time, it is reasonable that such behavioral temporal correlations were of neuronal origin, which can be related to the responses or performance in the previous trials, or fluctuations in spontaneous activity. It is also known that the inter-trial correlations observed in the performance of such tasks display a long memory that decays as a power-law over time [152, 153, 155]. Intriguingly, similar scale-free long-memory effects have been observed in 3–30-Hz neuronal oscillations recorded with MEG and EEG [78] (Study I). The aim of this experiment was to characterize the neuronal correlates of the trial-to-trial dependencies in a somatosensory detection task.

Setup. In Study III, we hypothesized that the long-range temporal correlations (LRTC) in behavioral performance and neuronal oscillations are governed through the same mechanism of slow fluctuations in cortical excitability [162]. To study the basis of trial-to-trial correlations in behavioral performance, the subjects were delivered constant-current stimuli with randomized 1.5 – 4.5 s intervals at an individually set intensity where they were able to report ~ 50 % of them. Such design has been shown to give rise to long-term behavioral correlations [152, 156, 157]. Fluctuations in the frequency range of 0.02–0.2 Hz were previously found to affect the occurrence of epileptiform EEG events and modulate neuronal oscillatory activity during sleep [162]. Variations in neuronal oscillatory amplitudes in similar time scales have already been encountered in studies of LRTC (see Fig. 4; [78]). In addition, spontaneous coherent fluctuations were observed in functional MRI (fMRI) data in a similar frequency range [163]. We thus recorded simultaneous direct-current coupled full-band EEG (FbEEG) to search for correlates of slowly changing oscillatory amplitudes and performance level [164].

Analysis. We analyzed the FbEEG data in the very low frequency band of 0.01–0.1 Hz to identify the phase and amplitude that are preferred for successful stimulus detection. In addition, we computed the amplitude modulation of faster neuronal oscillations (1–40 Hz) by the phase of the 0.01–0.1 Hz activity to uncover possible cross-frequency nested relationships. If the detection performance and oscillation amplitude were governed by the same mechanism related to the brain activity in this very low frequency band, they should have the same preferred phase or amplitude and their LRTC scaling behavior should be similar.

Visual working memory

Motivation. Visual working memory (VWM) is one of the essential functions provided by the human brain. A remarkable property of VWM is that although we sense a rich visual environment around us each moment, the actual capacity of VWM is surprisingly low, less than five objects [165]. The brain regions underlying VWM task execution and performance have been studied extensively, but the bases of the central executive and the sensory storage functions of VWM are still unclear [166–169]. In Study V, we hypothesized that the VWM-related brain regions complete the functions necessary for task performance by co-operating with each other to a large extent and in a highly organized manner.

Setup. To inspect our hypothesis, we measured concurrent MEG and EEG during a visual delayed-match-to-sample task. The number of colored square objects used as the memorized stimuli were varied randomly between 1 and 6 to modulate the memory load. The subjects' task was to report if the probe stimulus presented after a 1-s memory retention period matched the initial sample stimulus or not.

Analysis. We expected to find a large-scale task-relevant cortical network formed by oscillatory inter-areal interactions. We first developed the methodology required to assess inter-areal oscillatory phase synchrony in the extent of the whole cortex (Study IV). Then, we quantified synchronization between all brain regions during the retention period in the frequency band of 3–80 Hz. Finally, we assessed the topological properties of this synchronized network using methods adopted from graph theory (Study V).

Major depression

Motivation. Major depression is an affective disorder, where the patient's mood and self-esteem as well as abilities for enjoyment and interest are severely lowered. These feelings dominate the everyday life of the patients in most situations[1]. In the absence of explicit tasks or stimuli, one of the dominant psychological modes engaged is supposedly introspection [171]. In contrast, the patients' performance under specific tasks may reflect the various cognitive deficits that are brought about by the disorder. Therefore, the negative affect that directly characterizes the impaired mental state in major depression could be most clearly present during unconstrained rest. We hypothesized that the disorder is related to an altered neuronal state that can be detected by investigating the correlations in spontaneous neuronal oscillations.

Setup. In this clinical study, we recorded ongoing MEG from 12 acute, unmedicated major depression patients and age-matched control subjects during eyes-closed resting state for 20 minutes. The patients went through the Hamilton questionnaire to rate the degree of the disorder [172].

Analysis. In Study I, we attempted to find a neural correlate for the negative affect in major depression patients by quantifying the temporal correlations in oscillatory neuronal activity.

[1] World Health Organization, International Classification of Diseases: http://www.who.int/classifications/icd/en/

This could help in the diagnosis and follow-up of depressive disorders. To be called a neuronal correlate for depression, the measure should be prominent in the patients but negligible in healthy controls or vice versa, it's magnitude should correlate with the degree of depression and it should vanish upon recovery from the disorder. If the two last conditions are not met, the measure might indicate a trait dependency, an inclination for the disorder of possibly genetic background, rather than be a correlate of the depressed neuronal state *per se*. We quantified the oscillatory amplitudes and LRTC from combined MEG gradiometer signals to obtain separate time series to represent the neuronal oscillatory activity in the left and right somatomotor regions and the occipital region. In addition, we analyzed the signals from two prefrontal EEG derivations. We compared the values from these analyses between groups and correlated them with the Hamilton scores by linear regression.

Epilepsy

Motivation. Epilepsy is one of the most widely known central nervous system disorders because of the often dramatic convulsions associated with it. While many genetically, etiologically and phenomenologically different epileptic disorders exist, they are all thought to be symptoms of excessive neuronal activity. Accordingly, their treatment concentrates on controlling the excessive activity. The seizures are most often adequately reduced by medication, but sometimes a surgical resection of the seizure-generating tissue is made. In this case, localization of the pathological tissue becomes a necessary condition for a successful operation. However, localization of the seizure-generating region is not a straightforward task with the current methods.

Setup. In Study II, we aimed at finding new ways to locate and circumscribe the seizure-generating cortical tissue. To this end, we used intracranially recorded EEG data from five patients who were undergoing the evaluation period for resection surgery. We hypothesized that the neuronal activity in seizure-prone brain regions can be distinguished from normal even during non-convulsive inter-ictal periods. In all our patients, the epileptic zone had been located using combinations of conventional methods and was found to lie in the brain region covered by the electrode grid. The patients had also been successfully operated after the evaluation period, so the results from conventional localization methods was correct in these patients and could be used as a reference in our study.

Analysis. We attempted to locate the epileptic region from inter-ictal grid electrode data with no visible signs of epileptiform activity by computing local amplitudes, signal variability measures and LRTC in four narrow frequency bands in the range 1–48 Hz. The analysis was done blindly with respect to the reference regions, and was based on finding focal changes in the grid region. These foci were then compared with the reference region to identify the most suitable method to consistently delineate the epileptic zone in the subjects. The most promising methods could then be further tested and developed to give additional information when locating the seizure-generating regions for clinical needs.

Simulating MEG and EEG measurements to assess inter-areal synchrony

Motivation. When estimating inter-areal phase synchrony from inverse-modelled MEG / EEG data, it is not feasible to compute pair-wise synchrony between all the more than 10^7 source pairs formed by the several thousands of source nodes in realistic distributed source models. First reason for this is that computing such a large number of signal-to-signal correlations is a computationally encumbering task, and second is that measurement information is available only from a few hundreds of MEG / EEG channels. Thus, estimation of 10^7 synchrony values from these data is highly redundant. Because of these restrictions, we decided to estimate synchrony between small patches of cortex, each consisting of a number of source nodes. We hypothesized that an optimal parcellation for analyzing phase synchrony is obtained by investigating the spurious correlations between individual source nodes that emerge after a MEG / EEG measurement of uncorrelated sources and inverse modeling of the data.

Setup and analysis. In Study IV, we reasoned that to perform optimal brain-wide synchrony analysis, patches are needed for which the activity is maximally separable from the activity in other patches. Thus, source nodes that are inseparable from each other after recording their activity with MEG / EEG and inverse modeling the data should be clustered together into patches. To this end, we simulated patterns of uncorrelated neuronal activity in individual source models, performed a virtual MEG / EEG measurement by forward modeling the uncorrelated source activity, and inverse modeled the simulated sensor data. From this source-level data we quantified phase synchrony among all pairs of individual sources (see below for technical details on forward and inverse modeling and phase synchrony analysis).

Data acquisition

Measurement techniques

Scalp-recorded EEG. The scalp-recorded EEG is the workhorse of electrical measurements of brain activity in clinical settings and often in research as well [173]. The number of channels in EEG measurements varies from only a few to some hundreds: the recording electrodes are most often made of silver, coated with silver-chloride. These Ag|AgCl electrodes are coupled to the scalp electric potential with a conductive chloride ion-containing gel. In addition to the recording electrodes, a high input resistance amplifier is needed. EEG records the potential difference between two electrodes, the second of these usually being a dedicated reference electrode. Despite many advances in recording and signal processing technology, the lack of purely local measurements remains the principal drawback of EEG [174]. Mathematically, the EEG measurement channel reading, a potential difference between two electrodes, is obtained as a path integral of the electric field in the head. The arbitrariness of the path of integration highlights the low spatial resolution of the EEG measurement. From the point of view of source modeling, the low resolution is due to the wide sensitivity profile of the electrode pairs to the underlying currents. In addition, the electric field in the head is considerably affected by inhomogeneity and anisotropy of conductive tissue properties, which makes the forward

computations more difficult and sensitive to inaccuracies in tissue modeling. These factors together hamper the localization of the current sources that generate the measured EEG signal.

Intracranial EEG. In addition to scalp-recorded EEG, intracranially recorded EEG is sometimes needed in clinical settings, mainly when planning epilepsy surgery [175]. The recording electrodes are then either depth electrodes, which are thin wires inserted stereotaxically into the brain tissue, or sub- or epidurally positioned plate electrodes in the form of surface strips or grids (Study II). The latter option is often referred to as the electrocorticogram, or ECoG. The signal recorded by intracranial EEG is better localized than that from scalp EEG, as the channel derivations are often formed by subtracting neighboring electrodes or referencing to a relatively silent and distant scalp electrode. The fact that intracranial recordings are only performed upon clinical need with medically justified electrode setups restricts the possible experiments and limits their use in neuroscientific research.

Full-band EEG. The recording bandwidth of the EEG has conventionally been limited in the lower end to roughly 0.5 Hz. Recording the electrical activity at lower frequencies has been rather uncommon and is technically more demanding. The main challenge is electrode design, as these must be stable in direct-current (DC) coupled measurements [162, 164, 176]. The amplifier needs to have a wide dynamic range because of the high amplitude of the signals and electrode potentials, possible drifts due to electrode polarization, and the skin potential. The electrodes should be electrically connected to the subcutaneous tissue to short-circuit the skin potential. These artifactual sources of potential difference may result in signals of tens of millivolts, which is an order of magnitude more than the largest neuronal signals. With current full-band EEG (FbEEG) recording techniques, where the DC-stability of the electrodes, the amplifier and skin contact preparation are taken into account, the available measurement bandwidth extends from 0 Hz up to hundreds of Hz [164]. However, the very low frequency components of the signal measured on the scalp are most probably generated by several sources [177, 178].

MEG. MEG differs from the EEG in that it samples the magnetic flux generated by intracranial current sources using superconductive coils [179]. This gives MEG two significant advantages over EEG. First, the measurement of the magnetic flux is absolute, so there is no need for differential measurements using reference sensors. Second, because the MEG measurements are negligibly affected by the fine structure of the cranial tissues, the sensitivities of the sensors to the field-generating currents are more accurately known; hence, source modeling of multi-channel MEG data is possible with high accuracy. On the other hand, radial current dipoles do not produce an external magnetic field in a spherical conductor, a locally reasonable approximation of the real conductor, so MEG might entirely miss some sources that the EEG is sensitive to. Thus, the two modalities complement each other. The technology needed for MEG measurements is far more sophisticated than that needed for EEG, requiring cryogenics to keep the superconductive quantum interference device sensors in the superconductive state, and advanced electronics, software and a magnetically shielded measurement room to reduce the level of noise in the measured signals [179]. A central factor adding to the flexibility of MEG is that different sensor types and geometries can be used to sample different orientations and gradients of the magnetic flux.

Neuronal origins of the electric signal

At the neuronal level, there are two primary current sources, *i.e.*, non-ohmic currents, that could account for the electromagnetic signals measured outside the head: the currents related to the action potential and the post-synaptic currents [173, 179–181]. Because the MEG and EEG signals are measurable on the scalp, it is generally agreed that they are generated by a large number of simultaneously active neuronal sources with constructive summation. In addition, the field generated by the candidate mechanism must be slowly decaying with distance in order to reach the sensors. The action potentials in axons may be synchronized, although they are short-lived, but their associated source configuration is quadrupole-shaped and thus the generated magnetic field decays fast, as $\sim r^{-3}$ with distance r in homogeneous medium and as $\sim r^{-4}$ in the case of the sphere model and large r. [179, 180]. On the contrary, the post-synaptic currents, which are generated by ionic flow through transmitter-gated cell membrane channels, are longer-lived and hence sum up temporally with higher probability. Moreover, the source configuration of the current flowing along the dendritic tree of a neuron is dipolar, so the magnetic flux decays as $\sim r^{-2}$, significantly slower than for quadrupoles [179, 180]. Thus, the main sources of extracranially observed electromagnetic activity are the post-synaptic currents.

Assuming that the post-synaptic currents are the main contribution to the observed electromagnetic recordings, we must conclude that the MEG and EEG methods are mostly sensitive to input to cells rather than output generated by those cells. This has been partially confirmed experimentally by combining electric and optical measurements [182]. However, in the case of oscillatory activity that reverberates in a local neuronal population, which is the main interest of this Thesis, the synaptic input to and the spiking output from a brain region most probably are significantly correlated.

Data processing

Filtering for oscillations and extracting the phase and the amplitude

Two different approaches to time series filtering were used in the studies of this Thesis, Morlet wavelets and finite impulse response (FIR) filters [190–193]. In wavelet filtering, a data time series $y(t)$ was filtered with a Morlet wavelet $h(t,f)$, where f is the center frequency of the wavelet. The complex filtered signal, $y_c(t)$, is then given by $y_c(t, f) = y(t) \otimes h(t, f)$, where $h(t, f) = A \exp(-t^2 / 2\sigma_t^2) \exp(2i\pi f t)$, $\sigma_t = m / 2\pi f$ denotes the standard deviation of the wavelet in time domain, m defines the time-frequency resolution, A is a scaling factor and $y \otimes h$ indicates the convolution of y and h. The discrete FIR filtered signal was obtained by convoluting the signal $y(n)$ with the digital filter coefficient vector $[b_i]$, which can be written as $y_{FIR}(n) = \sum_{i=0}^{N} b(i)y(i-n)$ for each sample n, where N is the filter order. The phase and amplitude of a FIR-filtered signal y_{FIR} were obtained with the analytic signal approach by first constructing a complex-valued signal using the Hilbert transform H, $y_{FIR,c} = y_{FIR} + iH(y_{FIR})$. From a wavelet or FIR-filtered complex-valued signal the momentary signal amplitude was computed by $|y_c| = (y_{RE}^2 + y_{IM}^2)^{1/2}$, where y_{RE} and y_{IM} are the real and imaginary parts of y_c, respectively. The phase ϕ of $y_c(t)$ was estimated using $\phi = \text{atan2}(y_{IM}, y_{RE})$, where atan2 is a variant of the arctangent

function that gives the angle ϕ between the real axis (x-axis) and the point (x, y) in the complex plane.

Quantifying spatial correlations with phase synchrony

The degrees to which oscillations between brain areas are correlated was quantified by computing the phase synchrony between two signals, originating from a pair of sensors or brain regions, the latter after inverse modeling of the MEG or EEG signals (Studies IV, V). Phase synchrony, as any measure of functional connectivity, is a statistical index specifically of non-random phase correlations [195]. We quantified phase synchrony by first obtaining a pair of complex-valued narrow-band signals, $s_i(n)$ and $s_j(n)$, and then computing the phase-locking value, PLV, for each frequency band from samples across trials [192, 196]. We write $s_i = A_i \exp(i\phi_i)$, where A_i is the amplitude and ϕ_i is the phase of s_i. Now, PLV $= n^{-1}|\Sigma_t \exp(i\phi_{i,t} - i\phi_{j,t})|$ where $t = 0 \ldots n-1$, and n is the number of samples. The statistical significance of PLV was assessed using surrogate data (see below).

Quantifying temporal correlations with detrended fluctuation analysis

Temporal correlations are computed within a single time series, in contrast to paired signal analysis used in the computation of spatial correlations. The aim of this analysis is to quantify the "fractal patterns" that give rise to the LRTC in the signal [78, 197]. Here, fractality refers to self-similarity over time t, which gives rise to slowly decaying temporal correlations that scale as a power-law $\sim t^{-\alpha}$ where α is the power-law exponent. A common way to assess LRTC is the analysis of power spectral density (PSD), but the results derived from power spectra may suffer from non-stationarities in the data. Detrended fluctuation analysis (DFA) has become another widely used method to quantify LRTC [78, 139, 198, 199] (Studies I – III). The idea of DFA is to track the fluctuations in the signal across a wide range of time scales. It has been argued that the DFA performs robustly even in the presence of artifacts and non-stationarities in the data, but the analysis of LRTC still benefits from complementary use of other methods [200, 201] (see Fig. 4).

The DFA algorithm computes the root-mean-square deviation, F, of an integrated and windowed zero-mean amplitude signal from which the linear fit in each window has been subtracted, $y(\tau)$, in a number of window sizes, τ. The deviation is calculated with $F(\tau) = [n^{-1} \Sigma y(\tau)^2]^{1/2}$, where the sum runs over the n samples. The scaling exponent α is extracted with a least-squares fit in double-logarithmic coordinates; values of $0.5 < \alpha < 1$ imply self-similarity and positive LRTC. For further details about applying DFA, see [78, 202]. An interesting combination of the analyses of spatial and temporal correlations in oscillations has been presented in [203]. Recently, an approach to integrate the long-term memory properties in single time series and pair-wise correlations between them was formulated to estimate "fractal" functional networks [204].

Quantifying cross-frequency correlations with nested synchrony

The correlations between two oscillatory signals $x(t)$ and $y(t)$ characterized by amplitudes A_i and phases ϕ_i can take three forms: amplitude-to-amplitude correlation, phase-to-phase correlation and amplitude-to-phase correlation, which is called nesting. The PLV, which was used above to quantify phase synchrony, can be applied to quantify other forms of correlations as well. We estimated nested synchrony by computing the PLV between $x(t, f)$ and the amplitude envelope of $y(t)$, which had been further band-pass filtered to the center frequency f, $A_y(t, f)$. Then, PLV = $|\Sigma \exp[i\phi_x - i\phi(A_y)]| / n$, where ϕ_x is the phase of $x(t, f)$, $\phi(A_y)$ is the phase of $A_y(t, f)$, obtained with the Hilbert transform as above, and n is the number of samples. The statistical significance of the nested relationship was assessed using surrogate methods (Study III).

Quantifying indices of network topology

The structure of anatomical and functional networks has been characterized above in descriptive terms. Graph theory is a formalism for quantifying topological properties of a network [93, 94]. Characterizing the structure of synchronous oscillatory networks was the main target of Study V. Construction of a graph is based on the nodes, or vertices, and a connectivity matrix G, also called adjacency matrix, which describes the connections, or edges, between the nodes. Statistically processed phase synchrony matrices were thresholded to build undirected and unweighted graphs, where nodes i ($i = 1 \ldots N_n$) are given by the cortical areas and statistically significant inter-areal phase synchrony between i and j are the edges, $G_{i,j} = G_{j,i} = 1$ (Study IV). In the case of a lack of a significant interaction between i and j the edge is missing and $G_{i,j} = G_{j,i} = 0$. The structure of graph G was characterized using several graph theoretical measures. The degree, d_i, of vertex i is the simplest measure of the importance of a node and equals the number of edges connected to the vertex. The degree distribution of a graph is the distribution of d_i of all nodes i and is estimated with a histogram. Connection density K is the proportion of existing edges to all possible edges, $K = \Sigma G_{i,j} / [N_n (N_n - 1)]$. The clustering coefficient for node i indicates the proportion of connections in the neighborhood of vertex i relative to all possible connections and is given by $C_i = \Sigma_k d'_k / [d_i (d_i - 1)]$, where nodes k are those connected to the node i and d'_k is the degree of node k including only the connections among neighbors of node i. The clustering coefficient C of the graph is the mean C_i over all nodes. The shortest path length $l_{i,j}$ between vertices i and j is the minimum number of edges along a continuous path of edges between i and j. The mean of $l_{i,j}$ over all pairs of vertices in a one-component network is called the characteristic path length L. We defined $S = C / L$ and the small-world index, σ, as $\sigma = S / S_R$, where S_R is the mean S of mean-degree-matched random graphs. A graph's global efficiency, E_{glob}, is given by $E_{glob} = \Sigma_{i \neq j} [l_{i,j} N_n (N_n - 1)]^{-1}$ and cost efficiency κ relates this to the cost of the graph, which is evaluated as the connection density K, and is obtained with $\kappa = E_{glob} - K$ [99]. The most densely interconnected structures were identified with k-core analysis: vertices belonging to a k-core are those that remain after vertices with $d < k$ have been recursively removed. A graph's maximum k-core number is the value of k such that with $k + 1$ all vertices are removed.

Use of surrogate data in statistical analysis

Surrogate data is a general and robust way to determine the statistical significance of an original experimental finding. In surrogate analysis, the original data is replaced by surrogate data and processed identically to the original. Surrogate data can be generated by mixing, which usually has the benefit of conserving the main descriptive statistics in data. Another way to obtain surrogate data is to run numerical simulations with carefully selected parameters, which requires some knowledge of the original data. In this study, we use surrogate data to find significance levels for temporal (Study I) and spatial correlations (Study V) as well as cross-frequency nested relationships (Study III) among neuronal oscillations.

In general, phase synchrony can be estimated for samples across time or for samples with the same latency across trials. In both cases, surrogate data can be generated by means of temporal mixing, where the other signal is shifted in time. In Study V, we computed surrogate PLV from signals originated in separate trials to compensate for synchrony generated by the evoked response component [196]. Hence, only the temporal relationship between the signals was changed, whereas the time series were otherwise left intact.

Analyses of LRTC only employ one time series, so the minimal intervention of translating the signal is not valid. Here, it is the relation between samples within the signal that bears information, so random mixing of samples would remove the temporal correlations. However, this would also distort other signal statistics, such as the power spectrum. A more conservative mixing method is to mix clips of data [205]. In Study I, we abolished the temporal structure in the MEG time series by Fourier transforming the data to the spectral domain, randomizing the phases and inverse transforming back to the time domain [199].

From channel level to source level using inverse estimation

Although it has been long known that the results from MEG and EEG channel-level analyses are difficult to relate to neuronal processes in specific anatomical brain regions, a vast majority of EEG and MEG studies still report exclusively channel-based analyses. This tendency may be partly due to the clinical EEG tradition, which concentrates on interpreting the event-related averaged responses or ongoing oscillations in single leads placed at specific scalp locations.In addition, the mathematical rigor required for high-quality source-space analysis may act as a deterrent. Without inverse modeling, the locations of the current sources can barely even be judged in terms of the hemisphere of origin from scalp EEG recordings, while accuracy at the level of cerebral lobes may be attainable with MEG, depending on the sensor types. The task of estimating the source-space projection of the recorded MEG / EEG signal-space data is called the neuroelectromagnetic inverse problem. The term inverse arises from the need to estimate the causes of observed effects backwards in causality. In the neuroelectromagnetic forward problem the electromagnetic fields, the results of a MEG / EEG measurement, are calculated from known current sources. It is well known that there is no unique solution to the MEG / EEG inverse problem, which makes the inverse estimate highly dependent on the prior assumptions, such as the source model.

To further motivate analyzing MEG / EEG data in the source space, let us present the two major problems in estimating synchrony in the signal space. First, multiple brain regions contribute to the signal recorded in a single channel, so information about the spatial location of the interacting brain area is lost. Second, activity from single sources spreads to several channels, so the sensor signals display spurious correlations even in the absence of inter-areal correlations. Thus, in studies of phase synchrony using channel-level data, the ambiguity of underlying current sources severely hampers the interpretability of the results. The principal aim of Study IV was to develop methods for identifying the real between-regions neuronal interactions from such ambiguous measurement data. In addition, the spurious contribution from common signal sources in computed synchrony cannot be estimated in the signal space, because it depends on the sensitivity of the sensors to the sources giving rise to the data, and can thus be settled only in source space [206].

In the context of MEG and EEG, the most commonly applied inverse estimate is the single equivalent current dipole. However, dipole modeling is highly insufficient to describe spatial correlations in oscillatory activity. The signal processing methods applied in this Thesis require continuous activity in each brain area to quantify the inter-areal correlations. The minimum-norm estimate (MNE) is a distributed current estimate, originally proposed for MEG, that makes minimal *a priori* assumptions of the current sources [207]. MEG and EEG data can be inverted in an integrated way using the lead field concept, which takes into account the different sensitivity profiles of MEG and EEG sensors [208]. In Studies IV – V, we inverse modelled the concurrently acquired MEG and EEG data using the MNE Suite software[2]. Building an anatomically realistic inverse estimator for optimal accuracy requires a source model, a conductivity model, the solution to the forward problem and noise covariance statistics from the data. The information on individual anatomy was acquired with MRI. Here, the source model was a set of dipoles on the cortical mantle with ~7 mm separation and fixed orientation. A realistic three-layer conductivity model was applied in the forward computations with the boundary element method using realistic values for tissue compartment conductivities.

MEG and EEG sensor signals $Y = [y_j]$ with channels $j = 1 \ldots m$ are linearly related to current strengths in n source dipoles $X = [x_k]$ so that $Y(t) = G\,X(t) + N(t)$, where G is the lead field matrix and $N(t)$ accounts for unmodelled noise. We obtained $X(t)$ from measured $Y(t)$ using a minimum-norm estimator so that $X(t) = M\,Y(t) = RG^{\mathrm{T}}(GRG^{\mathrm{T}} + \lambda^2 C)^{-1}\,Y(t)$, where M is the inverse operator, λ is a regularization parameter, R is a source covariance matrix and C is a sensor noise covariance matrix. The complex inverse solution $X_{\mathrm{c}} = [x_{\mathrm{c},k}]$ was obtained from the inverse solutions for the real and imaginary parts of the narrow-band filtered data $Y = Y_{\mathrm{RE}} + \mathrm{i}Y_{\mathrm{IM}}$ so that $X_{\mathrm{c}} = M\,Y_{\mathrm{RE}} + \mathrm{i}M\,Y_{\mathrm{IM}}$. We collapsed the individual complex-valued sources $x_{\mathrm{c},k}$ in each cortical area a into amplitude-normalized complex phase time series θ_a so that $\theta_a = \rho_a / |\rho_a|$, where $\rho_a = \Sigma_a\, x_{\mathrm{c},k}$ and the sum runs over the sources in the cortical area a. Inter-areal synchrony between areas a and b was then computed at the source level as $\mathrm{PLV}_{a,b} = |\Sigma_s\, \theta_a\, \theta_b^*| / n$, where n is the number of samples s and θ_b^* denotes the complex conjugate of θ_b.

[2] The MNE software is courtesy of Matti Hämäläinen and is publicly available at:
`http://www.nmr.mgh.harvard.edu/martinos/userInfo/data/MNE_register/`

Main results

Infra-slow EEG correlates with stimulus detection and neuronal oscillations

In Study III, we recorded the FbEEG of subjects performing a somatosensory detection task. We found that the behavioral detection performance was clustered in time and presented scale-free long-range memory, in agreement with previous psychophysical data [152, 155–157, 159]. The detection dynamics included statistically significant detection bursts in time scales of > 3 trials, which corresponds to the > 10 s periodicity in the FbEEG data filtered in the frequency band of 0.01–0.1 Hz.

By analyzing the ongoing activity we identified very slow modulation of the FbEEG signal during task execution. We termed this finding infra-slow fluctuations (ISFs). Furthermore, we observed that behavioral performance was elevated in the rising phase of ISF and reduced in the falling phase (Fig. 2). We then characterized the cross-frequency nested relationships between ISFs and faster oscillations in frequencies > 1 Hz. We found that the amplitude dynamics of 1–40 Hz neuronal oscillations were correlated with the phase of the ISF in a similar way as the behavioral performance. Interestingly, the behavioral LRTC estimated with DFA of the trial-by-trial detection performance was highly similar to the LRTC found in 3–30 Hz EEG and MEG oscillations [78] (Study I). Taken together, the dynamics of both behavior and neuronal oscillations were similarly nested in the ISFs.

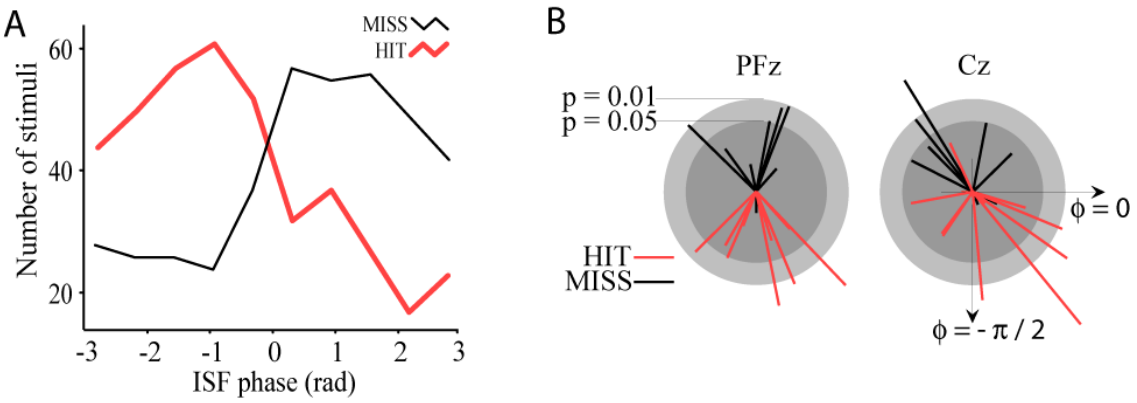

Fig. 2 The phase of infra-slow (0.01–0.1 Hz) fluctuations (ISFs) in scalp-recorded EEG is strongly correlated with the detection of threshold-level somatosensory stimuli. (A) The number of detected (HIT) and undetected (MISS) stimuli as the function of the ISF phase in a single experimental session. (B) Statistical significance and the mean phase ϕ of the phase-locking of HITs and MISSes to ISF in all subjects in two electrodes, a prefrontal (PFz) and a central (Cz) one.

Using phase synchrony to detect functional neuronal networks

In Study IV, we developed a methodology to estimate large-scale cortical interactions non-invasively with combined MEG and EEG recordings and source modeling based on individual cortical anatomy. Earlier, it was possible to obtain reliable synchrony estimates only by comparing synchrony between conditions. Now it is possible to estimate the absolute strength of interactions in ongoing data using the compensation method for spurious synchrony, which is based on investigating the contributions of data acquisition and inverse estimation on synchrony with simulated uncorrelated data (Study IV). We tested the applicability of the method by computing phase synchrony in the alpha-frequency band during the pre-stimulus period of a visual working memory (VWM) task. We found a network of oscillatory synchrony, where the posterior visual regions were strongly interconnected with central and frontal regions (Fig. 3).

The approach to map inter-areal interactions was applied in Study V, where we assessed inter-areal phase synchrony to characterize the graph properties of the functional networks found in frequencies in the range 3–90 Hz during the retention period of the VWM task. We found widespread phase synchrony in all frequency bands in both the source-level data and the MEG gradiometer data. However, the structure of synchronous networks in distinct frequency bands had different topology. More specifically, the alpha-band and beta-band networks displayed stronger small-world properties and had a more pronounced core-like structure than networks in the other frequencies. The degree distributions of alpha- and beta-band networks were characterized by a power-law, whereas exponential models suggesting a smaller amount of highly connected hubs were more appropriate for the degree distributions of the theta- and gamma-band networks. In addition, the gamma-band networks had higher cost efficiency than

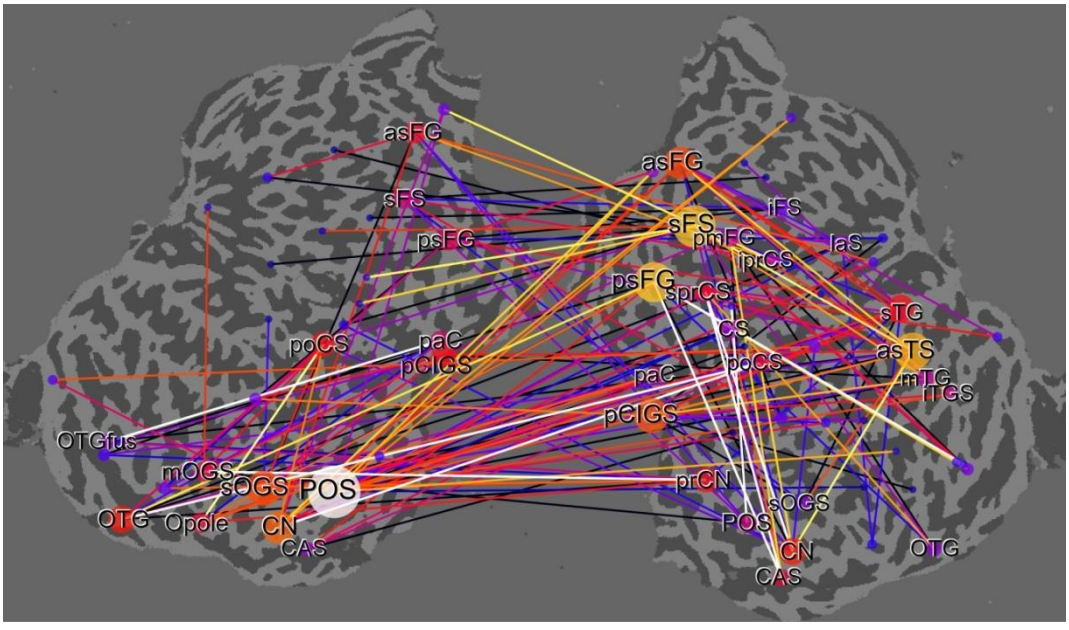

Fig. 3 The network of inter-areal phase synchrony in the pre-stimulus period of the visual working memory task presented on a flattened cortex. The dominating pattern of synchrony is between bilateral occipital visual cortices and widespread regions in the central, frontal and temporal cortices both within and between hemispheres (taken from Study IV).

networks in the other frequency bands. Finally, the effect of memory load was present as a more pronounced small-world structure in the alpha-frequency band for loads of 4 – 6 objects than for 1 – 3 objects. Thus, phase synchrony computed in the source-space can be used to identify behaviorally related functional networks.

Long-range temporal correlations are dissipated in depression

Study I is concerned with the possibility of dissociating the major depressive disorder patients from healthy age-matched controls on the basis of LRTC in neuronal oscillations that were recorded with MEG in the eyes-closed resting-state condition. We constructed spatial filters in the frequency-domain and projected the gradiometer data through these filters to obtain one time series for eachregion of interest [209]. We analyzed the LRTC from this data with the PSD and DFA methods [78]. We found that the LRTC were drastically weakened in the patients, practically to the level of white noise, in the theta frequency band of around 5 Hz, despite being robust in the alpha and beta frequency bands in the patients and in all bands in the subject group (Fig. 4). Intriguingly, the LRTC in the left temporo-parietal region was correlated with the severity of the disorder, which was quantified with the Hamilton depression rating score [172]. In addition, separate analyses of signals from two prefrontal EEG leads showed differences between patients and controls in the beta band.

We also found minor amplitude differences between the groups in the theta band, which were however not as significant statistically as the difference in DFA or PSD exponents. For this Thesis, separate analyses of changes in phase synchrony were performed. We computed channel-to-channel synchrony between the most anterior and posterior sensors and between right and left temporo-parietal sensors and found slightly larger alpha-band synchrony in the patient group (Fig. 5). Thus, the methods searching for correlations in neuronal oscillations were sensitive to changes in the spontaneous oscillatory activity in major depression patients.

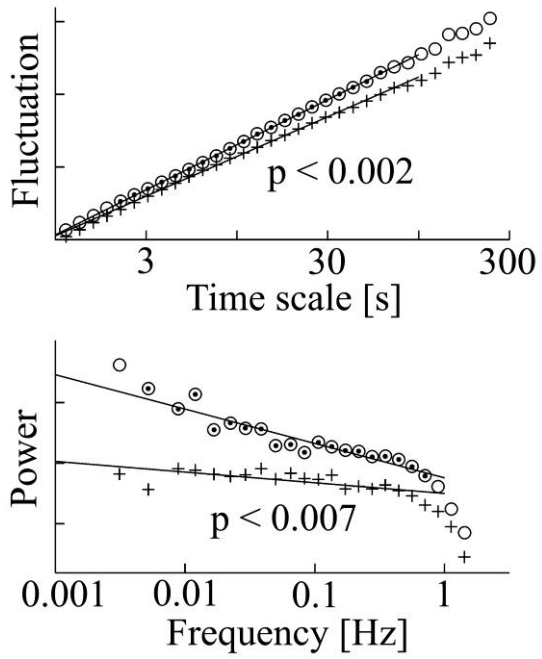

Fig. 4 Long-range temporal correlations in the 5–Hz theta-band are weaker in depressed patients than in healthy controls. Similar results and statistics between groups were obtained using either the detrended fluctuation analysis (DFA, $p < 0.002$, above) or power spectrum density (PSD, $p < 0.007$, below) method in a wide range of time scales (DFA) or frequencies (PSD). (Modified from Study I)

Persistent correlations localize the epileptic focus

The aim of Study II was clinically motivated: to find a feature in ongoing non-epileptiform brain activity that would reveal the location of the seizure-generating zone. An analysis of LRTC in ECoG data recorded with 45 – 64 channel subdural grids revealed that these correlations were emphasized in the vicinity of the epileptogenic focus. The location of the focus was clinically determined from seizure-onset recordings and confirmed by a positive outcome of resective surgery in each patient. We also found that LRTC was much more sensitive to the seizure onset zone than the oscillatory amplitude or deviations from the power-law scaling rule in DFA, which was quantified as the least-squares linear fitting error. Furthermore, DFA was not correlated with amplitude at a channel level in any frequency band, and a comparison between narrow band and broad band data showed that the fitting errors in DFA were larger in the broad band data. From these data alone it cannot be determined if the LRTC were actually strengthened close to the focus due to the epileptogenic mechanisms or decreased at a distance due to compensatory mechanisms. However, it is not the absolute values that are important in this case, but the gradient of LRTC towards the focus region.

Interestingly, we found that the spatial distribution of LRTC, which in unmedicated patients was inclined towards the focus, was leveled under medication with lorazepam, a drug widely used as an anti-epileptic. This effect was especially prominent in the beta-band, which was also the frequency band most sensitive to the epileptic focus. This balancing effect was caused by both an LRTC decrease in the regions proximal to the seizure focus and an increase in regions distal to it. This data is complemented by our previous findings of changes in phase synchrony in the same data (Fig. 1).

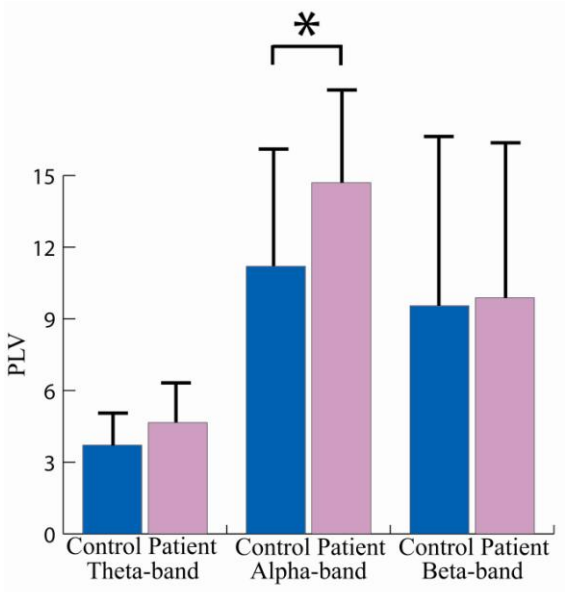

Fig. 5 Phase synchrony in the alpha-band, but not in theta- or beta-frequency bands, is altered between frontal and posterior MEG sensors in the depressed patients compared to the healthy controls. Phase-locking values on the *y*-axis are relative to the mean of mixed surrogate data.

Simulated data enables optimal estimation of inter-areal synchrony

In Study IV, we simulated neuronal activity by inserting random noise to dipoles in individual source models. Thereafter, we forward-modeled and inverse-modeled the simulated sources and computed the PLV between all source pairs. We clustered the most strongly correlated sources together using an iterative modification of the mean linkage clustering algorithm. We obtained a novel cortical parcellation using the clusters as cortical patches. The patches comprise a complete parcellation of the cortical mantle and have the highest possible source-to-source correlations within each patch. Cortex-wide inter-areal phase synchrony can then be estimated by inverse modeling the measured MEG / EEG data and computing phase synchrony among all patch pairs. We showed that using these patches in the estimation of inter-areal phase synchrony results in lower spurious synchrony than using parcellations based on anatomical information. Furthermore, we developed a method to compensate for the spurious synchrony arising in the data acquisition and inverse estimation stages to reduce methodological bias in the synchrony estimates. We also improved cross-subjects comparison by parcellating the cortex of each subject to the same neuroanatomical regions using the information obtained from MRI data. The synchrony data, which was initially computed in the individual source cluster parcellations, was then projected to the anatomical parcellation using weighted averaging. Then, the individual synchrony data represented on the common anatomical parcellation was directly comparable across subjects.

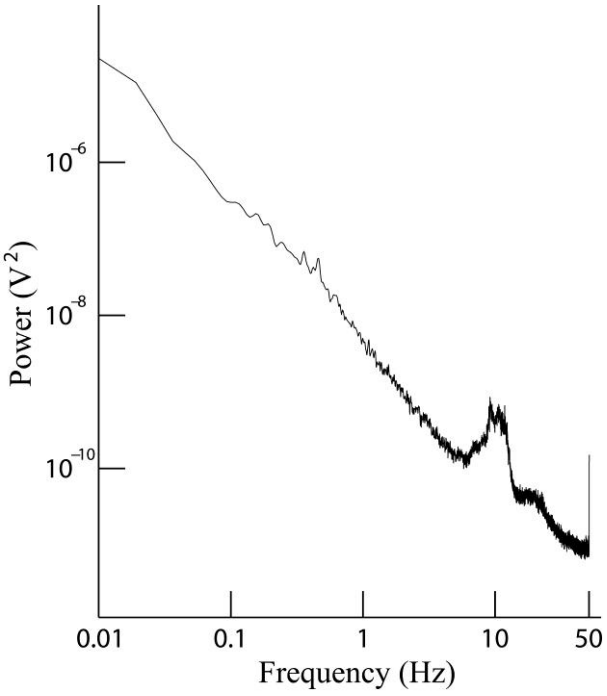

Fig. 6 The power in brain activity recorded with full-band EEG during a somatosensory detection task is distributed in a scale-free manner across a frequency range spanning several orders of magnitude. The power spectral density is computed in the central sensor (Cz) referenced to the mastoid and is averaged over 11 subjects. (Taken from Study III)

Discussion

Views on brain mechanisms of cognition

The significance of infra-slow activity in neuronal processing

We showed, for the first time, that electric infra-slow fluctuations (ISFs) are present and correlate with behavior in subjects during task execution (Study III; see Fig. 6). Earlier, such activity was found in sleeping patients [162]. On the other hand, our findings of correlations between ISF and behavioral performance and, similarly, between ISF and > 1 Hz neuronal oscillations show that behavior and oscillations are both nested in the temporal structure of the ISF. The results point towards a physiological mechanism linking the long-term variabilities in neuronal oscillations and behavior. The interconnectedness of behavior and > 1 Hz neuronal oscillations has been known long, but the finding of their common modulation is new. Additionally, the nested cross-frequency correlations identified in this study between ISF and > 1 Hz neuronal oscillations in several distinct frequency bands bring about the possibility of common coordination of neuronal oscillations over frequency. It should be investigated further if, indeed, ISFs have a modulatory role in neuronal processing (Study III).

Because of the long time scale of ISF, it is attractive to consider it in relation to metabolic activities that are imaged with methods such as fMRI and near-infrared spectroscopy. If there existed a link between ISF and metabolism, our results would be more easily interpreted. For example, the results would partly concur with an fMRI study in which subjective perceptions of weak laser-induced somatosensory stimuli were correlated with pre-stimulus activity levels in the thalamus and cortex [218]. A central issue that ISF and fMRI have in common is the time scale, with frequency ranges mostly below 0.2 Hz. In addition, whereas the fMRI blood oxygenation dependent (BOLD) signal is tightly linked to blood flow and metabolism, there are also indications that changes in blood flow and CO_2 give rise to measureable potential changes in the scalp, possibly through mechanisms related to pH and the blood-brain barrier [177, 188, 219]. Furthermore, the effects of hyperventilation-induced hypocapnia or otherwise down-regulated intravenous CO_2 can be seen with both fMRI and FbEEG [189, 219, 221]. Conversely, many neuronal phenomena are known to undergo very slow variations, especially the strength of oscillatory spatial correlations [148, 222–224]. The amplitude fluctuations of neuronal oscillations give rise to baseline shifts at all time-scales due to scale-free power variations and the asymmetry of oscillatory waveforms [58, 78, 148] (Studies I, II). Unfortunately, the mutual connections between ISF, LRTC and BOLD have not been investigated. There is, however, evidence on a connection between the amplitude of > 1 Hz neuronal oscillations and BOLD signal intensity [225–227]. In addition, ISFs are strongly correlated with a measure of cerebral blood volume (CBV) in a subject-dependent manner [220]. Neuronal activation is known to give rise to long-term metabolic changes [228, 229]. In light of our results (Study III) it would be interesting to examine whether the LRTC in the phase of ISF and in the amplitude of faster oscillations are correlated over cortical regions and in several frequencies. Hence, there are plenty of data on relatedness of slow modulations in electric neuronal activity on the one hand,

and blood flow and metabolism on the other, but the exact mechanisms behind these correlations are still unknown.

Spatial correlations from cortical phase synchrony

By utilizing the novel approaches developed in this Thesis, we found widespread phase synchrony among cortical sources in the pre-stimulus period and in the memory retention period of the visual working memory (VWM) task (Studies IV, V). The cortical locations found for the pre-stimulus alpha-band network overlap to a high degree with the brain regions associated with visual attention [211, 212]. This finding is thus compatible with the notion that in the VWM task the subjects attend to upcoming stimuli during the few hundreds of milliseconds before the stimulus appearance. The identified interactions among the network regions may be crucial for the neuronal implementation of the pre-stimulus attentional function [213, 214]. A study of lateralized visual attention recently showed that alpha-band synchronization between ipsilateral medial temporal and parietal regions increases with respect to the synchrony between the same regions in the contralateral hemisphere [215]. While our study design was not explicitly designed to study attention, we discovered that the pre-attentive state is generally characterized by an increase rather than a decrease in phase synchrony. However, it is still possible that unilateral attention causes further hemisphere-specific changes in synchrony.

The structure of the oscillatory synchronous networks varied significantly across frequencies (Study V). Robust small-world characteristics were displayed in the alpha- and beta-frequency bands. The small-world property with high local clustering of most connections and fewer long-range shortcuts between clusters was previously found in anatomical networks of the human brain and was attributed to simultaneous integration and segregation of information processing [107]. Our data showed that, indeed, the same organizational principle might apply to functional networks detected in the 3–90 Hz frequency range using phase synchrony. In addition to recognizing more pronounced small-world structure in the alpha and beta oscillations, we found that the structure of the phase synchrony networks in the gamma-band oscillations was organized to optimize efficient signal propagation. This spectral dissociation of network structure could mean that processing is distributed to distinct frequency bands having specific functional roles, which are integrated by cross-frequency interactions [87, 192, 216]. Future studies should aim at dissociating the correlates of frequency-specific networks during task execution, stimulus properties, responses and performance to elucidate their functional significance. Optimally, all the above factors should be separated already in the study design. At the same time, care should be taken that the task does not become too exhaustive for the subjects, because exhaustion increases the probability of task-independent thoughts and performance errors [217]. The principal conclusion is that phase synchrony between brain regions is very common during task execution and that different patterns of synchrony can be found in dissociated frequency bands.

Clinical prospects of neuronal oscillations

Diagnosing depression from abnormal oscillatory dynamics

The principal uses of EEG methods in the clinical environment are diagnostics and state monitoring. In our study of major depression patients we found that LRTC in theta-band oscillations were absent (Study I). Depression has earlier been related to amplitude abnormalities in the theta-band EEG activity [210]. This finding could simply be that of a trait indicator, *i.e.,* that persons with a tendency for mood disorders display diminished LRTC but that the onset of the actual disease is not associated with a further decrease in the indicator. However, the discovery that the strength of theta-band LRTC over the left temporoparietal regions inversely correlated with the severity of the disorder suggests that LRTC might actually be a state indicator. Proof of this postulate further requires that the indicator revert back to the normal range upon remission. This could be studied by measuring the same subjects that were measured in the acute state again after they have recovered.

The experiment was performed in the resting state, an inherent property of which is that the state of the subject is weakly controlled. Still, the physiological state of the subject in this condition is not random, as evidenced by high reproducibility of oscillatory peak frequencies and topography within and across subjects and the robust oscillatory LRTC found in this Thesis [79]. However, care should be taken that the subject does not become drowsy. We chose to probe the subjects' state offline by using the alpha-band amplitude in occipito-parietal sensors as an index of vigilance. We found no difference between patient and control groups, which suggests that our results are not due to different vigilance states of patients and controls. However, as motivation is known to be reduced in mood disorders along with several other factors related to behavioral control and cognition, the effects arising from issues related to motivation cannot be ruled out in this case [230].

After finding a correlation between the degree of the disorder and the LRTC, it is tempting to speculate that the diminished temporal correlations in neuronal oscillations could be causally related to at least some features in major depression, perhaps even the level of mood itself, instead of just signalling changed network activity. Arguably, losing the coordination of neuronal activity over time could compromise the ability of the individual to perform goal-directed activity or keep up coherent trains of thought during introspection. This kind of temporal fragmentation of the mental state could indeed underlie many cognitive impairments and explain the lack of long-term commitment observed in depressed patients.

Currently, we interpret these findings physiologically as reflecting the system-level dysregulation of the cortico-limbic-hippocampal loop, which is the leading candidate for generation of an array of symptoms known as the depressive disorder [231, 232]. As it happens, the MEG/EEG studies of depression can now be refined to inspect this hypothesis specifically, by applying the approach developed in this Thesis (Study IV).

Presurgical localization of the epileptic focus using autocorrelations

The prediction of seizures using nonlinear methods based on oscillatory power and synchrony is one emerging application of EEG-based methods in epilepsy [233–236]. However, the localization of seizure-generating zones from ongoing data has not been very successful (see, however, [237, 238]). We showed that LRTC are able to discriminate the epileptic focus with accuracy on the order of centimeters (Study II). Previously, epileptic hippocampi were shown to have SOC properties, and this finding was applied to lateralization of the epileptic hippocampus with results similar to ours, namely that the epileptic hippocampus had stronger LRTC than the non-epileptic [238, 239]. In addition, these studies found that the scaling behavior does not change when a seizure is approaching. This suggests either that seizures are an inherent dynamical property of networks that display strong LRTC, or that seizure generation is influenced from outside of the actual seizure-initiating regions. Our study presents a spatially more detailed structure of covariation between LRTC and the seizure-generating focus and shows that the LRTC changes are limited to a rather small region.

The classical view of generalized seizures is that they are generated by periods of excessive global synchrony originating from an epileptic network. However, this hypersynchrony principle has been challenged recently by theoretical studies showing that neural networks cannot maintain a high level of activity in presence of strong synchrony and, conversely, that synchrony is not needed for global high-amplitude activity [240–242]. Rather, it appears that global synchrony is increased when ictal activity spreads to subsequent regions, recruiting them to the same hyperactive neuronal mass in the process [243–245]. In this context it is interesting that benzodiazepines that promote the binding of GABA to the chloride-channel complex, prevents and even stops the seizures in some patients. While the main effect of GABAergic synaptic signaling is inhibition, it also has the potential to increase neuronal synchrony, because interneuron networks drive synchronized activity [32, 40]. Our ECoG data in patients as well as scalp EEG data in healthy subjects support the idea that benzodiazepine administration increases synchrony (Fig. 1) [246]. Interestingly, medication of patients with lorazepam also decreased the high LRTC observed in the seizure focus to a more normal level, despite increasing LRTC in the non-epileptic tissue surrounding the focus (Study II). Thus, the data on lorazepam-induced alterations in spatial and temporal correlations in neuronal oscillations suggest that GABA plays a role in regulating oscillatory correlations in epileptic neuronal networks. This idea is supported by the findings of altered GABAergic function during epileptogenesis [247–249]. Our results show that the LRTC may be state-dependent and suggest that the level of LRTC might indicate the probability of seizures originating in a cortical area.

One of the objectives in Study II was to extend the evaluation of the seizure-generating zone to non-invasive methods, which would further speed up the evaluation process and cut down its costs. First results obtained with scalp EEG have shown that the focus could indeed be localized with DFA even from non-invasive recordings [250]. This opens up the possibility to inspect whether the LRTC are normalized whenever an efficient treatment, most often medication, is found. Another view arising from our results is that the increase in LRTC is probably more related to generation of the epilepsy syndrome, or epileptogenesis, than to generation of the individual seizures, or ictogenesis. This hypothesis could be tested with animal models of epilepsy by following the development of the local LRTC from the start of the epileptogenic

process to the final stage of full-blown epilepsy syndrome characterized by recurrent seizures [251].

One way to interpret enhanced LRTC is that activity of high amplitude is more likely followed by further high-amplitude activity than low-amplitude one. Strongly recurrent activity in neuronal networks could underlie such behavior. Then, it could well be that strong LRTC are related to excitatory feedback structures, which in turn predispose to epileptic activity. While this connection between local neuronal structure, epilepsy and LRTC is speculative at this stage, it is of particular interest to note that oscillations and the strength of LRTC in healthy twins has a remarkable genetic background [205]. Thus, the well-established heritability of some epileptic disorders could be linked to increased LRTC through the influence of genetically determined structure and dynamic properties of neuronal networks.

The desire to develop clinical tools to aid in the pre-operative localization of the seizure focus was the long-term goal set when initiating Study II. Despite the promising results, the approach is not yet ready for routine use. Above all, the sensitivity and specificity of the index used in localization should be quantified and increased. The primary way to do this is to adjust the data acquisition and signal processing parameters, such as the patient's state, channel setup, filter settings and signal processing methods for scaling analysis and increase the amount of collected data to gain higher statistical power. Finally, the approach should be tested with non-invasive MEG/EEG recordings on a large number of patients.

Other disorders studied using neuronal correlations

In addition to major depression and epilepsy that were given attention to in this Thesis, methods to investigate spatial and temporal oscillatory correlations have been applied to other disorders as well. These studies give further support to the conclusion that such approaches can be used to identify brain disorders. Additional data on the correlational aspects of neuronal oscillations in well specified disorders might also help to elucidate the functional roles and origins of oscillatory correlations. Lowered memory function and level of consciousness in Alzheimer's disease have been assessed using both LRTC analysis of oscillatory amplitude and functional connectivity, with and without graph methods [252–254]. Changes in oscillatory synchrony in motor areas, thalamus and cerebellum associated to tremor have been found in Parkinsonian patients [255, 256]. Schizophrenia is a particularly interesting disorder for studies of synchrony, as neural connectivity lies at the heart of one of the most long-standing hypotheses for its origins, the disconnection hypothesis [257]. Lately, this hypothesis has received experimental support from EEG studies showing that cross-channel synchrony is decreased in the beta- and gamma-bands in schizophrenic patients performing Gestalt perception tasks [258, 259]. However, despite the task-dependent findings of lowered synchrony in signal space, a definite relation between the roots of the disorder and large-scale reduction in connectivity remains unspecified.

The endophenotype concept: biomarkers from brain dynamics

An endophenotype, sometimes also called an intermediate phenotype, is a heritable biological marker which can be related to a psychiatric disorder phenotype in the population level. Thus, it can be interpreted as a vulnerability marker that is influenced genetically but not directly related to the disorder itself [260]. The idea behind the use of the endophenotype concept in studying neurophysiological disorders is to investigate the neuronal correlates of the genetic influence without the effects of the acute disorder distracting the analysis. In research, brain imaging data of patients and their family members is often used. A commonly proposed candidate for the neuronal endophenotype is functional or effective connectivity [261]. The methodological advances in this Thesis help to perform connectivity studies with MEG and EEG recordings with higher accuracy (Study IV). This opens up new possibilities to track the biomarkers of various disorders. However, also oscillatory amplitudes and LRTC have been shown to be under genetic control and could therefore be considered as additional candidates of specific endophenotypes [205] (Studies I, II). More widespread use of the endophenotype concept in research could shed light on the issue of state versus trait dependency of neuronal correlates found for some disorders [71, 259] (Study I).

Methodological considerations

Restrictions of measurement techniques

When investigating the brain function of healthy human subjects and most patient groups we are restricted to non-invasive measurements. It is therefore of crucial importance to understand what kind of data can be collected with these methods and what kind of neuronal phenomena cannot be captured with them, as this knowledge also has implications on experimental design. To start off with, the electromagnetic fields that are strong enough to be measured extracranially are generated by post-synaptic neuronal activity that is temporally and spatially congruent over a macroscopic tissue volume, at least several millimeters in size [179]. The principle in brain processing of representing more refined information with progressively sparser neuronal coding could compromise the ability of MEG and EEG to measure higher-level information processing and neuronal representations of higher abstraction [262, 263]. Furthermore, even if a neuronal source is strong, coherent and temporally stable, it cannot be seen if the topography of the generated field does not extend to the distant sensors. This can be due to the multipolar nature of the source or its orientation [39, 179]. Furthermore, EEG is sensitive to all currents in the brain, but sources that are oriented radially to the local intracranial surface are more weakly detected with MEG. In an idealized spherical conductor model, radial current dipoles do not generate external magnetic fields. Luckily, most of the cortical surface is folded to the sulci, and the currents that flow normally to the cortical surface are then tangential to the approximately sphrerical conductor surface and therefore visible to MEG. Finally, several simultaneous sources that could be seen individually can mask each other. These limitations make clear that the oftentimes overlooked logic truism “absence of evidence is not evidence of absence” holds especially in the context of MEG and EEG studies.

The problem of source visibility is related to the problem of source separation. First, this problem arises when using channel-level data in performing complicated univariate or multivariate signal analyses, where the targets of these analyses are the neuronal currents. However, because of the complexities related to estimating the sources from MEG or EEG measurement data, the analyses are most often performed in signal space, which deteriorates their interpretability. Taking the dynamics into account make the signal space approach even more vulnerable, as the signal space data is very sensitive to changes in the geometry of the source configuration. As pointed out above, it is especially daring to draw conclusions from pairwise channel-to-channel correlation data. We proposed estimating pairwise oscillatory synchrony from minimum-norm modelled combined MEG and EEG data (Study IV). The only channel-level analyses that could give comparable results with inverse modeled data are analyses made with the planar gradiometer sensors after matching the head coordinate systems of all subjects to a common location with regard to the sensor array using the signal space separation method [264, 265]. However, our investigation of the networks formed by phase synchrony during VWM showed that this is not the case (Study V). One approach to validating phase synchrony captured by MEG and EEG methods is to compare their performance to the synchrony patterns measured with concurrent ECoG [266]. Simulations show that ECoG channel data is a valid tool for quantifying synchrony if the reference electrode is relatively silent, for example located in the scalp, whereas scalp-recorded EEG is not [267–269]. The best way to increase the locality of the EEG measurement data is to apply the bipolar montage, where the signals in adjacent electrodes are subtracted from each other. With proper inverse modeling, on the other hand, one can get over the reference electrode problem entirely.

Relationship of electric recordings to other functional imaging methods

Knowing the relationship between electrical and other functional brain imaging methods would allow integration of knowledge from various fields by enabling comparison between the results from different methodologies. The non-electric functional imaging methods are based on different aspects of metabolic activity, such as cerebral blood flow, the extraction of oxygen from blood by brain tissue, the proportions of oxygenated and non-oxygenated haemoglobin in blood, or distribution of radioactively labeled functional molecules. However, due to the complexity of the metabolic interactions in the brain and across the blood-brain barrier, no one-to-one relationship between these measures and the measures of electric brain activity in any scale can be defined [177, 183, 184]. Still, finding correlations in signal generation between different functional brain imaging modalities, most notably between the fMRI and the MEG / EEG, would have far-reaching consequences and they are therefore under intense investigation and debate [185–187].

From the point of view of this Thesis, the interrelationships between fast (> 1 Hz) oscillations, infra-slow (< 0.1 Hz) EEG fluctuations and the BOLD signal are of specific interest. It has been suggested that the ISFs reflect dendritic currents in the cortex [178]. However, it was recently demonstrated that the generation of infra-slow EEG signals is in many cases incompatible with a neuronal origin [220]. Instead, the ISFs were proposed to be generated across the blood-brain barrier in a CO_2-dependent manner [177]. The crucial point here is that both of these mechanisms may contribute to the excitability of the cortex, the first one by dendritic currents flowing to the cell soma and the other by pH-dependent mechanisms [188]. Thus, the

modulatory effect of ISF on neuronal oscillations is proposed to relate to changes in gross neuronal excitability ([162]; Study III). On the other hand, the fMRI signal has been found to co-vary with fast oscillatory activity and be altered after a hyperventilation challenge decreasing intravenous CO_2 [187, 189]. A concurrent FbEEG and fMRI measurement, using a DC-coupled amplifier having a wide dynamic range to withstand the fMRI magnetic field gradient-induced signals combined with advanced artefact correction methods, could shed more light on this issue. These data on the interrelationships between oscillatory neuronal activity recorded with EEG and MEG, infra-slow activity recorded with FbEEG and BOLD signal recorded with fMRI demonstrate the complex multi-scale and multi-mechanism nature of functional brain imaging data and illustrate the difficulties in integrating knowledge across the diverse fields of functional studies of the brain.

Developments and potential flaws in data analysis

When performing band-pass filtering to uncover oscillations one should be aware that artefactual oscillations that may be generated from non-oscillatory signal transients, for example epileptic spikes or artefactual signal baseline shifts. The simplest, although tedious, way to avoid this is to manually inspect the filtered and unfiltered signals side-by-side. On the other hand, considering that the origin of oscillatory time series is in neuronal dynamics, it is not conceivable that the recorded signals would display pure harmonic oscillations even in the absence of measurement noise. In dynamical terms, the neuronal oscillations can be smooth limit-cycle oscillations, either stable or not, or they can be generated by reverberation of more spike-like activity. Furthermore, the seemingly rhythmic activity from complex neuronal dynamics may be strictly non-periodic, or may change the principal frequency in short and long time scales [194]. These possibilities call for development of less simplistic adaptive filtering techniques for neuroscience applications.

The analysis for LRTC in MEG and EEG data with the DFA method may have some vulnerabilities in its established form [78, 198] (Study I). When linearly fitting for power-law scaling in double logarithmic coordinates the fitting range is a free parameter. The time scales used for fitting vary from sub-second time scales up to 500 s [78, 203, 205, 238, 252, 270–272] (Studies I, II). Finding the optimal range to be used in the analysis of neuronal oscillations and quantifying the quality of the fit have not received much attention. It has been suggested that the window in the lower end of the fitting range should be wider than the possible artefactual effect from signal filtering and that the maximum window width should not exceed one tenth of the length of the analyzed time series to maintain good statistics even in the longest time scale [273, 274]. The goodness-of-fit in DFA can be quantified for example by the mean squared error of the linear fit across all window lengths (Study II). This can be used to validate the fitting range by requiring that the error is smaller than a selected criterion for the goodness-of-fit. Fitting error can also be computed for other kinds of fits than the linear fit to check if non-linear fits have remarkably lower fitting error, which would reveal that the signal does not display power-law scaling. We tested this approach and found that in general the error from a linear fit was as small as the error from a second-order polynomial fit in analysis of oscillatory amplitude time series (Study II). Furthermore, we suggested that the sensitivity of DFA analysis to artefacts in the data, often of technical origin or produced by pathologic activity or movement, could be reduced by using the median instead of the mean when computing the typical fluctuation for

each time scale (Study II). This is because the median of a sample population is less sensitive to large outliers than the mean. Finally, another potential source for mis-interpretations of LRTC findings is the amount of available data, because the scaling exponent may change depending on the amount of data due to finite size effects. Therefore, surrogate data of the same length but with no correlations should be analyzed identically to the experimental data to rule out the effect from finite sample size (Studies I, II).

In addition to temporal correlations, methods to quantify correlations over the spatial dimension were also developed and applied to the analysis of MEG data in this Thesis (Studies IV, V). The approach of combining distributed inverse modeling to full-scale analysis of inter-areal synchrony makes a significant contribution to the field, as no comparable method to map phase synchrony in the extent of the entire cortex in a data-driven manner existed before. The previous approaches to mapping synchrony between oscillatory sources were restricted to selecting a few regions of interest (ROIs) and computing the correlations either from the ROIs to all other regions or solely between the ROIs [215, 275–278]. ROIs are most often fixed beforehand or deduced from the amplitude data [206]. In addition, the previous studies limited the analysis to a single or a few frequency bands. Another important advance in our study is the method to estimate spurious contributions from data acquisition and inverse modeling to inter-areal synchrony. This enables recognizing the functional connections even from ongoing data, without contrasting the results to another experimental condition, which is especially important in the case of synchrony with zero phase lag. These properties are based on an optimized clustering of sources, where optimization refers to maximizing the separability of source clusters in the sense of cluster-to-cluster phase synchrony (Study IV). The inter-cluster separability criterion is further motivated by the graph-based approach for analyzing the structure of source-level networks (Study V). There, a significant source of error in the estimation of the network parameters are the artifacts due to similar connectivity patterns of neighboring brain regions, or graph nodes, which arise in the data measurement and analysis. We argued that our separability criterion is optimal for computing the graph-theoretical measures of phase synchrony networks. Yet, rigorous simulations with various models for neuronal activations and inter-areal interactions are needed to judge the relative performance of the source-space and the signal-space approaches in terms of estimating the strengths and locations of the interactions. One necessary drawback of making the analysis in source space is that the results become dependent on the models used in inverse estimation. For example, in our approach the modeling is restricted to cortical sources, which makes the model inadequate if activity in the subcortical structures or the cerebellum significantly contributes to the MEG or EEG signals [256].

From correlations towards causal relations

In definitions of neuronal connectivity, a distinction is often made between functional and effective connectivity [94]. Whereas functional connectivity is determined as statistical relatedness between two brain regions, effective connectivity defines a causal relationship between the regions. The studies in this Thesis have not assessed the possible causalities in estimates of functional connectivity. However, real neuronal connections are directed, even though often reciprocal [91, 107, 108]. Furthermore, neuroscientists and clinical practitioners alike are more interested in causally separable effects. Several methods have been developed to

estimate causality from electrophysiological time series [279–282]. These mostly utilize the idea of Granger causality, defined as the additional benefit of using one time series to predict the other. This approach has the potential to give important insights to neuronal interactions, and allows the use of more sophisticated graph approaches for assessing the large-scale functional architecture of the brain.

The estimates of causality outlined above are still only statistical estimates. Effective connectivity can be directly studied in humans by combining transcranial magnetic stimulation (TMS) or transcranial alternating or direct current stimulation in conjunction with EEG measurements. The premise in all three approaches is to induce "virtual lesions" in the brain and to study the consequent changes in recorded brain activity [283, 284, 285]. Recently, it has been observed that direct brain stimulation can also speed up the processing of stimuli between several brain regions [286]. Combining brain stimulation to brain imaging is a promising approach to bring causal relationships to the investigation of brain and behavior [287–289]. These approaches benefit from the knowledge of connections in the underlying neuronal structure, which can be studied for example by diffusion-based MRI methods, because all functional and effective connectivity must be based on anatomical connectivity [111, 112].

Oscillatory correlations and organization of behavior

Oscillations pervade all temporal and spatial scales

In the studies composing this Thesis, ongoing activity was recorded in the brain in the frequency range 0.01–100 Hz, spanning four decades in magnitude. It appears that in long-time averages of spectral power no single frequency band dominates the electric activity either in wide-band EEG or in the modulation frequency distribution of narrow-band oscillatory amplitudes (Studies I – III; Figs. 4, 6; ref. [5]). This implies that brain activity is doubly scale-free, so that spectral densities scale as $\sim f^{-\beta}$. Because no single time scale dominates broad-band or narrow-band spontaneous brain activity there seems to be no reason to restrict the studies exclusively to only sparse frequency ranges of interest. Scale-freeness suggests that the brain flexibly recruits neuronal oscillatory assemblies upon need, and that these assemblies do not have common operating frequencies.

Oscillatory activity is coordinated by correlations

The $1/f^{\beta}$-type scaling of EEG power as a function of frequency seems to imply a non-stationary "random wandering" of oscillatory frequencies, instead of a collection of fixed-point oscillators. However, in this Thesis we found surprising regularity among neuronal oscillations in the form of spatial, temporal and nested correlations (Studies I – V). The correlations in 0.01–90 Hz oscillation were significantly different from random. One explanation for $1/f$ scaling could be that despite there being some characteristic operating frequencies, called "resonance frequencies", in freely oscillating neuronal networks, the interactions between oscillators affect these frequencies through frequency locking [1, 91]. Because the spontaneous brain activity is distributed to a wide frequency range, the activity with $1/f^{\beta}$-scaled power is often referred to as

background noise. However, even if the background activity would statistically resemble a noise process, it does not mean that the spontaneous neuronal activity would be noise, as in defining it "the opposite of signal". Furthermore, this is not random white noise but colored noise scaling as $\sim f^{-\beta}$ with $\beta \neq 0$, which is posed between random and predictable types of noise and displays LRTC. From $1/f^{-\beta}$-scaling it follows that oscillatory activity can be observed in any frequency band by narrow-band filtering.

In the context of this Thesis it is possible to draw a clear distinction between noise and coordinated neuronal activity: neuronal activity is not noise if it displays spatial or temporal correlation structure statistically different from random. This view is supported by the ideas that synchronized activity is more effective on downstream neurons and that the lack of correlations between neuronal oscillations would constitute an active mechanism prohibiting communication [31]. Although oscillations have been known since the advent of EEG, it is only now that we start to see how they are coordinated locally and globally and how this coordination possibly relates to system-level control of stimulus processing and behavior (Studies I – V).

Oscillatory organization has functional significance

The studies in this Thesis showed that there is inherent organization in oscillations that can be observed by estimating their correlation structure. Do these correlations display some kind of functional significance? Our studies provide preliminary evidence that the synchronous networks correlate with task execution, and that changes in some of these networks reflect task demands (Study V). Furthermore, we found that the behavioral dynamics in the somatosensory detection task are strongly correlated with the ISFs and that the faster neuronal oscillations are in a cross-frequency nested relationship with ISF (Study III). In the studies of major depression disorder and epilepsy we found that oscillatory temporal correlations might mediate the related symptoms and have diagnostic potential.

Traditionally, the amplitude of neuronal activity has held a central position as the target of study in research using EEG and MEG. Lately, the phase has emerged as a potentially important variable. The findings in this Thesis support the view that the phase plays a major role in organizing oscillatory neuronal activity [31, 85–87] (Studies III – V). From the theory of dynamical systems it is known that the phase exists in all systems. Interestingly, this is connected to the phase being sensitive to perturbations, as it does not recover from them but accumulates the effect of small deviations over time. This could be the basis for the sensitivity of the phase in quantification of interactions between systems. In practice, the phase has faster dynamics than the amplitude, and it can usually be estimated more accurately, *i.e.*, with higher SNR, from a noisy signal [57]. Furthermore, evidence is mounting to suggest that the phase can functionally entrain the amplitudes of faster oscillations [216, 290, 291] (Study III). To add to the importance of the phase, it is known from cellular-level studies that the phase of LFP oscillations is closely linked to population-wide spiking activity [20, 21]. These considerations suggest that the customary analysis of oscillatory amplitudes should be corroborated with analysis of phase to interpret data correctly.

Neuronal excitability and cross-frequency hierarchies of oscillations

We found that the ISF phase correlates with the detection probability of threshold-level stimuli and suggested that this is due to excitability-induced changes in responsiveness of the cortex to external stimuli (Study III). Similar conclusions have been reached in other experimental studies regarding oscillatory activity in higher frequency bands. The response amplitude to vibrissa deflection in mice was dependent on the phase of the oscillatory LFP, resulting in a skewed distribution of response amplitude as a function of the phase [292]. In humans, the auditory evoked potential was found to be dependent on the phase of ongoing broad band activity [293]. On the other hand, visual threshold-level flashes were more salient when presented in-phase with alpha- and beta-band EEG oscillations [294]. Finally, a visual mask paradigm showed that the phase of EEG alpha-band oscillations has an effect on the detectability of the masked stimulus [295].

It is interesting to compare these relationships between the phase of ongoing activity and event-related or behavioral responses to recently discovered modulations of ongoing oscillatory amplitude by the phase of a slower oscillation. These nested relationships have been found between theta and high-gamma bands as well as alpha and gamma bands in humans, and delta, theta and gamma band oscillatory activities in monkeys [216, 290, 291]. Although the causal relationships between these oscillations have not been estimated, the implicit assumption in all these studies is that the phase of the lower frequency modulates the amplitude of the higher one, as is the case with similar modulations of behavior (Study III). This growing body of data is compatible with the idea of an oscillatory hierarchy, where cross-frequency nested relationships coordinate excitability and information processing in the brain [88] (Study III). Such cross-scale organization has implications to mechanistic accounts of stimulus processing [88, 295, 296].

On structure–function relationships

In nature, form goes with function. The intricate form of the cerebral cortex has evolved to serve the variable functions of the brain. Indeed, inspecting the neuronal structure has offered profound insights to brain function. One of these insights that has special relevance for this Thesis is that the brain areas sharing similar connectivity also share similar functionality [124]. The local and large-scale structural connectivities thus generate the possible set of dynamic operations in brain function and set boundary conditions for it. For example, the same stimulus sometimes elicits different behavior in different contexts, and sometimes even in the same external context (Study III). For example, a change in the behavioral response to a stimulus could be due to a bottom-up effect leading to a different neuronal representation or due to a top-down effect of ongoing brain state leading to a different interpretation of the same neuronal representation. This difference must have its origins at the different fates of the neuronal momentum evoked in the sensory systems and spreading further along the possible structural connections as channeled by the functional brain state. According to this connectivity view on brain function, the patterns of neuronal interactions are central in the flow of stimulus-related information (Study V).

Modeling studies

Modeling can be used as a tool to investigate globally emerging functional structures in healthy and disordered neuronal networks by combining the network view, via understanding of graphs, with neuroscientific knowledge of local neuronal dynamics and interaction mechanisms. Modeling aims at finding and explaining universal behavior with minimal models, and it may yield results that are relevant for experimental observations. Modeling approaches have sometimes been criticized for that only such phenomena can be reproduced by the models that have been explicitly included in them. However, agent-based simulations of neuronal systems have produced qualitatively new kinds of global behavior that could not be predicted from the relatively simple local units that the system has been implemented with. A common approach to studying the relationship between local activity and global structure is to simulate simple neuronal models or physiologically more realistic neurons on different connectivity topologies, which can be constructed either mathematically or acquired from biological data. Modeling is becoming an important instrument on our way to the ultimate level of knowledge of cognitive systems, engineering them.

Recent modeling efforts show that the connectivity defined by the neuronal structure often dictates the dynamic behavior as well. However, the dynamics are highly flexible and may sometimes become almost independent of the underlying structure. In a pioneering study, the structural constraints that produce maximal complexity of functional connectivity were found to be highly similar to real cortical connectivity [107]. Here, the measure of complexity was motivated by the ideal of a balance between segregation and integration of functional processing and was defined as the combination of locally coherent activity and global variability [107, 125]. Interestingly, the segregated dynamically coherent clusters were associated with known functional roles for the corresponding brain regions. This efficient combination of segregation and integration was above linked to biologically realistic small-world graphs on the basis of their structural properties only. In another biologically motivated modeling study the aim was to characterize the structures that would give rise to both fast responses and ensuing coherent oscillations, as observed in the insect antennal lobe after odor perception [18, 297, 298]. The main finding was that whereas regular lattices maintained oscillations and random networks were able to respond quickly, only small-world networks combined these two central features of neuronal processing. In the context of this Thesis, the coherent oscillations are of special interest. Later, it was found that the small-world topology also enhances global synchronizability of the network compared to other types of graphs, but that a homogenous node degree distribution further differentiates a high synchronizability regime [299, 300].

The above findings mostly deal with the dependence of global dynamical properties of networks on the topological structure. However, simulated neuronal dynamics on graphs have also been analyzed for more detailed local structure, for instance modularity and hierarchical relationships. An interesting series of studies showed that the temporal dynamics in hierarchical graphs depend on the level of spontaneous activity, which is a finding with direct relevance for the analysis of data from real neuronal networks [301–303]. At the lowest level of excitation, the dynamics is dominated by waves or avalanches originating from the central hubs. When spontaneous activity increases, synchrony in the densely connected local communities starts to build, and the dynamics become modular. With yet higher spontaneous rates, the activity becomes less and less dependent of the underlying topology [301, 302]. The reasons for this

kind of behavior might be found from the shorter time scales required for synchronization and the higher stability in the lower levels of structural hierarchy [303]. These simulations have an interesting connection to a simulation made on macaque connectivity data. It was found that whereas the structural connectivity highly overlapped with the long-term average of functional connectivity, this average consisted of numerous metastable synchronous states at shorter time scales that were each largely independent of the underlying structure [304].

These simulation results show that varying the topological properties of underlying structural connectivity may substantially alter the global dynamics, and that the small-world network organization, earlier found in neuronal structures on both a local and a global scale, has some unique properties that support efficient information processing.

Interplay between structure and function in brain disorders

An age-old mystery in neurology is why the behavioral effects from even drastic brain insults, such as lesions and tumours, may be negligible, whereas certain rather local damages have catastrophic consequences to the individual. These findings originally led to a view of the brain as consisting of independent local processing units, the roles of which were determined based on anatomical and behavioral data from lesion patients. However, the emerging modern view of brain function consisting of co-operative networks is challenging this view. The minor effects of certain lesions imply that the brain structural and functional networks are very robust to random failures. This is a result predicted by analysis of the error tolerance of many natural and man-made networks with scale-free degree distributions [92, 96, 97]. The small effect of random node removal, the graph counterpart of local brain lesion, on system-level connectivity is a consequence not only of redundant multiple connections, but the central role of a small number of hubs on maintaining the global structure. The drawback of this organization is that such systems are highly sensitive to targeted attacks on these central hubs [97]. The possible links between neuronal interaction networks and brain disorders, again, extend from local lesions to system-level diseases. Many disorders are now seen as dysconnection syndromes, even if their origins are not currently understood [305].

Brain lesions. The vast majority of knowledge on the functional roles of different brain regions and structures has been obtained with animal *in vitro* and *in vivo* recordings. In humans, the function of specific brain regions are presently investigated with imaging methods such as fMRI, but lesion studies were, for a long time, the prevailing methodology and are in fact applicable even today [306–308]. However, the connectivity-based approach on brain function and, conversely, dysconnection syndrome view on brain disorders, suggests that lesions affect not only the local information processing, but that global effects may originate from severed inter-areal connections [305]. With the knowledge of the structural connectivity in the intact human brain, also the behavioral and cognitive effects of lesions can now be approached with modeling studies [309]. Large-scale modeling in realistic anatomical networks shows that the lesion often has non-local effects, more so for lesions in association cortices than for instance in sensory cortices, and that the effects on functional connectivity can to some extent be predicted from the structural information [310, 311]. Similar findings have been made in MEG and EEG studies of brain tumor patients by estimating oscillatory synchrony and comparing these patterns to healthy controls [312, 313]. However, full modeling of cognitive effects of lesions,

degenerative diseases and other disorders is still a stretch away. An interesting application of lesion modeling could be the re-modeling of task-related networks and related behavioral changes, when task execution is perturbed using TMS. This approach could be used as a way to corroborate the results from many modeling studies.

Schizophrenia. The most classical dysconnection syndrome is schizophrenia, the Greek meaning of "split mind" already carrying the idea of the roots of the symptoms. It is also a central topic in graph theory motivated network studies of brain disorders and is therefore briefly reviewed here. Specific findings of impaired perception-related synchrony in schizophrenia were reviewed above, but there are also network-level graph theoretical studies on the possible underpinnings of the disorder. They show that the structural hubs and the anatomical hierarchy in the cortical structure are different in schizophrenics compared with controls [314]. The functional small-world networks at rest have also been found to be disrupted in schizophrenics, as revealed by both fMRI and EEG methods [315, 316]. Furthermore, the cost-efficiency of networks in the alpha and beta frequency bands is reduced in the schizophrenic patients in an *n*-back working memory task [98]. Thus, the architecture of structural and functional networks has been changed in schizophrenia, but the causes underlying specific symptoms related to this disorder are yet to be elucidated [257–259, 317]. For this end, it might be fruitful to pursue also the dynamics, not only the structure, of the networks. To motivate this approach, it is known that schizophrenic patients display not only a different level of performance, compared with healthy subjects, in many cognitive tasks but also distinct temporal patterning of performance [158]. Drawing on the approaches presented in this Thesis, combining the study of spatial and temporal correlations to study the dynamics of the functional networks could be especially effective in schizophrenic patients.

Alzheimer's. Another brain disorder that has gained considerable attention lately is Alzheimer's disease, a currently incurable degenerative dementia. Using non-linear analyses of fMRI and MEG / EEG data, it has been found that individual brain regions have different behavior in Alzheimer's patients compared with healthy controls [252, 318]. Structural studies indicate that Alzheimer's is related to localized changes affecting global network properties, such as higher clustering and longer path lengths in patients [319]. MEG and fMRI studies performed in the resting state have shown that parameters of global functional networks also differ between patients and healthy controls, which could give rise to some of the symptoms of the disease [253, 320, 321]. Finally, network reactivity in change-of-task situations was evaluated with fMRI and found to be impaired in Alzheimer patients [322]. These findings suggest that Alzheimer's is a disease that affects the organization of neuronal structure and function at the level of the whole brain.

Epilepsy. Although not often related to changes in structural or functional connectivity, but rather to neurotransmitter functionality, the conventional notion of epilepsy as a hypersynchrony disorder lends itself well to analyses utilizing relationships between structure and function. Cortical changes in local structural networks have indeed been identified [323]. Furthermore, it has been pointed out that epilepsy syndromes are commonplace in the hippocampus, in which the neuronal structure involves recurrent connections, whereas epilepsy is very rare in the cerebellum, in which the neurons connect mostly locally and in a feedforward manner [324]. Thus, strong feedback loops could predispose to epileptic activity [325]. A close connection between epileptic seizures and local network structure is manifest in a realistic large-scale

dentate gyrus model, where granule-to-granule cell short-range connectivity organized around hubs was found to promote seizures, and even a small number of long-range projecting hilar cells was enough to keep the network in a hyperexcitability-promoting small-world regime [326, 327]. In a study with different types of neurons simulated in a small-world topology, more complicated transitions from normal to seizure and from seizure to bursting activity were observed with changing network parameters, but, remarkably, the seizure regime stayed always within the limits of a small-world network [328]. Finally, a glutamate-induced epilepsy in cell cultures was found to radically alter the network structure from small-world towards random [329]. Thus, although the changes in network structure associated with epilepsy and its functional consequences are not known exactly, it is clear from these studies that the non-random structure of local neuronal networks is intimately related to the probability of generating epileptic events. Regrettably, these studies did not quantify either LRTC or synchrony in the networks, so the relevance of network structure to LRTC remains to be determined. In conclusion, studying the neuronal bases of brain disorders and their symptoms offers an interesting field for applications of spatial and temporal correlations in neuronal oscillations.

Systems view on neuronal correlations

Functional network architectures from fMRI studies

The nature of the brain activity measured in the resting-state has some commonalities between MEG / EEG and fMRI. For example, many statistical properties of the signals are regular over time and the topographical patterns are similar between subjects. In addition, the amplitude of ongoing activity is high in comparison to stimulus-evoked activity. As pointed out above, the study of systems-level functional connectivity with EEG and MEG is still in its infancy, largely because of methodological challenges [206] (Study IV). Therefore, the correlation structure between brain regions has mainly been characterized with fMRI using different methods to assess functional connectivity. Popular ways to localize correlated voxels with fMRI are to search for connections starting from a seed region, to perform independent component analysis (ICA) of all recorded voxel signals, and to compute all pair-wise correlations in the level of ROIs or individual voxels [330–333]. Most often, the correlations are tracked from signals filtered to frequencies < 0.2 Hz.

Spatial correlations in the resting state. The first observations of coordinated and elevated resting-state activity came paradoxically from task-evoked studies, when it was noticed that the same areas were often reported to be negatively reactive across very different tasks. Thus, the baseline state prior to engagement in a task-specific action was invariant across studies and the regions showing this effect were therefore coined to comprise the default-mode network [334–336]. In the light of EEG and MEG studies reporting robust eyes-closed and eyes-open oscillations and task-related deactivations, these findings might not come as a surprise, but the direct functional correlations established between the deactivated regions have interesting consequences on studying brain activity [163, 333, 335]. In addition, the very slow time scales involved in the deactivations and mutual correlations are of interest, and should be compared

with electrically recorded data. Furthermore, it has turned out that the default-mode network is not the only network that can be recovered from correlations in resting-state data, but many regions observed to activate in task settings also are functionally connected during the resting-state [331, 332]. Interestingly, there is increasing evidence that the activities in the default-mode network and in the task-related networks are anticorrelated not only during task execution but also during rest [330, 333, 337]. Changes in the default-mode network structure and task-related dynamics have been related to several neuronal disorders, including depression, schizophrenia and attention-deficit hyperactivity disorder [338, 339]. Together, the fMRI data strongly suggest that the ongoing human brain activity is highly organized even in the absence of task or external stimuli, and the significance of resting-state functional connectivity to task performance and brain disorders should be addressed with specific experimental setups [340, 341].

Task performance and the default mode. Psychologically, ongoing activity is not stable in either the resting state or during task execution, but is highly prone to wander [171] (Study III). Therefore, a natural question is whether the functional networks found with brain imaging are different during successful task execution than during periods of poor task performance that is often associated with "mind wandering" or "task-unrelated thought" [217]. Indeed, it has been demonstrated that impaired task performance and subjective reports of mind wandering are related to elevated activity in regions associated with the default-mode network, sometimes in conjunction with an active executive network, and that high anticorrelation between the default-mode network and the task-related network activations predicts good task performance [342–345]. The interesting connections between impaired task performance, task-unrelated thoughts and functional connectivity should be pursued further to investigate whether, for instance, changes in modularity or other graph theoretical measures play a role there.

Function follows structure. Although structural and functional connectivity on the systems scale seem to be intimately related, it is an important question whether this is just an unavoidable statistical consequence of all the functionality residing on an underlying structural connectivity, or whether large-scale functional connectivity carries the signatures of cognitive processing at each instant of time. The topology of functional system-level networks has been delineated mainly with fMRI methods [93]. As expected, functional connectivity is largely restricted by the structural connections, as evidenced by a high similarity between BOLD resting-state connectivity and anatomical connections from diffusion tensor imaging [346]. Thus, studies of long-term average resting-state connectivity largely replicate results from structural imaging. The correlated BOLD networks have been reported to be small-world and scale-free at rest and during task execution [347–350]. Hubs were discovered mainly in the association cortices [349]. Also increased processing efficacy, compared to the elderly or to subjects medicated with a dopamine antagonist, was associated with the specific topology of the functional networks [99]. In addition, pronounced modular structures has been found, which is believed to be essential for adaptability, flexibility and stability of the networks [122, 348, 351]. Furthermore, the few high-level modules have been decomposed into smaller modules, which suggests a hierarchical modular structure [352, 353]. It is encouraging that roughly the same anatomical structures have been discovered by directly analysing the inter-areal correlations in resting-state BOLD signals as by decomposing the functional network topology to highly inter-connected modules by using graph theoretical tools. Taken together, the functional architecture seems to be related to task activations through its organization into co-operative hierarchical

modules that often occupy a certain cortical region with dense inter-regional structural connections.

Network properties from MEG and EEG imaging studies

Resting-state recordings of MEG and EEG have been used to characterize the nature of sensor networks from synchronized oscillatory activity. These results promote the view that the oscillatory networks operate in a small-world topology, especially during rest but also during task and in most frequencies less than 50 Hz [98, 170, 354–356]. Whereas the previous studies only assessed graph properties at the level of sensors, this Thesis presented the first findings from source-level analysis of graph properties of networks of synchronized neuronal oscillations (Studies IV, V). In addition, our study provides an interesting view on the task-dependency of the network structure, instead of being limited to the resting state or to other single-condition approaches prevalent in previous studies (Study V).

One missing link in the resting-state studies of functional connectivity is that these networks, in particular the default-mode network, have not yet been observed with direct electric recordings. To date, the electric default-mode network has been thought to be recoverable by regressing the BOLD patterns with simultaneously measured EEG waveforms, after controlling for technical measurement artefacts in the EEG and deconvolving the hemodynamic response function from BOLD signals [225–227, 357]. However, after some contradictory results and inherent difficulties in combining the neurophysiological information obtained with fMRI and EEG measurements, it seems that estimating source-level correlations from resting-state MEG/EEG recordings using realistic source modeling could be the most straightforward way to uncover these networks [358, 359]. As yet, this has not been done, but the methods needed are analogous to the ones used in this Thesis (Studies IV, V). For a direct comparison with fMRI BOLD data, one could correlate the ISFs or the slow variations in amplitude envelopes of neuronal oscillations between brain areas. In this context, it would be interesting to see if the LRTC in oscillations, thus far quantified at the sensor level, arise from certain cortical areas or if they are uniformly distributed all over the cortex.

An important but often overlooked difference between studies of electric and metabolic brain activity, such as neuronal oscillations and BOLD signal, is the time scale of activation. With fMRI, the neuronal underpinnings of the signal remain unsettled, and the time windows required for computing inter-voxel correlations are long. Therefore, to observe neuronal activity correlations at time scales that are relevant for cognitive processing in humans, MEG and EEG methods are needed. The networks of neuronal oscillatory synchrony in spontaneous data become detectable when different forms of spurious synchrony are controlled for (Study IV). Even then, the transient neuronal interactions are often too short-lived to be directly observed with statistical estimation from measured time series. The functional connectivities and graph topologies obtained with fMRI or long-term averaging of MEG/EEG pairwise synchrony might then not correspond to genuine neuronal processing architectures that take place in real-time. Robust real-time networks can be detected by analyzing single-trial data from an experiment with a repeating-trials design, an approach not possible when focusing on the resting-state condition (Studies IV, V) [360].

Power laws in time and space – signs of a critical state?

In light of the considerations above, some interesting links are readily observable between small-world graphs and dynamical systems self-organized into a critical state. First, scale-free, or fractal, statistics can be found in the power-law degree distribution and modular structure of graphs, as well as in the power-law temporal and spatial correlations in SOC systems [4, 96, 123]. Second, they can both be described to exist somewhere between regular order and random disorder: small-world networks combine the dominant features from lattice and random graphs, whereas the critical state reflects dynamics that are statistically between predictable and random [95, 149, 361, 362]. Third, small-world graphs and the SOC dynamical state have both been claimed to render neuronal networks with optimal information transmission capabilities [95, 144, 363]. Thus, using both the viewpoints of graph theory and those of SOC theory for the study of brain dynamics spawns new approaches and helps interpret the obtained results [364].

Connectivity in SOC. In physical inspections of SOC, the underlying connectivity structure has not been paid much attention to, and nearest-neighbor lattices have often been used in the models [4, 137, 138, 140, 142, 149, 361]. The possible significance of connectivity has been motivated mainly by neuroscience applications [107, 362, 365]. There, modeling studies suggest that although SOC does not require specific connection patterns it might be more easily generated in small-world networks of simulated neurons [362, 365]. In fact, simulations with physiologically plausible model neurons have revealed that the self-organization process directs the connectivity of the network from random to one with a scale-free and small-world topology [366]. Furthermore, dynamics of model neuron networks have been shown to self-organize to the critical state through mutual interactions and Hebbian or spike timing-dependent plasticity rules [362, 366, 367]. These neuronal models of SOC thus implement locality and structural modification, which are both central requirements for systems to be classified as SOC [140, 142].

Origins of brain network topology. Graphs have been proposed to self-organize to a scale-free topology by a mechanism called preferential attachment, where new nodes are attached to the existing ones at random, but with a higher probability to the nodes that already are highly connected [96]. This mechanism is a plausible candidate to re-configure the connectivity of dynamical neuronal systems that display synaptic plasticity, because then the most active neurons or areas tend to enhance their connections to other cells or areas, while inactive ones lose connections. Other network assembly criteria have been proposed to prevail in the development of brain structure, such as the economy of neuronal wiring and the ability of the network topology to support complex dynamics [94, 107, 368]. Finally, it was recently discovered that during post-natal development, neuronal activity undergoes a profound reduction in correlation that is independent of external stimulation [369]. Thus, although the exact mechanisms of neuronal network development are incompletely known, it seems clear that they are self-organized by ntrinsic neuronal activity, rather than being determined purely by genetics or driven by external stimuli.

Avalanche dynamics and oscillatory correlations. Power-law scaling of sizes and lifetimes of discrete neuronal events, called avalanches, has been demonstrated on neuron cultures and cortical slices [144]. This behavior was associated with high flexibility and information processing capabilities. Indeed, compared to avalanches that are either very localized or global,

the scale-free avalanche distibution allows a large amount of different activity patterns and variety in cross-cortical correlations. These results were later confirmed with *in vivo* recordings in monkey cortex, where the cortical connectivity was intact [146]. Interestingly, avalanches were also found to be mediated by a small-world structure [370]. In human MEG and EEG recordings, power laws were previously found in LRTC of oscillatory amplitudes [78, 205] (Studies I – II). Recently, ongoing oscillatory activity was examined by quantifying avalanche sizes and lifetimes. In accordance with the fractal properties observed in animal studies on a smaller scale, these studies showed scale-free distributions of lifetimes of oscillatory events, thus linking the iconic sand-pile avalanche model of SOC to neuronal activity in a wide range of spatial and temporal scales [147, 252]. The existence of a direct relationship between the avalanche studies in animals and the studies of oscillatory activity in humans is unclear. The animal studies deal mostly with events at scales of millimeters and tens or hundreds of milliseconds, whereas the analyses of human neuronal oscillations cover larger scales. Hence, the avalanches in the animal microelectrode recordings could be seen as oscillatory activity in larger-scale MEG and EEG recordings. The scale-free nature of avalanche life times would then predict the observed scale-free spectral density distribution [147, 252]. As a matter of fact, scale-free avalanche organization of local cortical oscillations has also been found in microelectrode array data [150]. Finally, both global synchrony metrics in MEG and functional connectivity network structure in fMRI data have been shown to be indistinguishable from the corresponding statistics in a two-dimensional Ising model of ferromagnetism that was fine-tuned to the critical state by modifying external parameters [149, 361]. These findings together provide further evidence for a critical state in the operation of brain neuronal networks.

Distinctions by frequency – systems within a system?

The analyses of phase synchrony and long-range temporal correlations, in this Thesis as well as in most other studies, are performed separately for distinct frequency bands. On the other hand, the most conclusive evidence for a critical state of the cortical networks comes from studies of broad-band data [144, 146, 371]. This potential discrepancy between theory and analysis was already discussed above, but additional justification for restricting the analyses to narrow-band oscillations can be found. Most importantly, the data justifies the methods by showing frequency-dependent sensitivity to disorders as well as distinct effects in cognitive studies. In pathophysiological findings, the beta-band seems to be specifically affected. The LRTC in the beta-band are sensitive to the epileptic focus, the effects from lorazepam seem to be pronounced in the beta-band and the LRTC in pre-frontal EEG in depressed patients were diminished in the beta-band (Studies I – III). Interestingly, beta-band oscillations seem to be involved in synchrony in the occipital visual regions as well, although these areas are often associated with their prominent alpha-band activity. Other groups have shown that the visual system is most easily excited with direct electric stimulation at around 20 Hz and that photosensitive seizures are most readily triggered by roughly 15–20 Hz visual stimulation [372, 373] (Study IV). Apart from the beta-band, neuronal oscillations in other frequency bands have been linked to several functions, the hypothesized central role of the gamma-band oscillations in a wide range of cognitive tasks being a prominent example [42].

In this Thesis, we found consistent spatial and temporal correlations among neuronal oscillations by analyzing phase synchrony and LRTC. This observation is consistent with the

idea that the narrow bands of oscillatory brain activity, traditionally named after Greek letters, indeed form separate systems with specific and rather independent, although context-sensitive, roles. In support of oscillatory sub-systems, we found that the goodness-of-fit in the DFA power-law estimation was better for narrow-band data than for wide-band data, suggesting that narrow-band activity fits better into the framework of self-organized criticality than wide-band activity (Study III). Other studies also have found robust LRTC, synchrony and scaling of oscillatory activity in several narrow frequency bands and found that these distinct frequency bands behave in statistically similar ways [78, 149, 170]. These observations have lead to suggestions that brain operation is broad-band critical or fractally organized to a wide frequency range [149, 170].

The views of broad-band or fractal criticality, or other ideas of brain operation spread and coordinated across several frequencies, need to be corroborated with actual cross-frequency mechanisms that integrate the systems at different scales of time or frequency, in addition to integration over space and time in distinct oscillatory sub-systems by spatial and temporal correlations. Two mechanisms for cross-frequency binding have been proposed, *n:m* phase synchrony and nested oscillations [87, 150, 192, 216, 290, 374] (Study III). The difference between these is that phase synchrony is a relationship between the phases of two oscillators, whereas in nested oscillations the phase of the slower oscillator modulates the amplitude of the faster one. Above, it was discussed that the phase variable might be more intimately related to the dynamics of the system than the amplitude. It has been proposed that the nested relationship signals a cross-hierarchical relationship between neuronal processes [290, 375, 376] (Study III). In light of this, *n:m* phase synchrony could be seen to signal the interrelatedness of neuronal constructs that reside in parallel in the processing hierarchy.

Neurodynamics of cognition and behavior

One of the main tasks of the brain is to construct a model of the environment and learn the regularities in it. This ability should include capturing long time-scale interrelatedness among events, as well as hierarchical structures and nested dynamics therein. The information is then used to predict upcoming changes in sensory streams and simulate the effects of possible actions to enhance survival [381]. This prediction principle could, for example, explain simple conditioning, provide a functional role for imagery and control stimulus selection. Moreover, it could clarify the role of ongoing neuronal activity, which is often deemed as mere noise, by suggesting that ongoing activity is related to constructing the predictions.

It seems highly reasonable that the neuronal implementation of high-level perception and action are intimately interlinked, for arguments of economy and unambiguity. For instance, only one functional module, placed high in the processing hierarchy, should suffice to both encode and decode spoken language. Indeed, a lesion to Broca's area, which is located in the inferior frontal gyrus, may cause disorders in speech production as well as in its understanding [382, 383]. The link of perception and action gains support from animal and human experiments in social settings, which show that certain brain areas are activated both when executing and when observing an action, the function of the advocated mirror neuron system [384–386].

The hierarchical structure of neuronal processing is linked to the notion that the neuronal representations of the environment are transformed from simple reconstructions in the sensory cortices to more sparse and abstract descriptions of objects and their spatiotemporal relations in later processing stages. If perception actively employs the hierarchical structures inherited from the environment, the nested neuronal dynamics in the hierarchy could become evident. Indeed, the processing of rhythmic input, including the processing of speech in the human auditory cortex, takes place via entrainment of oscillatory neuronal activity to the rhythmic stimulus sequence. In the case of speech, the rhythmicity in the syllabic structure facilitates neuronal processing of lower-level stimulus features [375, 378, 379]. It has been proposed that the facilitating effect on understanding of also seeing the speaker could be due to oscillatory entrainment to the syllable-related temporal structure in the mouth motor movements [387]. In addition to a hierarchy in perception, evidence for a hierarchy in sound production is provided by studies in songbirds. There, the notes and the large-scale syllable sequences in the song of mature birds are produced in separate brain nuclei, which are connected through a hierarchical interaction [388]. However, this relationship does not exist in unstructured juvenile babbling [389]. Although perception and production of social vocalizations were used as examples here, hierarchical relationships in action planning and execution can be broadened to cover goal-directed and context-dependent behavior [130, 390].

A simple model of hierarchical perception and action interprets slow oscillations as entrainment to either externally or internally generated modulation of excitability, and nested interactions as mediating a functional hierarchy that has similar dynamic features in production and perception. A general rule that higher hierarchical levels, longer windows of temporal integration and more intricate dynamic structures are represented in the brain with a caudal-rostral gradient has been discovered [377, 380, 390]. However, the hierarchical and modular structures found in the connectivity of the human brain predicts a more complex pattern of temporal and hierarchical relationships in neuronal processing [93, 118, 348, 351–353, 391]. These considerations should be taken into account when defining the dynamic “brain state” that is suggested to control the information flow and to provide the context for stimulus processing in the brain [13, 85].

Summary and Conclusions

This work is concerned with quantifying correlations in ongoing neuronal oscillations that reflect local neuronal computations and are measured using electromagnetic recordings. The leading proposition in this Thesis is that the spatial, temporal and spectral correlations in the neuronal oscillations reveals information-rich dynamical structure. These correlations were shown to identify novel system-level neuronal phenomena that were behaviorally significant during cognitive processing. Furthermore, their abnormalities were shown to be sensitive to brain disorders. The findings in this Thesis suggest that dynamic correlations in ongoing oscillations may have an impact on how information is represented, processed and transmitted in neuronal networks. Some of the main motivations for these studies were the parallels between models of self-organized criticality and neuronal networks, and the results lend further support to the view of the brain as a self-organizing system operating near criticality.

I recognize three main scientific contributions in the Studies composing this Thesis. First, novel approaches were used to discover markers of neuronal disorders in data recorded from epilepsy

and major depression patients (Studies I, II). Second, the regime of EEG methods that are applied in cognitive studies was extended below the conventional frequency range by revealing that infra-slow activity in the range 0.01–0.1 Hz similarly modulated behavioral task performance and amplitudes of > 1 Hz neuronal oscillation (Study III). Third, a method using MEG and EEG to map inter-areal phase synchrony among neuronal oscillations across the whole cortex was developed and applied to identify the properties of synchronous networks in the frequency range 3–90 Hz (Studies IV, V).

References

1. Buzsáki G (2006) *Rhythms of the brain,* (Oxford University Press, New York, USA).
2. Barabási AL (2003) *Linked,* (Penguin Group, New York, USA).
3. Strogatz SH (2003) *Sync: how order emerges from chaos in the universe, nature, and daily life,* (Hyperion, New York, USA).
4. Bak P, Tang C & Wiesenfeld K (1987) Self-organized criticality: An explanation of the 1/f noise. *Phys Rev Lett* 59, 381384.
5. Buzsáki G & Draguhn A (2004) Neuronal oscillations in cortical networks. *Science* 304, 1926–1929.
6. Berger H (1929) Über das Elektroenkephalogramm des Menschen. *Arch Psychiatr Nervenkr* 87, 527–570.
7. Gray CM & McCormick DA (1996) Chattering cells: Superficial pyramidal neurons contributing to the generation of synchronous oscillations in the visual cortex. *Science* 274, 109–113.
8. Llinás RR (1988) The intrinsic electrophysiological properties of mammalian neurons: Insights into central nervous system function. *Science* 242, 1654–1664.
9. Hutcheon B & Yarom Y (2000) Resonance, oscillation and the intrinsic frequency preferences of neurons. *Trends Neurosci* 23, 216–222.
10. Fuhrmann G, Markram H & Tsodyks M (2002) Spike frequency adaptation and neocortical rhythms. *J Neurophysiol* 88, 761–770.
11. Gautrais J & Thorpe S (1998) Rate coding versus temporal order coding: A theoretical approach. *BioSystems* 48, 57–65.
12. Bear MF, Connors BW & Paradiso MA (1996) *Neuroscience: exploring the brain,* (Lippincott Williams & Wilkins, Baltimore, MD, USA).
13. Salinas E & Sejnowski TJ (2001) Correlated neuronal activity and the flow of neural information. *Nat Rev Neurosci* 2, 539–550.
14. Rudolph M & Destexhe A (2001) Correlation detection and resonance in neural systems with distributed noise sources. *Phys Rev Lett* 86, 3662–3665.
15. Stopfer M, Bhagavan S, Smith BH & Laurent G (1997) Impaired odour discrimination on desynchronization of odour-encoding neural assemblies. *Nature* 390, 70–74.
16. Pillow JW, Shlens J, Paninski L, Sher A, Litke AM, Chichilnisky EJ & Simoncelli EP (2008) Spatio-temporal correlations and visual signalling in a complete neuronal population. *Nature* 454, 995–999.
17. Dan Y, Alonso JM, Usrey WM & Reid RC (1998) Coding of visual information by precisely correlated spikes in the lateral geniculate nucleus. *Nat Neurosci* 1, 501–507.
18. Wehr M & Laurent G (1996) Odour encoding by temporal sequences of firing in oscillating neural assemblies. *Nature* 384, 162–166.
19. Gray CM & Singer W (1989) Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. *Proc Natl Acad Sci U S A* 86, 1698–1702.
20. Perez-Orive J, Mazor O, Turner GC, Cassenaer S, Wilson RI & Laurent G (2002) Oscillations and sparsening of odor representations in the mushroom body. *Science* 297, 359–365.
21. Fries P, Reynolds JH, Rorie AE & Desimone R (2001) Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* 291, 1560–1563.
22. Tsodyks M, Kenet T, Grinvald A & Arieli A (1999) Linking spontaneous activity of single cortical neurons and the underlying functional architecture. *Science* 286, 1943–1946.
23. O'Keefe J & Recce ML (1993) Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3, 317–330.

24. Jensen O & Lisman JE (2000) Position reconstruction from an ensemble of hippocampal place cells: Contribution of theta phase coding. *J Neurophysiol* 83, 2602–2609.
25. McLelland D & Paulsen O (2009) Neuronal oscillations and the rate-to-phase transform: Mechanism, model and mutual information. *J Physiol* 587, 769–785.
26. Shannon CE (1997) The mathematical theory of communication. 1963. *MD Comput* 14, 306–317.
27. Abbott LF (1999) Lapicque's introduction of the integrate-and-fire model neuron (1907). *Brain Res Bull* 50, 303–304.
28. Hodgkin AL & Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. *J Physiol* 117, 500–544.
29. König P, Engel AK & Singer W (1996) Integrator or coincidence detector? The role of the cortical neuron revisited. *Trends Neurosci* 19, 130–137.
30. MacLeod K, Bäcker A & Laurent G (1998) Who reads temporal information contained across synchronized and oscillatory spike trains? *Nature* 395, 693–698.
31. Fries P (2005) A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends Cogn Sci* 9, 474–480.
32. Cardin JA, Carlén M, Meletis K, Knoblich U, Zhang F, Deisseroth K, Tsai L & Moore CI (2009) Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature* 459, 663–667.
33. Whittington MA, Traub RD, Kopell N, Ermentrout B & Buhl EH (2000) Inhibition-based rhythms: experimental and mathematical observations on network dynamics. *Int J Psychophysiol* 38, 315–336.
34. Ritz R & Sejnowski TJ (1997) Synchronous oscillatory activity in sensory systems: New vistas on mechanisms. *Curr Opin Neurobiol* 7, 536–546.
35. Blatow M, Rozov A, Katona I, Hormuzdi SG, Meyer A, Whittington M, Caputi A & Monyer H (2003) A novel network of multipolar bursting interneurons generates theta frequency oscillations in neocortex. *Neuron* 38, 805–817.
36. Galarreta M & Hestrin S (2001) Spike transmission and synchrony detection in networks of GABAergic interneurons. *Science* 292, 2295–2299.
37. Hestrin S & Galarreta M (2005) Electrical synapses define networks of neocortical GABAergic neurons. *Trends Neurosci* 28, 304–309.
38. Bartos M, Vida I & Jonas P (2007) Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nat Rev Neurosci* 8, 45–56.
39. Bollimunta A, Chen Y, Schroeder CE & Ding M (2008) Neuronal mechanisms of cortical alpha oscillations in awake-behaving macaques. *J Neurosci* 28, 9976–9988.
40. Sohal VS, Zhang F, Yizhar O & Deisseroth K (2009) Parvalbumin neurons and gamma rhythms enhance cortical circuit performance. *Nature* 459, 698–702.
41. Kahana MJ (2006) The cognitive correlates of human brain oscillations. *J Neurosci* 26, 1669–1672.
42. Tallon-Baudry C (2009) The roles of gamma-band oscillatory synchrony in human visual cognition. *Front Biosci* 14, 321–332.
43. Tallon-Baudry C & Bertrand O (1999) Oscillatory gamma activity in humans and its role in object representation. *Trends Cogn Sci* 3, 151–162.
44. Lachaux JP, George N, Tallon-Baudry C, Martinerie J, Hugueville L, Minotti L, Kahane P & Renault B (2005) The many faces of the gamma band response to complex visual stimuli. *Neuroimage* 25, 491–501.
45. Tiitinen H, Sinkkonen J, Reinikainen K, Alho K, Lavikainen J & Näätänen R (1993) Selective attention enhances the auditory 40-Hz transient response in humans. *Nature* 364, 59–60.
46. Bauer F, Cheadle SW, Parton A, Müller HJ & Usher M (2009) Gamma flicker triggers attentional selection without awareness. *Proc Natl Acad Sci U S A* 106, 1666–1671.

47. Jensen O, Gelfand J, Kounios J & Lisman JE (2002) Oscillations in the alpha band (9-12 Hz) increase with memory load during retention in a short-term memory task. *Cereb Cortex* 12, 877-882.
48. Sederberg PB, Kahana MJ, Howard MW, Donner EJ & Madsen JR (2003) Theta and gamma oscillations during encoding predict subsequent recall. *J Neurosci* 23, 10809–10814.
49. Pantazis D, Simpson GV, Weber DL, Dale CL, Nichols TE & Leahy RM (2009) A novel ANCOVA design for analysis of MEG data with application to a visual attention study. *Neuroimage* 44, 164–174.
50. John ER, Prichep LS, Fridman J & Easton P (1988) Neurometrics: Computer-assisted differential diagnosis of brain dysfunctions. *Science* 239, 162–169.
51. Llinás RR, Ribary U, Jeanmonod D, Kronberg E & Mitra PP (1999) Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci U S A* 96, 15222–15227.
52. Lounasmaa OV, Hämäläinen M, Hari R & Salmelin R (1996) Information processing in the human brain: Magnetoencephalographic approach. *Proc Natl Acad Sci U S A* 93, 8809–8815.
53. Crone NE, Miglioretti DL, Gordon B, Sieracki JM, Wilson MT, Uematsu S & Lesser RP (1998) Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. I. alpha and beta event-related desynchronization. *Brain* 121, 2271–2299.
54. Neuper C & Pfurtscheller G (2001) Event-related dynamics of cortical rhythms: Frequency-specific features and functional correlates. *Int J Psychophysiol* 43, 41–58.
55. Rizzuto DS, Madsen JR, Bromfield EB, Schulze-Bonhage A, Seelig D, Aschenbrenner-Scheibe R & Kahana MJ (2003) Reset of human neocortical oscillations during a working memory task. *Proc Natl Acad Sci U S A* 100, 7931–7936.
56. Makeig S, Westerfield M, Jung TP, Enghoff S, Townsend J, Courchesne E & Sejnowski TJ (2002) Dynamic brain sources of visual evoked responses. *Science* 295, 690–694.
57. Palva S, Linkenkaer-Hansen K, Näätänen R & Palva JM (2005) Early neural correlates of conscious somatosensory perception. *J Neurosci* 25, 5248–5258.
58. Nikulin VV, Linkenkaer-Hansen K, Nolte G, Lemm S, Müller KR, Ilmoniemi RJ & Curio G. (2007) A novel mechanism for evoked responses in the human brain. *Eur J Neurosci* 25, 3146–3154.
59. Traub RD, Whittington MA, Stanford IM & Jefferys JG (1996) A mechanism for generation of long-range synchronous fast oscillations in the cortex. *Nature* 383, 621–624.
60. Engel AK, König P, Kreiter AK & Singer W (1991) Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science* 252, 1177–1179.
61. von der Malsburg C (1999) The what and why of binding: The modeler's perspective. *Neuron* 24, 95–104, 111–25.
62. Bibbig A, Traub RD & Whittington MA (2002) Long-range synchronization of gamma and beta oscillations and the plasticity of excitatory and inhibitory synapses: A network model. *J Neurophysiol* 88, 1634–1654.
63. Traub RD, Spruston N, Soltesz I, Konnerth A, Whittington MA & Jefferys GR (1998) Gamma-frequency oscillations: A neuronal population phenomenon, regulated by synaptic and intrinsic cellular processes, and inducing synaptic plasticity. *Prog Neurobiol* 55, 563–575.
64. Destexhe A, Contreras D & Steriade M (1998) Mechanisms underlying the synchronizing action of corticothalamic feedback through inhibition of thalamic relay cells. *J Neurophysiol* 79, 999–1016.
65. Roskies AL (1999) The binding problem. *Neuron* 24, 7–9, 111–25.
66. Roelfsema PR, Engel AK, König P & Singer W (1997) Visuomotor integration is associated with zero time-lag synchronization among cortical areas. *Nature* 385, 157–161.
67. Bressler SL, Coppola R & Nakamura R (1993) Episodic multiregional cortical coherence at multiple frequencies during visual task performance. *Nature* 366, 153–156.
68. von Stein A, Chiang C & König P (2000) Top-down processing mediated by interareal synchronization. *Proc Natl Acad Sci U S A* 97, 14748–14753.

69. Rodriguez E, George N, Lachaux JP, Martinerie J, Renault B & Varela FJ (1999) Perception's shadow: Long-distance synchronization of human brain activity. *Nature* 397, 430–433.
70. Miltner WH, Braun C, Arnold M, Witte H & Taub E (1999) Coherence of gamma-band EEG activity as a basis for associative learning. *Nature* 397, 434–436.
71. Uhlhaas PJ & Singer W (2006) Neural synchrony in brain disorders: Relevance for cognitive dysfunctions and pathophysiology. *Neuron* 52, 155–168.
72. Fuhrmann G, Segev I, Markram H & Tsodyks M (2002) Coding of temporal information by activity-dependent synapses. *J Neurophysiol* 87, 140–148.
73. Stopfer M & Laurent G (1999) Short-term memory in olfactory network dynamics. *Nature* 402, 664–668.
74. Yao H, Shi L, Han F, Gao H & Dan Y (2007) Rapid learning in cortical coding of visual scenes. *Nat Neurosci* 10, 772–778.
75. Ikegaya Y, Aaron G, Cossart R, Aronov D, Lampl I, Ferster D & Yuste R (2004) Synfire chains and cortical songs: Temporal modules of cortical activity. *Science* 304, 559–564.
76. Beggs JM & Plenz D (2004) Neuronal avalanches are diverse and precise activity patterns that are stable for many hours in cortical slice cultures. *J Neurosci* 24, 5216–5229.
77. Hasegawa RP, Blitz AM, Geller NL & Goldberg ME (2000) Neurons in monkey prefrontal cortex that track past or predict future performance. *Science* 290, 1786–1789.
78. Linkenkaer-Hansen K, Nikouline VV, Palva JM & Ilmoniemi RJ (2001) Long-range temporal correlations and scaling behavior in human brain oscillations. *J Neurosci* 21, 1370–1377.
79. Hari R & Salmelin R (1997) Human cortical oscillations: A neuromagnetic view through the skull. *Trends Neurosci* 20, 44–49.
80. Destexhe A, Contreras D & Steriade M (1999) Spatiotemporal analysis of local field potentials and unit discharges in cat cerebral cortex during natural wake and sleep states. *J Neurosci* 19, 4595–4608.
81. Azouz R & Gray CM (1999) Cellular mechanisms contributing to response variability of cortical neurons in vivo. *J Neurosci* 19, 2209–2223.
82. Arieli A, Sterkin A, Grinvald A & Aertsen A (1996) Dynamics of ongoing activity: Explanation of the large variability in evoked cortical responses. *Science* 273, 1868–1871.
83. Destexhe A & Contreras D (2006) Neuronal computations with stochastic network states. *Science* 314, 85–90.
84. Kenet T, Bibitchkov D, Tsodyks M, Grinvald A & Arieli A (2003) Spontaneously emerging cortical representations of visual attributes. *Nature* 425, 954–956.
85. Engel AK, Fries P & Singer W (2001) Dynamic predictions: Oscillations and synchrony in top-down processing. *Nat Rev Neurosci* 2, 704–716.
86. Varela F, Lachaux JP, Rodriguez E & Martinerie J (2001) The brainweb: Phase synchronization and large-scale integration. *Nat Rev Neurosci* 2, 229–239.
87. Palva S & Palva JM (2007) New vistas for alpha-frequency band oscillations. *Trends Neurosci* 30, 150–158.
88. Schroeder CE & Lakatos P (2009) Low-frequency neuronal oscillations as instruments of sensory selection. *Trends Neurosci* 32, 9–18.
89. Spitzer NC (2006) Electrical activity in early neuronal development. *Nature* 444, 707–712.
90. Watts DJ (2004) *Small Worlds*, (Princeton University Press, Princeton, NJ, USA).
91. Strogatz SH (2001) Exploring complex networks. *Nature* 410, 268–276.
92. Barabási AL (2009) Scale-free networks: A decade and beyond. *Science* 325, 412–413.
93. Bullmore E & Sporns O (2009) Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 10, 186–198.
94. Sporns O, Chialvo DR, Kaiser M & Hilgetag CC (2004) Organization, development and function of complex brain networks. *Trends Cogn Sci* 8, 418–425.
95. Watts DJ & Strogatz SH (1998) Collective dynamics of 'small-world' networks. *Nature* 393, 440–442.

96. Barabási AL & Albert R (1999) Emergence of scaling in random networks. *Science* 286, 509–512.
97. Albert R, Jeong H & Barabási AL (2000) Error and attack tolerance of complex networks. *Nature* 406, 378–382.
98. Bassett DS, Bullmore ET, Meyer-Lindenberg A, Apud JA, Weinberger DR & Coppola R (2009) Cognitive fitness of cost-efficient brain functional networks. *Proc Natl Acad Sci U S A*
99. Achard S & Bullmore E (2007) Efficiency and cost of economical brain functional networks. *PLoS Comput Biol* 3, e17.
100. Mountcastle VB (1997) The columnar organization of the neocortex. *Brain* 120, 701–722.
101. Markram H, Toledo-Rodriguez M, Wang Y, Gupta A, Silberberg G & Wu C (2004) Interneurons of the neocortical inhibitory system. *Nat Rev Neurosci* 5, 793–807.
102. Sporns O & Kötter R (2004) Motifs in brain networks. *PLoS Biol* 2, e369.
103. Milo R, Itzkovitz S, Kashtan N, Levitt R, Shen-Orr S, Ayzenshtat I, Sheffer M & Alon U (2004) Superfamilies of evolved and designed networks. *Science* 303, 1538–1542.
104. Milo R, Shen-Orr S, Itzkovitz S, Kashtan N, Chklovskii D & Alon U (2002) Network motifs: Simple building blocks of complex networks. *Science* 298, 824–827.
105. Prill RJ, Iglesias PA & Levchenko A (2005) Dynamic properties of network motifs contribute to biological network organization. *PLoS Biol* 3, e343.
106. Klemm K & Bornholdt S (2005) Topology of biological networks and reliability of information processing. *Proc Natl Acad Sci U S A* 102, 18414–18419.
107. Sporns O, Tononi G & Edelman GM (2002) Theoretical neuroanatomy and the connectivity of the cerebral cortex. *Behav Brain Res* 135, 69–74.
108. Song S, Sjöström PJ, Reigl M, Nelson S & Chklovskii DB (2005) Highly nonrandom features of synaptic connectivity in local cortical circuits. *PLoS Biol* 3, e68.
109. Bassett DS & Bullmore E (2006) Small-world brain networks. *Neuroscientist* 12, 512–523.
110. Sporns O, Tononi G & Kötter R (2005) The human connectome: A structural description of the human brain. *PLoS Comput Biol* 1, e42.
111. Behrens TE, Berg HJ, Jbabdi S, Rushworth MF & Woolrich MW (2007) Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *Neuroimage* 34, 144–155.
112. Hagmann P, Kurant M, Gigandet X, Thiran P, Wedeen VJ, Meuli R & Thiran JP (2007) Mapping human whole-brain structural networks with diffusion MRI. *PLoS One* 2, e597.
113. Iturria-Medina Y, Canales-Rodríguez EJ, Melie-García L, Valdés-Hernández PA, Martínez-Montes E, Alemán-Gómez Y & Sánchez-Bornot JM (2007) Characterizing brain anatomical connections using diffusion weighted MRI and graph theory. *Neuroimage* 36, 645–660.
114. Iturria-Medina Y, Sotero RC, Canales-Rodríguez EJ, Alemán-Gómez Y & Melie-García L (2008) Studying the human brain anatomical network via diffusion-weighted MRI and graph theory. *Neuroimage* 40, 1064–1076.
115. Gong G, He Y, Concha L, Lebel C, Gross DW, Evans AC & Beaulieu C (2009) Mapping anatomical connectivity patterns of human cerebral cortex using in vivo diffusion tensor imaging tractography. *Cereb Cortex* 19, 524–536.
116. He Y, Chen ZJ & Evans AC (2007) Small-world anatomical networks in the human brain revealed by cortical thickness from MRI. *Cereb Cortex* 17, 2407–2419.
117. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ & Sporns O (2008) Mapping the structural core of human cerebral cortex. *PLoS Biol* 6, e159.
118. Chen ZJ, He Y, Rosa-Neto P, Germann J & Evans AC (2008) Revealing modular architecture of human brain structural networks by using cortical thickness from MRI. *Cereb Cortex* 18, 2374–2381.
119. Felleman DJ & Van Essen DC (1991) Distributed hierarchical processing in the primate cerebral cortex. *Cereb Cortex* 1, 1–47.
120. Hilgetag CC, O'Neill MA & Young MP (1996) Indeterminate organization of the visual system. *Science* 271, 776–777.

121. Hilgetag CC, Burns GA, O'Neill MA, Scannell JW & Young MP (2000) Anatomical connectivity defines the organization of clusters of cortical areas in the macaque monkey and the cat. *Philos Trans R Soc B* 355, 91–110.
122. Bullmore E, Barnes A, Bassett DS, Fornito A, Kitzbichler M, Meunier D & Suckling J (2009) Generic aspects of complexity in brain imaging data and other biological systems. *Neuroimage*
123. Ravasz E, Somera AL, Mongru DA, Oltvai ZN & Barabási AL (2002) Hierarchical organization of modularity in metabolic networks. *Science* 297, 1551–1555.
124. Passingham RE, Stephan KE & Kötter R (2002) The anatomical basis of functional localization in the cortex. *Nat Rev Neurosci* 3, 606–616.
125. Tononi G, Sporns O & Edelman GM (1994) A measure for brain complexity: Relating functional segregation and integration in the nervous system. *Proc Natl Acad Sci U S A* 91, 5033–5037.
126. Koch C & Laurent G (1999) Complexity and the nervous system. *Science* 284, 96–98.
127. Rabinovich M, Huerta R & Laurent G (2008) Neuroscience. transient dynamics for neural processing. *Science* 321, 48–50.
128. Abarbanel HD & Rabinovich MI (2001) Neurodynamics: Nonlinear dynamics and neurobiology. *Curr Opin Neurobiol* 11, 423–430.
129. Haken H (2006) Synergetics of brain function. *Int J Psychophysiol* 60, 110–124.
130. Kiebel SJ, Daunizeau J & Friston KJ (2009) Perception and hierarchical dynamics. *Front Neuroinformatics* 3, 20.
131. So P, Francis JT, Netoff TI, Gluckman BJ & Schiff SJ (1998) Periodic orbits: A new language for neuronal dynamics. *Biophys J* 74, 2776–2785.
132. Stam CJ (2005) Nonlinear dynamical analysis of EEG and MEG: Review of an emerging field. *Clin Neurophysiol* 116, 2266–2301.
133. Makeig S, Gramann K, Jung TP, Sejnowski TJ & Poizner H (2009) Linking brain, mind and behavior. *Int J Psychophysiol* 73, 95–100.
134. Breakspear M, Roberts JA, Terry JR, Rodrigues S, Mahant N & Robinson PA (2006) A unifying explanation of primary generalized seizures through nonlinear brain modeling and bifurcation analysis. *Cereb Cortex* 16, 1296–1313.
135. Laurent G, Stopfer M, Friedrich RW, Rabinovich MI, Volkovskii A & Abarbanel HD (2001) Odor encoding as an active, dynamical process: Experiments, computation, and theory. *Annu Rev Neurosci* 24, 263–297.
136. Izhikevich EM & Edelman GM (2008) Large-scale model of mammalian thalamocortical systems. *Proc Natl Acad Sci U S A* 105, 3593–3598.
137. Bak P, Tang C & Wiesenfeld K (1988) Self-organized criticality. *Phys Rev A* 38, 364–374.
138. Malamud BD, Morein G & Turcotte DL (1998) Forest fires: An example of self-organized critical behavior. *Science* 281, 1840–1842.
139. Lux T & Marchesi M (1999) Scaling and criticality in a stochastic multi-agent model of a financial market. *Nature* 397, 498–2.
140. Nagler J, Hauert C & Schuster HG (1999) Self-organized criticality in a nutshell. *Phys Rev E* 60, 2706–2709.
141. Yang CB, Cai X & Zhou ZM (2000) Spatial-temporal correlations in the process to self-organized criticality. *Phys Rev E* 61, 7243–7245.
142. Flyvbjerg H (1996) Simplest possible self-organized critical system. *Phys Rev Lett* 76, 940–943.
143. Jung P, Cornell-Bell A, Madden KS & Moss F (1998) Noise-induced spiral waves in astrocyte syncytia show evidence of self-organized criticality. *J Neurophysiol* 79, 1098–1101.
144. Beggs JM & Plenz D (2003) Neuronal avalanches in neocortical circuits. *J Neurosci* 23, 11167–11177.
145. Haldeman C & Beggs JM (2005) Critical branching captures activity in living neural networks and maximizes the number of metastable states. *Phys Rev Lett* 94, 058101.

146. Petermann T, Thiagarajan TC, Lebedev MA, Nicolelis MA, Chialvo DR & Plenz D (2009) Spontaneous cortical activity in awake monkeys composed of neuronal avalanches. *Proc Natl Acad Sci U S A* 106, 15921–15926.
147. Poil SS, van Ooyen A & Linkenkaer-Hansen K (2008) Avalanche dynamics of human brain oscillations: Relation to critical branching processes and temporal correlations. *Hum Brain Mapp* 29, 770–777.
148. Leopold DA, Murayama Y & Logothetis NK (2003) Very slow activity fluctuations in monkey visual cortex: Implications for functional brain imaging. *Cereb Cortex* 13, 422–433.
149. Kitzbichler MG, Smith ML, Christensen SR & Bullmore E (2009) Broadband criticality of human brain network synchronization. *PLoS Comput Biol* 5, e1000314.
150. Gireesh ED & Plenz D (2008) Neuronal avalanches organize as nested theta- and beta/gamma-oscillations during development of cortical layer 2/3. *Proc Natl Acad Sci U S A* 105, 7576–7581.
151. Gilden DL & Wilson SG (1995) On the nature of streaks in signal detection. *Cognit Psychol* 28, 17–64.
152. Gilden DL, Thornton T & Mallon MW (1995) 1/f noise in human cognition. *Science* 267, 1837–1839.
153. Gilden DL (2001) Cognitive emissions of 1/f noise. *Psychol Rev* 108, 33–56.
154. Gilden DL & Hancock H (2007) Response variability in attention-deficit disorders. *Psychol Sci* 18, 796–802.
155. Chen Y, Ding M & Kelso JA (2001) Origins of timing errors in human sensorimotor coordination. *J Mot Behav* 33, 3–8.
156. Wertheimer M (1953) An investigation of the randomness of threshold measurements. *J Exp Psychol* 45, 294–303.
157. Verplanck WS, Collier GH & Cotton JW (1952) Nonindependence of successive responses in measurements of the visual threshold. *J Exp Psychol* 44, 273–282.
158. Fishkin SM, Lovallo WR, Whitaker LC & Pishkin V (1979) Randomness and the "streaking" phenomenon: Attentional anomalies in performance on the Whitaker index of schizophrenic thinking (WIST). *J Clin Psychol* 35, 289–295.
159. Van Orden GC, Holden JG & Turvey MT (2005) Human cognition and 1/f scaling. *J Exp Psychol Gen* 134, 117–123.
160. Verplanck WS, Cotton JW & Collier GH (1953) Previous training as a determinant of response dependency at the threshold. *J Exp Psychol* 46, 10–14.
161. Verplanck WS & Blough DS (1958) Randomized stimuli and the non-independence of successive responses at the visual threshold. *J Gen Psychol* 59, 263–272.
162. Vanhatalo S, Palva JM, Holmes MD, Miller JW, Voipio J & Kaila K (2004) Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. *Proc Natl Acad Sci U S A* 101, 5053–5057.
163. Fox MD & Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 8, 700–711.
164. Vanhatalo S, Voipio J & Kaila K (2005) Full-band EEG (FbEEG): An emerging standard in electroencephalography. *Clin Neurophysiol* 116, 1–8.
165. Cowan N (2001) The magical number 4 in short-term memory: A reconsideration of mental storage capacity. *Behav Brain Sci* 24, 87–114
166. Curtis CE & D'Esposito M (2003) Persistent activity in the prefrontal cortex during working memory. *Trends Cogn Sci* 7, 415–423.
167. Rowe JB, Toni I, Josephs O, Frackowiak RS & Passingham RE (2000) The prefrontal cortex: Response selection or maintenance within working memory? *Science* 288, 1656–1660.
168. Baddeley A (1996) The fractionation of working memory. *Proc Natl Acad Sci U S A* 93, 13468–13472.
169. Baddeley A (1992) Working memory. *Science* 255, 556–559.

170. Bassett DS, Meyer-Lindenberg A, Achard S, Duke T & Bullmore E (2006) Adaptive reconfiguration of fractal small-world human brain functional networks. *Proc Natl Acad Sci U S A* 103, 19518–19523.
171. Smallwood J & Schooler JW (2006) The restless mind. *Psychol Bull* 132, 946–958.
172. Hamilton M (1960) A rating scale for depression. *J Neurol Neurosurg Psychiatry* 23, 56–62.
173. Niedermeyer E & Lopes da Silva FH (1999) *Electroencephalography: basic principles, clinical applications, and related fields* (Lippincott Williams and Wilkins, Baltimore)
174. Nunez PL (1995) *Neocortical dynamics and human EEG rhythms* (Oxford University Press, USA).
175. Speckmann EJ & Elger EC (1999) in *Electroencephalography: Basic Principles, Clinical Applications, and Related Fields,* ed Niedermeyer E, Lopes da Silva F (Lippincott Williams and Wilkins, Baltimore), pp 15–27.
176. Tallgren P, Vanhatalo S, Kaila K & Voipio J (2005) Evaluation of commercially available electrodes and gels for recording of slow EEG potentials. *Clin Neurophysiol* 116, 799–806.
177. Voipio J, Tallgren P, Heinonen E, Vanhatalo S & Kaila K (2003) Millivolt-scale DC shifts in the human scalp EEG: Evidence for a nonneuronal generator. *J Neurophysiol* 89, 2208–2214.
178. Birbaumer N, Elbert T, Canavan AG & Rockstroh B (1990) Slow potentials of the cerebral cortex and behavior. *Physiol Rev* 70, 1–41.
179. Hämäläinen M, Hari R, Ilmoniemi RJ, Knuutila J & Lounasmaa OV (1993) Magnetoencephalography—theory, instrumentation, and applications to noninvasive studies of the working human brain. *Rev Mod Phys* 65, 413–497.
180. Malmivuo J & Plonsey R (1995) *Bioelectromagnetism: Principles and applications of bioelectric and biomagnetic fields* (Oxford University Press, USA).
181. Murakami S & Okada Y (2006) Contributions of principal neocortical neurons to magnetoencephalography and electroencephalography signals. *J Physiol* 575, 925–936.
182. Kerr JN, Greenberg D & Helmchen F (2005) Imaging input and output of neocortical networks in vivo. *Proc Natl Acad Sci U S A* 102, 14063–14068.
183. Logothetis NK (2003) The underpinnings of the BOLD functional magnetic resonance imaging signal. *J Neurosci* 23, 3963–3971.
184. Buzsáki G, Kaila K & Raichle M (2007) Inhibition and brain work. *Neuron* 56, 771–783.
185. Logothetis NK, Pauls J, Augath M, Trinath T & Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412, 150–157.
186. Mukamel R, Gelbard H, Arieli A, Hasson U, Fried I & Malach R (2005) Coupling between neuronal firing, field potentials, and fMRI in human auditory cortex. *Science* 309, 951–954.
187. Niessing J, Ebisch B, Schmidt KE, Niessing M, Singer W & Galuske RA (2005) Hemodynamic signals correlate tightly with synchronized gamma oscillations. *Science* 309, 948–951.
188. Lee J, Taira T, Pihlaja P, Ransom BR & Kaila K (1996) Effects of CO2 on excitatory transmission apparently caused by changes in intracellular pH in the rat hippocampal slice. *Brain Res* 706, 210–216.
189. Kiviniemi V, Remes J, Starck T, Nikkinen J, Haapea M, Silven O & Tervonen O (2009) Mapping transient hyperventilation induced alterations with estimates of the multi-scale dynamics of BOLD signal. *Front Neuroinformatics* 3, 18.
190. Bartnik EA, Blinowska KJ & Durka PJ (1992) Single evoked potential reconstruction by means of wavelet transform. *Biol Cybern* 67, 175–181.
191. Sinkkonen J, Tiitinen H & Näätänen R (1995) Gabor filters: An informative way for analysing event-related brain activity. *J Neurosci Methods* 56, 99–104.
192. Palva JM, Palva S & Kaila K (2005) Phase synchrony among neuronal oscillations in the human cortex. *J Neurosci* 25, 3962–3972.
193. Mitra SK (2001) *Digital signal processing: A computer-based approach* (McGraw-Hill Science)

194. Bullock TH, McClune MC & Enright JT (2003) Are the electroencephalograms mainly rhythmic? Assessment of periodicity in wide-band time series. *Neuroscience* 121, 233–252.
195. Pereda E, Quiroga RQ & Bhattacharya J (2005) Nonlinear multivariate analysis of neurophysiological signals. *Prog Neurobiol* 77, 1–37.
196. Lachaux JP, Rodriguez E, Martinerie J & Varela FJ (1999) Measuring phase synchrony in brain signals. *Hum Brain Mapp* 8, 194–208.
197. Goldberger AL, Amaral LA, Hausdorff JM, Ivanov PCh, Peng CK & Stanley HE (2002) Fractal dynamics in physiology: Alterations with disease and aging. *Proc Natl Acad Sci U S A* 99 Suppl 1, 2466–2472.
198. Peng CK, Havlin S, Stanley HE & Goldberger AL (1995) Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos* 5, 82–87.
199. Ivanov PC, Rosenblum MG, Peng CK, Mietus J, Havlin S, Stanley HE & Goldberger AL (1996) Scaling behaviour of heartbeat intervals obtained by wavelet-based time-series analysis. *Nature* 383, 323–327.
200. Rangarajan G & Ding M (2000) Integrated approach to the assessment of long range correlation in time series data. *Phys Rev E* 61, 4991–5001.
201. Heneghan C & McDarby G (2000) Establishing the relation between detrended fluctuation analysis and power spectral density analysis for stochastic processes. *Phys Rev E* 62, 6103–6110.
202. Nikulin VV & Brismar T (2005) Long-range temporal correlations in electroencephalographic oscillations: Relation to topography, frequency band, age and gender. *Neuroscience* 130, 549–558.
203. Stam CJ & de Bruin EA (2004) Scale-free dynamics of global functional connectivity in the human brain. *Hum Brain Mapp* 22, 97–109.
204. Achard S, Bassett DS, Meyer-Lindenberg A & Bullmore E (2008) Fractal connectivity of long–memory networks. *Phys Rev E* 77, 036104.
205. Linkenkaer-Hansen K, Smit DJ, Barkil A, van Beijsterveldt TE, Brussaard AB, Boomsma DI, van Ooyen A & de Geus EJ (2007) Genetic contributions to long-range temporal correlations in ongoing oscillations. *J Neurosci* 27, 13882–13889.
206. Schoffelen JM & Gross J (2009) Source connectivity analysis with MEG and EEG. *Hum Brain Mapp* 30, 1857–1865.
207. Hämäläinen MS & Ilmoniemi RJ (1994) Interpreting magnetic fields of the brain: Minimum norm estimates. *Med Biol Eng Comput* 32, 35–42.
208. Nenonen JT, Hämäläinen MS & Ilmoniemi RJ (1994) Minimum-norm estimation in a boundary-element torso model. *Med Biol Eng Comput* 32, 43–48.
209. Tesche CD, Uusitalo MA, Ilmoniemi RJ, Huotilainen M, Kajola M & Salonen O (1995) Signal-space projections of MEG data characterize both distributed and well-localized neuronal sources. *Electroencephalogr Clin Neurophysiol* 95, 189–200.
210. Knott V, Mahoney C, Kennedy S & Evans K (2001) EEG power, frequency, asymmetry and coherence in male depression. *Psychiatry Res* 106, 123–140.
211. Corbetta M (1998) Frontoparietal cortical networks for directing attention and the eye to visual locations: Identical, independent, or overlapping neural systems? *Proc Natl Acad Sci U S A* 95, 831–838.
212. Corbetta M, Akbudak E, Conturo TE, Snyder AZ, Ollinger JM, Drury HA, Linenweber MR, Petersen SE, Raichle ME, Van Essen DC & Shulman GL (1998) A common network of functional areas for attention and eye movements. *Neuron* 21, 761–773.
213. Womelsdorf T & Fries P (2007) The role of neuronal synchronization in selective attention. *Curr Opin Neurobiol* 17, 154–160.
214. Womelsdorf T, Schoffelen JM, Oostenveld R, Singer W, Desimone R, Engel AK & Fries P (2007) Modulation of neuronal interactions through neuronal synchronization. *Science* 316, 1609–1612.

215. Siegel M, Donner TH, Oostenveld R, Fries P & Engel AK (2008) Neuronal synchronization along the dorsal visual pathway reflects the focus of spatial attention. *Neuron* 60, 709–719.
216. Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, Berger MS, Barbaro NM & Knight RT (2006) High gamma power is phase-locked to theta oscillations in human neocortex. *Science* 313, 1626–1628.
217. Smallwood J, Davies JB, Heim D, Finnigan F, Sudberry M, O'Connor R & Obonsawin M (2004) Subjective experience and the attentional lapse: Task engagement and disengagement during sustained attention. *Conscious Cogn* 13, 657–690.
218. Boly M, Balteau E, Schnakers C, Degueldre C, Moonen G, Luxen A, Phillips C, Peigneux P, Maquet P & Laureys S (2007) Baseline brain activity fluctuations predict somatosensory perception in humans. *Proc Natl Acad Sci U S A* 104, 12187–12192.
219. Nita DA, Vanhatalo S, Lafortune FD, Voipio J, Kaila K & Amzica F (2004) Nonneuronal origin of CO2-related DC-EEG shifts: An in vivo study in the cat. *J Neurophysiol* 92, 1011–1022.
220. Vanhatalo S, Tallgren P, Becker C, Holmes MD, Miller JW, Kaila K & Voipio J (2003) Scalp-recorded slow EEG responses generated in response to hemodynamic changes in the human brain. *Clin Neurophysiol* 114, 1744–1754.
221. Ogawa S, Lee TM, Kay AR & Tank DW (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proc Natl Acad Sci U S A* 87, 9868–9872.
222. Castellanos NP, Malmierca E, Nunez A & Makarov VA (2007) Corticofugal modulation of the tactile response coherence of projecting neurons in the gracilis nucleus. *J Neurophysiol* 98, 2537–2549.
223. Nir Y, Mukamel R, Dinstein I, Privman E, Harel M, Fisch L, Gelbard-Sagiv H, Kipervasser S, Andelman F, Neufeld MY, Kramer U, Arieli A, Fried I & Malach R (2008) Interhemispheric correlations of slow spontaneous neuronal fluctuations revealed in human sensory cortex. *Nat Neurosci* 11, 1100–1108.
224. Bullock TH, McClune MC, Achimowicz JZ, Iragui-Madoz VJ, Duckrow RB & Spencer SS (1995) Temporal fluctuations in coherence of brain waves. *Proc Natl Acad Sci U S A* 92, 11568–11572.
225. Laufs H, Krakow K, Sterzer P, Eger E, Beyerle A, Salek-Haddadi A & Kleinschmidt A (2003) Electroencephalographic signatures of attentional and cognitive default modes in spontaneous brain activity fluctuations at rest. *Proc Natl Acad Sci U S A* 100, 11053–11058.
226. Mantini D, Perrucci MG, Del Gratta C, Romani GL & Corbetta M (2007) Electrophysiological signatures of resting state networks in the human brain. *Proc Natl Acad Sci U S A* 104, 13170–13175.
227. de Munck JC, Gonçalves SI, Mammoliti R, Heethaar RM & Lopes da Silva FH (2009) Interactions between different EEG frequency bands and their effect on alpha-fMRI correlations. *Neuroimage* 47, 69–76.
228. Allen EA, Pasley BN, Duong T & Freeman RD (2007) Transcranial magnetic stimulation elicits coupled neural and hemodynamic consequences. *Science* 317, 1918–1921.
229. Devor A, Ulbert I, Dunn AK, Narayanan SN, Jones SR, Andermann ML, Boas DA & Dale AM (2005) Coupling of the cortical hemodynamic response to cortical and thalamic neuronal activity. *Proc Natl Acad Sci U S A* 102, 3822–3827.
230. Austin MP, Mitchell P & Goodwin GM (2001) Cognitive deficits in depression: Possible implications for functional neuropathology. *Br J Psychiatry* 178, 200–206.
231. Drevets WC (2000) Neuroimaging studies of mood disorders. *Biol Psychiatry* 48, 813–829.
232. Mayberg HS (2003) Modulating dysfunctional limbic-cortical circuits in depression: Towards development of brain-based algorithms for diagnosis and optimised treatment. *Br Med Bull* 65, 193–207.

233. Litt B, Esteller R, Echauz J, D'Alessandro M, Shor R, Henry T, Pennell P, Epstein C, Bakay R, Dichter M & Vachtsevanos G (2001) Epileptic seizures may begin hours in advance of clinical onset: A report of five patients. *Neuron* 30, 51–64.
234. Chavez M, Le Van Quyen M, Navarro V, Baulac M & Martinerie J (2003) Spatio-temporal dynamics prior to neocortical seizures: Amplitude versus phase couplings. *IEEE Trans Biomed Eng* 50, 571–583.
235. Lehnertz K, Mormann F, Kreuz T, Andrzejak RG, Rieke C, David P & Elger CE (2003) Seizure prediction by nonlinear EEG analysis. *IEEE Eng Med Biol Mag* 22, 57–63.
236. Ouyang G, Li X, Li Y & Guan X (2007) Application of wavelet-based similarity analysis to epileptic seizures prediction. *Comput Biol Med* 37, 430–437.
237. Zaveri HP, Pincus SM, Goncharova II, Duckrow RB, Spencer DD & Spencer SS (2009) Localization-related epilepsy exhibits significant connectivity away from the seizure-onset area. *Neuroreport* 20, 891–895.
238. Parish LM, Worrell GA, Cranstoun SD, Stead SM, Pennell P & Litt B (2004) Long-range temporal correlations in epileptogenic and non-epileptogenic human hippocampus. *Neuroscience* 125, 1069–1076.
239. Worrell GA, Cranstoun SD, Echauz J & Litt B (2002) Evidence for self-organized criticality in human epileptic hippocampus. *Neuroreport* 13, 2017–2021.
240. Golomb D (1998) Models of neuronal transient synchrony during propagation of activity through neocortical circuitry. *J Neurophysiol* 79, 1–12.
241. Gutkin BS, Laing CR, Colby CL, Chow CC & Ermentrout GB (2001) Turning on and off with excitation: The role of spike-timing asynchrony and synchrony in sustained neural activity. *J Comput Neurosci* 11, 121–134.
242. Netoff TI & Schiff SJ (2002) Decreased neuronal synchronization during experimental seizures. *J Neurosci* 22, 7297–7307.
243. Garcia Dominguez L, Wennberg RA, Gaetz W, Cheyne D, Snead OC III & Perez Velazquez JL (2005) Enhanced synchrony in epileptiform activity? local versus distant phase synchronization in generalized seizures. *J Neurosci* 25, 8077–8084.
244. Amor F, Baillet S, Navarro V, Adam C, Martinerie J & Le Van Quyen M (2009) Cortical local and long-range synchronization interplay in human absence seizure initiation. *Neuroimage* 45, 950–962.
245. Lian J, Bikson M, Shuai J & Durand DM (2001) Propagation of non-synaptic epileptiform activity across a lesion in rat hippocampal slices. *J Physiol* 537, 191–199.
246. Fingelkurts AA, Fingelkurts AA, Kivisaari R, Pekkonen E, Ilmoniemi RJ & Kähkönen S (2004) Enhancement of GABA-related signalling is associated with increase of functional connectivity in human cortex. *Hum Brain Mapp* 22, 27–39.
247. Muñoz A, Mendez P, DeFelipe J & Alvarez-Leefmans FJ (2007) Cation-chloride cotransporters and GABA-ergic innervation in the human epileptic hippocampus. *Epilepsia* 48, 663–673.
248. Huberfeld G, Wittner L, Clemenceau S, Baulac M, Kaila K, Miles R & Rivera C (2007) Perturbed chloride homeostasis and GABAergic signaling in human temporal lobe epilepsy. *J Neurosci* 27, 9866–9873.
249. Payne JA, Rivera C, Voipio J & Kaila K (2003) Cation-chloride co-transporters in neuronal communication, development and trauma. *Trends Neurosci* 26, 199–206.
250. Ramon C, Holmes MD, Freeman WJ, McElroy R & Rezvanian E (2008) Comparative analysis of temporal dynamics of EEG and phase synchronization of EEG to localize epileptic sites from high density scalp EEG interictal recordings. *Conf Proc IEEE Eng Med Biol Soc* 2008, 4548–4550.
251. Pitkänen A, Kharatishvili I, Karhunen H, Lukasiuk K, Immonen R, Nairismägi J, Gröhn O & Nissinen J (2007) Epileptogenesis in experimental models. *Epilepsia* 48 Suppl 2, 13–20.
252. Montez T, Poil SS, Jones BF, Manshanden I, Verbunt JP, van Dijk BW, Brussaard AB, van Ooyen A, Stam CJ, Scheltens P & Linkenkaer-Hansen K (2009) Altered temporal

correlations in parietal alpha and prefrontal theta oscillations in early-stage Alzheimer disease. *Proc Natl Acad Sci U S A* 106, 1614–1619.
253. Stam CJ, de Haan W, Daffertshofer A, Jones BF, Manshanden I, van Cappellen van Walsum AM, Montez T, Verbunt JP, de Munck JC, van Dijk BW, Berendse HW & Scheltens P (2009) Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer's disease. *Brain* 132, 213–224.
254. Stam CJ, Jones BF, Manshanden I, van Cappellen van Walsum AM, Montez T, Verbunt JP, de Munck JC, van Dijk BW, Berendse HW & Scheltens P (2006) Magnetoencephalographic evaluation of resting-state functional connectivity in Alzheimer's disease. *Neuroimage* 32, 1335–1344.
255. Tass PA, Rosenblum MG, Weule J, Kurths J, Pikovsky A, Volkmann J, Schnitzler A & Freund H-J (1998) Detection of n:m phase locking from noisy data: application to magnetoencephalography. *Phys Rev Lett* 81, 3291–4.
256. Timmermann L, Gross J, Dirks M, Volkmann J, Freund HJ & Schnitzler A (2003) The cerebral oscillatory network of parkinsonian resting tremor. *Brain* 126, 199–212.
257. Stephan KE, Friston KJ & Frith CD (2009) Dysconnection in schizophrenia: From abnormal synaptic plasticity to failures of self-monitoring. *Schizophr Bull* 35, 509–527.
258. Spencer KM, Nestor PG, Niznikiewicz MA, Salisbury DF, Shenton ME & McCarley RW (2003) Abnormal neural synchrony in schizophrenia. *J Neurosci* 23, 7407–7411.
259. Uhlhaas PJ, Linden DE, Singer W, Haenschel C, Lindner M, Maurer K & Rodriguez E (2006) Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J Neurosci* 26, 8168–8175.
260. Gottesman II & Gould TD (2003) The endophenotype concept in psychiatry: Etymology and strategic intentions. *Am J Psychiatry* 160, 636–645.
261. Meyer-Lindenberg A (2009) Neural connectivity as an intermediate phenotype: Brain networks under genetic control. *Hum Brain Mapp* 30, 1938–1946.
262. Olshausen BA & Field DJ (1996) Emergence of simple-cell receptive field properties by learning a sparse code for natural images. *Nature* 381, 607–609.
263. Quiroga RQ, Reddy L, Kreiman G, Koch C & Fried I (2005) Invariant visual representation by single neurons in the human brain. *Nature* 435, 1102–1107.
264. Taulu S, Kajola M & Simola J (2004) Suppression of interference and artifacts by the signal space separation method. *Brain Topogr* 16, 269–275.
265. Taulu S & Kajola M (2005) Presentation of electromagnetic multichannel data: The signal space separation method. *J Appl Phys* 97, 120495-1-9.
266. Dalal SS, Baillet S, Adam C, Ducorps A, Schwartz D, Jerbi K, Bertrand O, Garnero L, Martinerie J & Lachaux JP (2009) Simultaneous MEG and intracranial EEG recordings during attentive reading. *Neuroimage* 45, 1289–1304.
267. Nunez PL, Srinivasan R, Westdorp AF, Wijesinghe RS, Tucker DM, Silberstein RB & Cadusch PJ (1997) EEG coherency. I: Statistics, reference electrode, volume conduction, laplacians, cortical imaging, and interpretation at multiple scales. *Electroencephalogr Clin Neurophysiol* 103, 499–515.
268. Monto S (2004) Cortical synchrony in intracranial electric studies of epileptic patients. M.Sc. dissertation (Helsinki University of Technology, Espoo, Finland)
269. Schiff SJ (2005) Dangerous phase. *Neuroinformatics* 3, 315–318.
270. Ferri R, Rundo F, Bruni O, Terzano MG & Stam CJ (2005) Dynamics of the EEG slow-wave synchronization during sleep. *Clin Neurophysiol* 116, 2783–2795.
271. Ferree TC & Hwa RC (2005) Electrophysiological measures of acute cerebral ischaemia. *Phys Med Biol* 50, 3927–3939.
272. Watters PA & Martin F (2004) A method for estimating long-range power law correlations from the electroencephalogram. *Biol Psychol* 66, 79–89.
273. Nikulin VV & Brismar T (2004) Long-range temporal correlations in alpha and beta oscillations: Effect of arousal level and test-retest reliability. *Clin Neurophysiol* 115, 1896–1908.

274. Hu K, Ivanov PC, Chen Z, Carpena P & Stanley HE (2001) Effect of trends on detrended fluctuation analysis. *Phys Rev E* 64, 011114.
275. Gross J, Kujala J, Hämäläinen M, Timmermann L, Schnitzler A & Salmelin R (2001) Dynamic imaging of coherent sources: Studying neural interactions in the human brain. *Proc Natl Acad Sci U S A* 98, 694–699.
276. Kujala J, Pammer K, Cornelissen P, Roebroeck A, Formisano E & Salmelin R (2007) Phase coupling in a cerebro-cerebellar network at 8–13 Hz during reading. *Cereb Cortex* 17, 1476–1485.
277. David O, Garnero L, Cosmelli D & Varela FJ (2002) Estimation of neural dynamics from MEG/EEG cortical current density maps: Application to the reconstruction of large-scale cortical synchrony. *IEEE Trans Biomed Eng* 49, 975–987.
278. Jerbi K, Lachaux JP, N'Diaye K, Pantazis D, Leahy RM, Garnero L & Baillet S (2007) Coherent neural representation of hand speed in humans revealed by MEG imaging. *Proc Natl Acad Sci U S A* 104, 7676–7681.
279. Baccala LA & Sameshima K (2001) Partial directed coherence: A new concept in neural structure determination. *Biol Cybern* 84, 463–474.
280. Schreiber T (2000) Measuring information transfer. *Phys Rev Lett* 85, 461–464.
281. Rosenblum MG & Pikovsky AS (2001) Detecting direction of coupling in interacting oscillators. *Phys Rev E* 64, 045202.
282. Ishiguro K, Otsu N, Lungarella M & Kuniyoshi Y (2008) Comparison of nonlinear Granger causality extensions for low-dimensional systems. *Phys Rev E* 77, 036217.
283. Smith DV & Clithero JA (2009) Manipulating executive function with transcranial direct current stimulation. *Front Integr Neurosci* 3, 26.
284. Silvanto J & Muggleton NG (2008) New light through old windows: Moving beyond the "virtual lesion" approach to transcranial magnetic stimulation. *Neuroimage* 39, 549–552.
285. Thut G & Miniussi C (2009) New insights into rhythmic brain activity from TMS-EEG studies. *Trends Cogn Sci* 13, 182–189.
286. Raij T, Karhu J, Kicić D, Lioumis P, Julkunen P, Lin FH, Ahveninen J, Ilmoniemi RJ, Mäkelä JP, Hämäläinen M, Rosen BR & Belliveau JW (2008) Parallel input makes the brain run faster. *Neuroimage* 40, 1792–1797.
287. Hamidi M, Slagter HA, Tononi G & Postle BR (2009) Repetitive transcranial magnetic stimulation affects behavior by biasing endogenous cortical oscillations. *Front Integr Neurosci* 3, 14.
288. Hannula H, Neuvonen T, Savolainen P, Hiltunen J, Ma YY, Antila H, Salonen O, Carlson S & Pertovaara A (2010) Increasing top-down suppression from prefrontal cortex facilitates tactile working memory. *Neuroimage* 49, 1091–1098.
289. Capotosto P, Babiloni C, Romani GL & Corbetta M (2009) Frontoparietal cortex controls spatial attention through modulation of anticipatory alpha rhythms. *J Neurosci* 29, 5863–5872.
290. Lakatos P, Shah AS, Knuth KH, Ulbert I, Karmos G & Schroeder CE (2005) An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. *J Neurophysiol* 94, 1904–1911.
291. Osipova D, Hermes D & Jensen O (2008) Gamma power is phase-locked to posterior alpha activity. *PLoS One* 3, e3990.
292. Haslinger R, Ulbert I, Moore CI, Brown EN & Devor A (2006) Analysis of LFP phase predicts sensory response of barrel cortex. *J Neurophysiol* 96, 1658–1663.
293. Kruglikov SY & Schiff SJ (2003) Interplay of electroencephalogram phase and auditory-evoked neural activity. *J Neurosci* 23, 10122–10127.
294. Busch NA, Dubois J & VanRullen R (2009) The phase of ongoing EEG oscillations predicts visual perception. *J Neurosci* 29, 7869–7876.
295. Mathewson KE, Gratton G, Fabiani M, Beck DM & Ro T (2009) To see or not to see: Prestimulus alpha phase predicts visual awareness. *J Neurosci* 29, 2725–2732.
296. VanRullen R & Koch C (2003) Is perception discrete or continuous? *Trends Cogn Sci* 7, 207–213.

297. Lago-Fernández LF, Huerta R, Corbacho F & Sigüenza JA (2000) Fast response and temporal coherent oscillations in small-world networks. *Phys Rev Lett* 84, 2758–2761.
298. MacLeod K & Laurent G (1996) Distinct mechanisms for synchronization and temporal patterning of odor-encoding neural assemblies. *Science* 274, 976–979.
299. Barahona M & Pecora LM (2002) Synchronization in small-world systems. *Phys Rev Lett* 89, 054101.
300. Nishikawa T, Motter AE, Lai YC & Hoppensteadt FC (2003) Heterogeneity in oscillator networks: Are smaller worlds easier to synchronize? *Phys Rev Lett* 91, 014101.
301. Hütt MT & Lesne A (2009) Interplay between topology and dynamics in excitation patterns on hierarchical graphs. *Front Neuroinformatics* 3, 28.
302. Müller-Linow M, Hilgetag CC & Hütt MT (2008) Organization of excitable dynamics in hierarchical biological networks. *PLoS Comput Biol* 4, e1000190.
303. Arenas A, Díaz-Guilera A & Pérez-Vicente CJ (2006) Synchronization reveals topological scales in complex networks. *Phys Rev Lett* 96, 114102.
304. Honey CJ, Kötter R, Breakspear M & Sporns O (2007) Network structure of cerebral cortex shapes functional connectivity on multiple time scales. *Proc Natl Acad Sci U S A* 104, 10240–10245.
305. Catani M & ffytche DH (2005) The rises and falls of disconnection syndromes. *Brain* 128, 2224–2239.
306. Särkämö T, Tervaniemi M, Soinila S, Autti T, Silvennoinen HM, Laine M & Hietanen M (2009) Cognitive deficits associated with acquired amusia after stroke: A neuropsychological follow-up study. *Neuropsychologia* 47, 2642–2651.
307. van Asselen M, Kessels RP, Frijns CJ, Kappelle LJ, Neggers SF & Postma A (2009) Object-location memory: A lesion-behavior mapping study in stroke patients. *Brain Cogn (in press)*
308. Schmahmann JD, Macmore J & Vangel M (2009) Cerebellar stroke without motor deficit: Clinical evidence for motor and non-motor domains within the human cerebellum. *Neuroscience* 162, 852–861.
309. Young MP, Hilgetag CC & Scannell JW (2000) On imputing function to structure from the behavioural effects of brain lesions. *Phil Trans R Soc B* 355, 147–161.
310. Alstott J, Breakspear M, Hagmann P, Cammoun L & Sporns O (2009) Modeling the impact of lesions in the human brain. *PLoS Comput Biol* 5, e1000408.
311. Honey CJ & Sporns O (2008) Dynamical consequences of lesions in cortical networks. *Hum Brain Mapp* 29, 802–809.
312. Bartolomei F, Bosma I, Klein M, Baayen JC, Reijneveld JC, Postma TJ, Heimans JJ, van Dijk BW, de Munck JC, de Jongh A, Cover KS & Stam CJ (2006) How do brain tumors alter functional connectivity? A magnetoencephalography study. *Ann Neurol* 59, 128–138.
313. Bartolomei F, Bosma I, Klein M, Baayen JC, Reijneveld JC, Postma TJ, Heimans JJ, van Dijk BW, de Munck JC, de Jongh A, Cover KS & Stam CJ (2006) Disturbed functional connectivity in brain tumour patients: Evaluation by graph analysis of synchronization matrices. *Clin Neurophysiol* 117, 2039–2049.
314. Bassett DS, Bullmore E, Verchinski BA, Mattay VS, Weinberger DR, Meyer-Lindenberg A (2008) Hierarchical organization of human cortical networks in health and schizophrenia. *J Neurosci* 28, 9239–9248.
315. Liu Y, Liang M, Zhou Y, He Y, Hao Y, Song M, Yu C, Liu H, Liu Z & Jiang T (2008) Disrupted small-world networks in schizophrenia. *Brain* 131, 945–961.
316. Rubinov M, Knock SA, Stam CJ, Micheloyannis S, Harris AW, Williams LM & Breakspear M (2009) Small-world properties of nonlinear brain activity in schizophrenia. *Hum Brain Mapp* 30, 403–416.
317. Calhoun VD, Eichele T & Pearlson G (2009) Functional brain networks in schizophrenia: A review. *Front Hum Neurosci* 3, 17.

318. van Cappellen van Walsum AM, Pijnenburg YA, Berendse HW, van Dijk BW, Knol DL, Scheltens P & Stam CJ (2003) A neural complexity measure applied to MEG data in Alzheimer's disease. *Clin Neurophysiol* 114, 1034–1040.
319. He Y, Chen Z & Evans A (2008) Structural insights into aberrant topological patterns of large-scale cortical networks in Alzheimer's disease. *J Neurosci* 28, 4756–4766.
320. Supekar K, Menon V, Rubin D, Musen M & Greicius MD (2008) Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Comput Biol* 4, e1000100.
321. Sorg C, Riedl V, Mühlau M, Calhoun VD, Eichele T, Läer L, Drzezga A, Förstl H, Kurz A, Zimmer C & Wohlschläger AM (2007) Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. *Proc Natl Acad Sci U S A* 104, 18760–18765.
322. Rombouts SA, Barkhof F, Goekoop R, Stam CJ & Scheltens P (2005) Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: An fMRI study. *Hum Brain Mapp* 26, 231–239.
323. Nissinen J, Lukasiuk K & Pitkänen A (2001) Is mossy fiber sprouting present at the time of the first spontaneous seizures in rat experimental temporal lobe epilepsy? *Hippocampus* 11, 299–310.
324. Buzsáki G (2007) The structure of consciousness. *Nature* 446, 267.
325. Crick F & Koch C (1998) Constraints on cortical and thalamic projections: The no-strong-loops hypothesis. *Nature* 391, 245–250.
326. Morgan RJ & Soltesz I (2008) Nonrandom connectivity of the epileptic dentate gyrus predicts a major role for neuronal hubs in seizures. *Proc Natl Acad Sci U S A* 105, 6179–6184.
327. Dyhrfjeld-Johnsen J, Santhakumar V, Morgan RJ, Huerta R, Tsimring L & Soltesz I (2007) Topological determinants of epileptogenesis in large-scale structural and functional models of the dentate gyrus derived from experimental data. *J Neurophysiol* 97, 1566–1587.
328. Netoff TI, Clewley R, Arno S, Keck T & White JA (2004) Epilepsy in small-world networks. *J Neurosci* 24, 8075–8083.
329. Srinivas KV, Jain R, Saurav S & Sikdar SK (2007) Small-world network topology of hippocampal neuronal network is lost, in an in vitro glutamate injury model of epilepsy. *Eur J Neurosci* 25, 3276–3286.
330. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC & Raichle ME (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proc Natl Acad Sci U S A* 102, 9673–9678.
331. De Luca M, Beckmann CF, De Stefano N, Matthews PM & Smith SM (2006) fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *Neuroimage* 29, 1359–1367.
332. Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM & Beckmann CF (2006) Consistent resting-state networks across healthy subjects. *Proc Natl Acad Sci U S A* 103, 13848–13853.
333. Greicius MD, Krasnow B, Reiss AL & Menon V (2003) Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proc Natl Acad Sci U S A* 100, 253–258.
334. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA & Shulman GL (2001) A default mode of brain function. *Proc Natl Acad Sci U S A* 98, 676–682.
335. Gusnard DA & Raichle ME (2001) Searching for a baseline: Functional imaging and the resting human brain. *Nat Rev Neurosci* 2, 685–694.
336. Yan C, Liu D, He Y, Zou Q, Zhu C, Zuo X, Long X & Zang Y (2009) Spontaneous brain activity in the default mode network is sensitive to different resting-state conditions with limited cognitive load. *PLoS One* 4, e5743.
337. Fox MD, Zhang D, Snyder AZ & Raichle ME (2009) The global signal and observed anticorrelated resting state brain networks. *J Neurophysiol* 101, 3270–3283.
338. Sonuga-Barke EJ & Castellanos FX (2007) Spontaneous attentional fluctuations in impaired states and pathological conditions: A neurobiological hypothesis. *Neurosci Biobehav Rev* 31, 977–986.

339. Broyd SJ, Demanuele C, Debener S, Helps SK, James CJ & Sonuga-Barke EJ (2009) Default-mode brain dysfunction in mental disorders: A systematic review. *Neurosci Biobehav Rev* 33, 279–296.
340. Hesselmann G, Kell CA, Eger E & Kleinschmidt A (2008) Spontaneous local variations in ongoing neural activity bias perceptual decisions. *Proc Natl Acad Sci U S A* 105, 10984-10989.
341. Sadaghiani S, Hesselmann G & Kleinschmidt A (2009) Distributed and antagonistic contributions of ongoing activity fluctuations to auditory stimulus detection. *J Neurosci* 29, 13410–13417.
342. Christoff K, Gordon AM, Smallwood J, Smith R & Schooler JW (2009) Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proc Natl Acad Sci U S A* 106, 8719–8724.
343. Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST & Macrae CN (2007) Wandering minds: The default network and stimulus-independent thought. *Science* 315, 393–395.
344. Eichele T, Debener S, Calhoun VD, Specht K, Engel AK, Hugdahl K, von Cramon DY & Ullsperger M (2008) Prediction of human errors by maladaptive changes in event-related brain networks. *Proc Natl Acad Sci U S A* 105, 6173–6178.
345. Clare Kelly AM, Uddin LQ, Biswal BB, Castellanos FX & Milham MP (2008) Competition between functional brain networks mediates behavioral variability. *Neuroimage* 39, 527–537.
346. Skudlarski P, Jagannathan K, Calhoun VD, Hampson M, Skudlarska BA & Pearlson G (2008) Measuring brain connectivity: Diffusion tensor imaging validates resting state temporal correlations. *Neuroimage* 43, 554–561.
347. Eguíluz VM, Chialvo DR, Cecchi GA, Baliki M & Apkarian AV (2005) Scale-free brain functional networks. *Phys Rev Lett* 94, 018102.
348. Salvador R, Suckling J, Coleman MR, Pickard JD, Menon D & Bullmore E (2005) Neurophysiological architecture of functional magnetic resonance images of human brain. *Cereb Cortex* 15, 1332–1342.
349. Achard S, Salvador R, Whitcher B, Suckling J & Bullmore E (2006) A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *J Neurosci* 26, 63–72.
350. van den Heuvel MP, Stam CJ, Boersma M & Hulshoff Pol HE (2008) Small-world and scale-free organization of voxel-based resting-state functional connectivity in the human brain. *Neuroimage* 43, 528–539.
351. He Y, Wang J, Wang L, Chen ZJ, Yan C, Yang H, Tang H, Zhu C, Gong Q, Zang Y & Evans AC (2009) Uncovering intrinsic modular organization of spontaneous brain activity in humans. *PLoS One* 4, e5226.
352. Meunier D, Achard S, Morcom A & Bullmore E (2009) Age-related changes in modular organization of human brain functional networks. *Neuroimage* 44, 715–723.
353. Ferrarini L, Veer IM, Baerends E, van Tol MJ, Renken RJ, van der Wee NJ, Veltman DJ, Aleman A, Zitman FG, Penninx BW, van Buchem MA, Reiber JH, Rombouts SA & Milles J (2009) Hierarchical functional modularity in the resting-state human brain. *Hum Brain Mapp* 30, 2220–2231.
354. Micheloyannis S, Vourkas M, Tsirka V, Karakonstantaki E, Kanatsouli K & Stam CJ (2009) The influence of ageing on complex brain networks: A graph theoretical analysis. *Hum Brain Mapp* 30, 200–208.
355. Smit DJ, Stam CJ, Posthuma D, Boomsma DI & de Geus EJ (2008) Heritability of "small-world" networks in the brain: A graph theoretical analysis of resting-state EEG functional connectivity. *Hum Brain Mapp* 29, 1368–1378.
356. Stam CJ (2004) Functional connectivity patterns of human magnetoencephalographic recordings: A 'small-world' network? *Neurosci Lett* 355, 25–28.
357. Jann K, Dierks T, Boesch C, Kottlow M, Strik W & Koenig T (2009) BOLD correlates of EEG alpha phase-locking and the fMRI default mode network. *Neuroimage* 45, 903–916.

358. Gonçalves SI, de Munck JC, Pouwels PJ, Schoonhoven R, Kuijer JP, Maurits NM, Hoogduin JM, Van Someren EJ, Heethaar RM & Lopes da Silva FH (2006) Correlating the alpha rhythm to BOLD using simultaneous EEG/fMRI: Inter-subject variability. *Neuroimage* 30, 203–213.
359. Chen AC, Feng W, Zhao H, Yin Y & Wang P (2008) EEG default mode network in the human brain: Spectral regional field powers. *Neuroimage* 41, 561–574.
360. Yu S, Huang D, Singer W & Nikolić D (2008) A small world of neuronal synchrony. *Cereb Cortex* 18, 2891–2901.
361. Fraiman D, Balenzuela P, Foss J & Chialvo DR (2009) Ising-like dynamics in large–scale functional brain networks. *Phys Rev E* 79, 061922.
362. Bornholdt S & Röhl T (2003) Self-organized critical neural networks. *Phys Rev E* 67, 066118.
363. Beggs JM (2008) The criticality hypothesis: How local cortical networks might optimize information processing. *Phil Trans R Soc A* 366, 329–343.
364. Freeman WJ (2005) A field-theoretic approach to understanding scale-free neocortical dynamics. *Biol Cybern* 92, 350–359.
365. Corral A, Pérez CJ, Díaz-Guilera A & Arenas A (1995) Self-organized criticality and synchronization in a lattice model of integrate-and-fire oscillators. *Phys Rev Lett* 74, 118–121.
366. Shin CW & Kim S (2006) Self-organized criticality and scale-free properties in emergent functional neural networks. *Phys Rev E* 74, 045101.
367. Levina A, Herrmann JM & Geisel T (2009) Phase transitions towards criticality in a neural system with adaptive interactions. *Phys Rev Lett* 102, 118110.
368. Sporns O, Tononi G & Edelman GM (2000) Theoretical neuroanatomy: Relating anatomical and functional connectivity in graphs and cortical connection matrices. *Cereb Cortex* 10, 127–141.
369. Golshani P, Gonçalves JT, Khoshkhoo S, Mostany R, Smirnakis S & Portera-Cailliau C (2009) Internally mediated developmental desynchronization of neocortical network activity. *J Neurosci* 29(35):10890–10899
370. Pajevic S & Plenz D (2009) Efficient network reconstruction from dynamical cascades identifies small-world topology of neuronal avalanches. *PLoS Comput Biol* 5, e1000271.
371. Plenz D & Thiagarajan TC (2007) The organizing principles of neuronal avalanches: Cell assemblies in the cortex? *Trends Neurosci* 30, 101–110.
372. Kanai R, Chaieb L, Antal A, Walsh V & Paulus W (2008) Frequency-dependent electrical stimulation of the visual cortex. *Curr Biol* 18, 1839–1843.
373. Parra J, Kalitzin SN, Iriarte J, Blanes W, Velis DN & Lopes da Silva FH (2003) Gamma-band phase clustering and photosensitivity: Is there an underlying mechanism common to photosensitive epilepsy and visual perception? *Brain* 126, 1164–1172.
374. Lisman JE & Idiart MA (1995) Storage of 7 +/- 2 short-term memories in oscillatory subcycles. *Science* 267, 1512–1515.
375. Lakatos P, Karmos G, Mehta AD, Ulbert I & Schroeder CE (2008) Entrainment of neuronal oscillations as a mechanism of attentional selection. *Science* 320, 110–113.
376. Schroeder CE & Lakatos P (2009) The gamma oscillation: Master or slave? *Brain Topogr*
377. Hasson U, Yang E, Vallines I, Heeger DJ & Rubin N (2008) A hierarchy of temporal receptive windows in human cortex. *J Neurosci* 28, 2539–2550.
378. Giraud AL, Kleinschmidt A, Poeppel D, Lund TE, Frackowiak RS & Laufs H (2007) Endogenous cortical rhythms determine cerebral specialization for speech perception and production. *Neuron* 56, 1127–1134.
379. Luo H & Poeppel D (2007) Phase patterns of neuronal responses reliably discriminate speech in human auditory cortex. *Neuron* 54, 1001–1010.
380. Kiebel SJ, Daunizeau J & Friston KJ (2008) A hierarchy of time-scales and the brain. *PLoS Comput Biol* 4, e1000209.
381. Bar M (2009) Predictions: A universal principle in the operation of the human brain. introduction. *Phil Trans R Soc B* 364, 1181–1182.

382. Grodzinsky Y & Santi A (2008) The battle for broca's region. *Trends Cogn Sci* 12, 474–480.
383. Willems RM & Hagoort P (2009) Broca's region: Battles are not won by ignoring half of the facts. *Trends Cogn Sci* 13, 101
384. Rizzolatti G, Fogassi L & Gallese V (2001) Neurophysiological mechanisms underlying the understanding and imitation of action. *Nat Rev Neurosci* 2, 661–670.
385. Nishitani N & Hari R (2000) Temporal dynamics of cortical representation for action. *Proc Natl Acad Sci U S A* 97, 913–918.
386. Kilner JM, Neal A, Weiskopf N, Friston KJ & Frith CD (2009) Evidence of mirror neurons in human inferior frontal gyrus. *J Neurosci* 29, 10153–10159.
387. Schroeder CE, Lakatos P, Kajikawa Y, Partan S & Puce A (2008) Neuronal oscillations and visual amplification of speech. *Trends Cogn Sci* 12, 106–113.
388. Yu AC & Margoliash D (1996) Temporal hierarchical control of singing in birds. *Science* 273, 1871–1875.
389. Aronov D, Andalman AS & Fee MS (2008) A specialized forebrain circuit for vocal babbling in the juvenile songbird. *Science* 320, 630–634.
390. Botvinick MM (2008) Hierarchical models of behavior and prefrontal function. *Trends Cogn Sci* 12, 201–208.
391. Breakspear M & Stam CJ (2005) Dynamics of a neural system with a multiscale architecture. *Phil Trans R Soc B* 360, 1051–1074.