Oscillations: From Neuron to MEG

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Krish Singh
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What are we trying to achieve?

• **Bridge the gap** from neuron to whole-human behaviour.
• A **comprehensive understanding** of how the brain works.
• What drives **individual variability** in human behavioural performance?
• What changes **from birth to old age**?
• What is going wrong in **neurological disease**?
Building the perfect neuroimaging tool:
Is Neuronal Firing Rate the Only Thing We Need to Know?
Single-unit recording demonstrating orientation specificity of neurons in visual cortex

1959;148;574-591 J. Physiol. D. H. Hubel and T. N. Wiesel
Invariant visual representation by single neurons in the human brain

R. Quiroga, L. Reddy, G. Kreiman, C. Koch & I. Fried

It takes a fraction of a second to recognize a person or an object even when seen under strikingly different conditions. How such a robust, high-level representation is achieved by neurons in the human brain is still unclear. In monkeys, neurons in the upper stages of the ventral visual pathway respond to complex images such as faces and objects and show some degree of invariance to metric properties such as the stimulus size, position and viewing angle. We have previously shown that neurons in the human medial temporal lobe (MTL) fire selectively to images of faces, animals, objects or scenes. Here we report on a remarkable subset of MTL neurons that are selectively activated by strikingly different pictures of given individuals, landmarks or objects and in some cases even by letter strings with their names. These results suggest an invariant, sparse and explicit code, which might be important in the transformation of complex visual percepts into long-term and more abstract memories.
In this study, firing-rate was not the important correlate of perception - changes in oscillation amplitude were the key parameter...
How do we measure these signals and where do they come from?
There are *multiple levels* of electrical signals that we can measure from the cortex

1. Single-electrode recordings: *invasive*
2. Multiple-unit (MUA) recordings: invasive
3. Local field potential (LFP) recordings: invasive
4. Electrocorticography (ECOG): *invasive*
5. EEG and MEG: *non-invasive*
Oscillations in the LFP

- LFP recordings show oscillatory behaviours that appear to be frequency-specific and stimulus and task related.
- These are generated either in cortico-cortico networks or thalamocortical loops.
- Could reflect local processing or inter-regional communication.
LFP recordings in Cat V1

First published May 15, 2003; 10.1152/jn.00195.2003.

**Responses to Natural Scenes in Cat V1**

Christoph Kayser, Rodrigo F. Salazar, and Peter König
Different response components arise in different layers of primary visual cortex - Monkey V1 LFP data
Temporal evolution of gamma
A beta2-frequency (20–30 Hz) oscillation in nonsynaptic networks of somatosensory cortex

Anita K. Roopun*, Steven J. Middleton*, Mark O. Cunningham*, Fiona E. N. LeBeau*, Andrea Bibbig†, Miles A. Whittington*, and Roger D. Traub‡

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Beta2 frequency (20–30 Hz) oscillations appear over somatosen-
naptic excitation. Beta2 generation in layer γ.

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**Diagram A**

- LII/III
- LIV
- LV

- Frequency (Hz)
- Time (sec)

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**Diagram B**

- a
- b
- c
- d
- e

- Power (10⁻¹ V²/Hz)
- 10
- 100
If we could measure these signals, non-invasively in humans - we would have a new ‘window’ on to layer-specific synaptic physiology and dynamics.
Correlated with firing rates

Not-correlated with firing rates
Cortical mapping of gamma oscillations in areas V1 and V4 of the macaque monkey.
ECoG gamma activity during a language task: differentiating expressive and receptive speech areas

Vernon L. Towle,1,2,3,4 Hyun-Ah Yoon,1 Michael Castelle,1 J. Christopher Edgar,5,6 Nadia M. Blassou,7 David M. Frim,2 Jean-Paul Spire12 and Michael H. Kohrman7

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Electrocorticographic (ECoG) spectral patterns obtained during language tasks from 12 epilepsy patients (age: 12–44 years) were analysed in order to identify and characterize cortical language areas. ECoG from 63 subdural electrodes (500 Hz/channel) chronically implanted over frontal, parietal and temporal lobes were examined. Two language tasks were performed. During the first language task, patients listened to a series of 50 words preceded by warning tones, and were asked to repeat each word. During a second memory task, subjects heard the 50 words from the first task randomly mixed with 50 new words and were asked to repeat the word only if it was a new word. Increases in ECoG gamma power (70–100 Hz) were observed in response to hearing tones (primary auditory cortex), hearing words (posterior temporal and parietal cortex) and repeating words...
Figure 3.
The spatial distribution of alpha, beta, and gamma-band responses during a visual search task. (a) Paradigm: The patients were asked to search for a gray 'T' within an array of distracters (gray 'L's'). (b) Cortical areas within direct vicinity of electrode sites across all ten patients (green). (c) Following the same convention as in Supplementary Figure 1b, 3D brain reconstructions show the distribution of alpha (8–12 Hz), beta (13–25 Hz) and gamma (50–150 Hz) responses 800 ms after stimulus onset, i.e., while patients are actively searching for the target. Response is expressed in energy variation relative to pre-stimulus baseline (Wilcoxon Z score, FDR corrected).
EEG and MEG: Task-related changes in cortical oscillations

Noticed by Berger - not assigned much significance (until recently)

Alpha wave (8-10 Hz) activity is modulated by visual attention
Fig. 2. Simultaneous MEG and EEG recordings. (A) Alpha rhythm from the brain of a normal subject, clearly seen in both MEG and EEG. The magnetometer was located at the left occipital region, as were the bipolar set of EEG leads. The bandwidth on both channels was 4 to 15 hz. (B) Large events, induced by hyperventilating, from the brain of an epileptic subject. The magnetometer was at the right temple. The three EEG bipolar leads all have the vertex in common, and the other lead at these locations about 3 cm above the ear line: (a) at the right temple, (b) above the right ear, and (c) above the inion. The bandwidth was matched on all four channels to be 0.4 to 15 hz. One difference between the MEG and EEG is that the 5-hz waves, present in all three EEG’s, is largely missing from the MEG.
Beamformer localisation of alpha suppression
Transient Induced Gamma-Band Response in EEG as a Manifestation of Miniature Saccades

Shlomit Yuval-Greenberg,¹,4,* Orr Tomer,¹,4 Alon S. Keren,² Israel Nelken,²,³ and Leon Y. Deouell¹,²

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Much EEG Gamma work may actually be related to eye movement artifacts, rather than cognition itself.

EcoG and MEG should not be contaminated in the same way
Scalp electrical recording during paralysis: Quantitative evidence that EEG frequencies above 20 Hz are contaminated by EMG

Emma M. Whitham a, Kenneth J. Pope b, Sean P. Fitzgibbon c, Trent Lewis b, C. Richard Clark c, Stephen Loveless d, Marita Broberg e, Angus Wallace e, Dylan DeLosAngeles e, Peter Lillic f, Andrew Hardy f, Rik Fronske f, Alvson Pulbrook g, John O. Willoughby e,*

[Graph showing log power vs. frequency]
Beamformers produce statistical maps of the difference in signal power between Active and Passive states (in a particular frequency band).
Can we measure from deep sources?

Behavioral/Systems/Cognitive

Human Hippocampal and Parahippocampal Theta during Goal-Directed Spatial Navigation Predicts Performance on a Virtual Morris Water Maze

Nice match with invasive recordings of theta activity
MEG: Multiple evoked and induced effects in human visual cortex
Matt Brookes, Nottingham
Rich, complex, phenomenology from a very simple experiment
Human MEG Gamma

Monkey LFP
In our human subjects, visual gamma is **variable** in frequency but a remarkably **stable trait marker** across sessions.
80 pairs of twins
Figure 3. Correlation between gamma-peak frequencies. A, MZ twins. B, DZ twins. Each data point represents the peak frequency of one twin versus that of his or her cotwin (random axis assignment). Slope values are estimated by random permutations of x- and y-values. C, Example set of 20 unrelated subject pairs. The presented ICC is an average of 100 of such sets. $h^2$, heritability estimate based on genetic structural equation modeling of the total of MZ and DZ data.
Narrow-band Gamma oscillations in Layer 2/3 and Beta in Layer 5/6 arise from the interactions and dynamics of inhibitory interneurons (black) and pyramidal cells (red).

Frequency and amplitude in an individual are set by the excitation/inhibition balance and hence reflect GABAergic and Glutamatergic processes.
Narrow-band Gamma oscillations in Layer 2/3 and Beta in Layer 5/6 arise from the interactions and dynamics of inhibitory interneurons (black) and pyramidal cells (red). Frequency and amplitude in an individual are set by the excitation/inhibition balance and hence reflect GABAergic and Glutamatergic processes.

Again, being able to robustly and repeatably characterise gamma/beta oscillations in humans provides a direct link to synaptic physiology.
GABA Neurons and the Mechanisms of Network Oscillations: Implications for Understanding Cortical Dysfunction in Schizophrenia

Guillermo Gonzalez-Burgos and David A. Lewis
Translational Neuroscience Program, Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA 15213

Synchronization of neuronal activity in the neocortex may underlie the coordination of neural representations and thus is critical for optimal cognitive function. Because cognitive deficits are the major determinant of functional outcome in schizophrenia, identifying their neural basis is important for the development of new therapeutic interventions. Here we review the data suggesting that phasic synaptic inhibition mediated by specific subtypes of cortical γ-aminobutyric acid (GABA) neurons is essential for the production of synchronized network oscillations. We also discuss evidence indicating that GABA neurotransmission is altered in schizophrenia and propose mechanisms by which such alterations can decrease the strength of inhibitory connections in a cell-type-specific manner. We suggest that some alterations observed in the neocortex of schizophrenia subjects may be compensatory responses that partially restore inhibitory synaptic efficacy. The findings of altered neural synchrony and impaired cognitive function in schizophrenia suggest that such compensatory responses are insufficient and that interventions aimed at augmenting the efficacy of GABA neurotransmission might be of therapeutic value.

Key words: interneuron/schizophrenia/synchronization/GABA-A/GAD67

Therefore, the alterations of neural synchrony revealed by electroencephalogram (EEG) studies of subjects with schizophrenia might contribute to the cognitive impairments characteristic of the illness. Synchronized neural activity can be irregular and not necessarily rhythmic; however, synchrony based on rhythmic neuronal activity is an energy-efficient mechanism that seems to predominate in the brain of many mammalian species. Consequently, knowledge of the physiological mechanisms that give rise to and regulate synchronized neural oscillations in cortical networks may be critical for the development and assessment of therapeutic interventions aimed at improving cognitive function in individuals with schizophrenia.

EEG rhythms originate from the synchronized activity of cortical pyramidal cells, which is reflected in changes of electrical potential in the extracellular space. Because more pyramidal neurons are synchronized, these changes become larger and when sufficiently large, they increase the amplitude of the EEG signal above noise. In cortical microcircuits, several physiological mechanisms may play a role in synchronizing the activity of large numbers of pyramidal cells. In particular, fast synaptic inhibition mediated by γ-aminobutyric acid (GABA) neurons appears to be efficient for generating network synchrony. Interestingly, convergent lines of evidence suggest that schizophrenia is associated with alterations of cortical GABA neurotransmission. Consequently, in this review, we focus on the role of GABA neurons in the generation of synchronized oscillations and on how their disturbances may contribute to impaired cortical synchrony in schizophrenia.
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Circuits and brain rhythms in schizophrenia: a wealth of convergent targets

Miles A Whittington¹, Anita K Roopun¹, Roger D Traub² and Ceri H Davies³

Few common neurological illnesses trace back to single molecular disturbances. Many disparate putative causes may co-associate with a single disease state. However, uncovering functional, hierarchical networks of underlying mechanisms can provide a framework in which many primary pathologies converge on more complex, single higher level correlates of disease. This article focuses on cognitive deficits associated with schizophrenia to illustrate: a) How non-invasive EEG biomarkers of cognitive function constitute such a ‘higher level correlate’ of underlying pathologies. b) How derangement of multiple, cell-specific, molecular processes can converge on such EEG-visible, correlates of disrupted cognitive function. This approach suggests that evidence-based design of multi-target therapies may take advantage of hierarchical patterns of convergence to improve both efficacy and selectivity of disease-intervention.

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is also clear that cognition requires the intercommunication between many regions. In patients with schizophrenia early connectomic studies led to the suggestion that the syndrome was primarily one of cortical disconnection – a failure of large-scale functional connectivity [6**]. Many substrates for such connectivity have been proposed, but the most compelling working hypothesis involves the use of brain rhythms to provide ‘temporal windows’ in which neurons in many regions can be simultaneously active – forming a computationally advantageous assembly of cellular responses. In using rhythmic activity to perform this task the cortex has the ability to control the extent of functional connectivity through coherence [7**].

Many facets of EEG-visible brain rhythms are observed to be disrupted in patients. However, evidence is growing to suggest that activity in the gamma band (30–90 Hz) is particularly correlated with pathology in schizophrenia. We know more about the mechanisms and functions of gamma activity than perhaps any other single brain rhythm, and what is clear is that this pattern of cortical dynamics is absolutely dependent on the activity of subsets of inhibitory interneurons. These in turn have been well characterised in terms of responses to neuro-modulators, their developmental profile and their connectivity. These aspects are essential...
Circuits and brain rhythms in schizophrenia: a wealth of convergent targets
Miles A Whittington

Few common neurophysiological features of the disease are thus far well documented. Molecular and functional, hierarchical, composites may provide a framework to converge on more common disease. This article features work with schizophrenia to provide evidence for a variety of convergent targets. This approach suggests that target therapies may be needed to converge on improved disease intervention.

Abnormal neural oscillations and synchrony in schizophrenia
Peter J. Uhlhaas *"1 and Wolf Singer *1

Abstract | Converging evidence from electrophysiological, physiological and anatomical studies suggests that abnormalities in the synchronized oscillatory activity of neurons may have a central role in the pathophysiology of schizophrenia. Neural oscillations are a fundamental mechanism for the establishment of precise temporal relationships between neuronal responses that are in turn relevant for memory, perception and consciousness. In patients with schizophrenia, the synchronization of beta- and gamma-band activity is abnormal, suggesting a crucial role for dysfunctional oscillations in the generation of the cognitive deficits and other symptoms of the disorder. Dysfunctional oscillations may arise owing to anomalies in the brain's rhythm-generating networks of GABA (g-aminobutyric acid) interneurons and in cortico-cortical connections.

Key words
Schizophrenia, GABA, GABA agonists, GABA antagonists, synchrony, oscillations, GABA receptor, GABA transporter, N-methyl-D-aspartate (NMDA) receptor, dopamine receptor, serotonergic neurotransmitter, glutamate neurotransmitter.
NORMAL AND PATHOLOGICAL OSCILLATORY COMMUNICATION IN THE BRAIN

Alfons Schnitzler and Joachim Gross

Abstract | The huge number of neurons in the human brain are connected to form functionally specialized assemblies. The brain's amazing processing capabilities rest on local communication within and long-range communication between these assemblies. Even simple sensory, motor and cognitive tasks depend on the precise coordination of many brain areas. Recent improvements in the methods of studying long-range communication have allowed us to address several important questions. What are the common mechanisms that govern local and long-range communication and how do they relate to the structure of the brain? How does oscillatory synchronization subserve neural communication? And what are the consequences of abnormal synchronization?

The human brain has remarkable processing capabilities. Consider, for example, a badminton player preparing to defend a smash by his opponent. During a jump smash, the shuttlecock can reach up to 300 km h⁻¹, which bridges the few metres distance between the opponents in less than 300 ms. However, it is often possible to return the shuttlecock. So, how are the ~10¹¹ neurons in the human brain organized to support these computations? As no behaviourally relevant task is performed independently by a single neuron, communication is of the utmost importance and, ultimately, optimal computational performance relies on optimal communication. Here we use a broad definition of neural communication, in which a neural element (a single neuron or a population of neurons) conveys certain aspects of its functional state to another neural element. Neural communication depends on the anatomical components that connect individual neurons (structure) and the process of transmitting information (function). Both aspects affect the overall performance of the system.

Structurally, the most striking neuroanatomical feature of the brain is the abundant connectivity between neurons, which reflects the importance of neural communication. Functionally, oscillations are a prominent feature of neuronal activity (BOX 1) and the synchronization of oscillations — which reflects the temporally precise interaction of neural activities — is a likely mechanism for neural communication (BOX 2).

Previously, oscillatory synchronization in the gamma band has been proposed to be a binding mechanism that suberves perceptual and cognitive functions. Recent findings have led to an extension of the concept of synchronization by showing that oscillatory networks in the motor system emerge from long-range synchronization in distinct frequency bands — often below the gamma range — between cortical and subcortical areas and the spinal cord in various motor tasks. Importantly, evidence is emerging that a delicately balanced pattern of synchronization and desynchronization in space and time is fundamental to the functional consequences of synchronization. For example, an abnormal pattern of synchronization in parts of the motor system seems to be a key pathophysiological mechanism that underlies motor symptoms, such as tremor and poverty of movement, in Parkinson's disease. Similarly, a balanced and temporally-precise pattern of synchronization and desynchronization is pertinent to cognitive function. Synchronized oscillatory networks can be identified and dynamically characterized in humans by applying new methods of analysis to non-invasive whole-head magnetoencephalographic (MEG) recordings (BOX 3).
Figure 6 | **Long-range synchronization in Parkinson’s disease.** Maps of spatially normalized cerebro-muscular and cerebro-cerebral coherence averaged across 4 patients with right-sided rest tremor. Cerebro-muscular coherence at double tremor frequency occurs in the contralateral primary motor cortex (b). Cerebro-cerebral coherence was computed with the reference region in the primary motor cortex and averaged for all patients. Areas of consistent coherence are the lateral (a) and medial (c) premotor areas, secondary somatosensory cortex (a), posterior parietal cortex (a) as well as the thalamus/basal ganglia (d) contralateral to the tremor hand and the cerebellum (e) ipsilateral to the tremor hand. Note that because of the large distance to the magnetoencephalogram (MEG) sensors, localization in both subcortical areas is not as precise as at the cortical level.
What are oscillations for?
Neuronal Gamma-Band Synchronization as a Fundamental Process in Cortical Computation

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Gamma oscillations may locally enhance processing, but also facilitate inter-regional communication and selection.

Neuronal Gamma-Band Synchronization as a Fundamental Process in Cortical Computation

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Problem for binding by synchrony type theories though..

• Gamma is not stable to stimulus properties...
Differences in Gamma Frequencies across Visual Cortex Restrict Their Possible Use in Computation

New paper from Pascal Fries’ group: Gamma CAN be used to bind information, at least from V1 to V2
Opinion

A framework for local cortical oscillation patterns

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High-frequency (gamma) -> local stimulus processing

Low-frequency (alpha/beta) -> communication integration over longer distances.
Shaping functional architecture by oscillatory alpha activity: gating by inhibition

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In order to understand the working brain as a network, it is essential to identify the mechanisms by which information is gated between regions. We here propose that information is gated by inhibiting task-irrelevant regions, thus routing information to task-relevant regions. The functional inhibition is reflected in oscillatory activity in the alpha band (8–13 Hz). From a physiological perspective the alpha activity provides pulsed inhibition reducing the processing capabilities of a given area. Active processing in the engaged areas is reflected by neuronal synchronization in the gamma band (30–100 Hz) accompanied by an alpha band decrease. According to this framework the brain could be studied as a network by investigating cross-frequency interactions between gamma and alpha activity. Specifically the framework predicts that optimal task performance will correlate with alpha activity in task-irrelevant areas. In this review we will discuss the empirical support for this framework. Given that alpha activity is by far the strongest signal recorded by EEG and MEG, we propose that a major part of the electrophysiological activity detected from the working brain reflects gating by inhibition.

Keywords: magnetoencephalography, electroencephalography, alpha, gamma, functional connectivity, effective connectivity
FIGURE 1 | Different principles by which information can be gated through a network. Consider a situation in which information is supposed to be routed from node a to node b but not from node a to node c. (A) One possibility is that the synaptic connections from node a to b are strengthened on a fast time scale and weakened from node a to c. This would require a mechanism for synaptic plasticity that works on a fast time scale. (B) Information might be gated through neuronal phase-synchronization between node a and c. The information flow from node b to c is blocked by adjusting the phase difference. (C) We here promote the principle of gating by inhibition. Node c is actively suppressed by functional inhibition. This serves to gate the information flow from a to b. The functional inhibition is reflected in the 9–13 Hz alpha band.
Spectral fingerprints of large-scale neuronal interactions

Markus Siegel\textsuperscript{1} *, Tobias H. Donner\textsuperscript{2} * and Andreas K. Engel\textsuperscript{3}

Abstract | Cognition results from interactions among functionally specialized but widely distributed brain regions; however, neuroscience has so far largely focused on characterizing the function of individual brain regions and neurons therein. Here we discuss recent studies that have instead investigated the interactions between brain regions during cognitive processes by assessing correlations between neuronal oscillations in different regions of the primate cerebral cortex. These studies have opened a new window onto the large-scale circuit mechanisms underlying sensorimotor decision-making and top-down attention. We propose that frequency-specific neuronal correlations in large-scale cortical networks may be ‘fingerprints’ of canonical neuronal computations underlying cognitive processes.
Phase coherence quantifies the consistency of the relative phase between two simultaneous signals that have the same frequency. The left panel shows an example of two oscillatory signals that are phase coherent with zero phase lag. Signals can also be phase coherent with non-zero phase lag (right panel), that is, they can be phase-shifted relative to each other.

Amplitude correlation is a measure of the correlation of the envelopes (shown in red) of two simultaneous oscillatory signals (amplitude correlation is also often referred to as 'power-to-power correlation' or 'amplitude–amplitude coupling'). Amplitude correlation can be measured between oscillatory signals of the same or different underlying carrier frequencies. Furthermore, amplitudes can be positively correlated or negatively correlated (that is, anti-correlated). The panels show examples of a positive amplitude correlation between two oscillatory signals of the same (left) and different (right) underlying carrier frequencies. Importantly, phase coherence and amplitude correlation are independent of one another. This is exemplified in the left panel of part b, in which the amplitudes of the two oscillations are correlated but the underlying oscillations are not phase coherent. $f$, frequency.
Dynamic imaging of coherent sources: Studying neural interactions in the human brain

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Functional connectivity between cortical areas may appear as correlated time behavior of neural activity. It has been suggested that merging of separate brain states into a single percept ("binding") is associated with coherent gamma band activity across the cortical areas involved. Therefore, it would be of utmost interest to image cortico-cortical coherence in the working human brain. The frequency specificity and transient nature of these interactions requires time-sensitive tools such as magneto- or electroencephalography (MEG/EEG). Coherence between signals of sensors covering different scalp areas is commonly taken as a measure of functional coupling. However, this approach provides vague information on the actual cortical areas involved, owing to the complex relation between the active brain areas and the sensor recordings. We propose a solution to the crucial issue of proceeding beyond the MEG sensor level to estimate coherences between cortical areas. Dynamic imaging of coherent sources (DICS) uses a spatial filter to localize coherent brain regions and provides the time courses of their activity. Reference points for the computation of neural coupling may be based on brain areas of maximum power or other physiologically meaningful information, or they may be estimated starting from sensor coherences. The performance of DICS is evaluated with simulated data and illustrated with recordings of spontaneous activity in a healthy subject and a parkinsonian patient. Methods for estimating functional connectivities between brain areas will facilitate characterization of cortical networks involved in sensory, motor, or cognitive tasks and will allow investigation of pathological connectivities in neurological disorders.

The hypothesis that relevant information in the brain is coded by accurate timing of neuronal discharges has received strong support from recent reports of synchronization of neuronal firing within and across areas of the cat visual cortex (1). The synchronization of neuronal activity, which was modulated by gamma-band oscillations, was shown to depend on stimulus properties like continuity, similarity, and common motion, and on receptive field correlations (for review, see ref. 2). This and similar findings seem to support the concept that synchronized rhythmic neuronal firing has a role in solving the binding problem, i.e., the integration of distributed information into a unified representation (1–4).

To investigate cortico-cortical synchrony noninvasively in the human brain, new analysis tools must be developed. In functional magnetic resonance imaging (fMRI) studies, structural equation models have been used to estimate connectivities between brain areas (5, 6). Although this is a very promising approach, it lacks the temporal resolution required to measure oscillatory activity and to observe the expected transient formation of neuronal assemblies (7).

Magnetoencephalography (MEG) and electroencephalography (EEG) have the necessary millisecond resolution to characterize neuronal coupling. Indeed, task-dependent interactions in the frequency domain have been reported between signals recorded by different MEG sensors or EEG electrodes during cognitive (8–12) and motor tasks (13–15). However, these findings are limited to correlations within the measurement device and reveal little on the synchrony between specific cortical areas.

The signal recorded by a MEG sensor or an EEG electrode cannot be directly attributed to the underlying cortical region. The complex relationship between the signal detected by a sensor and an activated brain area is given by the solution of the forward problem (i.e., the calculation of the magnetic field or electric potential generated by a point source). Especially electric potentials (EEG) are smeared out because of the inhomogeneous conductivity structure of the human head. The activity of even a small cortical area is recorded by several sensors, leading to severe spreading in sensor-based measures. The spreading is particularly problematic when describing interdependencies between signals (16–18).

Here, we present an analysis method, dynamic imaging of coherent sources (DICS), that allows studies of cortico-cortical and cortico-muscular interactions by imaging power and coherence estimates within the human brain.

Methods

We employ the cross spectral density matrix as the basic representation of the oscillatory components and their dependencies in MEG/EEG and electromyographic (EMG) signals. In this paper, DICS was applied to MEG data although it can be applied to EEG as well. In the first step, which is identification of the interacting brain areas, we restrict the analysis to linear dependencies. In the next step, the time course for each region of interest is estimated and can be subject to a more complex (and possibly nonlinear) analysis.

The complex cross spectral density $C$ for signals $x(t)$ and $y(t)$ is computed by using Welch's method of spectral density estimation (19). A Hanning window is applied to the segments of signals $x(t)$ and $y(t)$. The Fourier-transformed $X(f)$ and $Y(f)$ are used to compute the cross spectral density, $C(f) = X(f)Y^*(f)$, where $Y^*$ denotes the complex conjugate of $Y$. Finally, $C$ is averaged over successive data segments, which are overlapping by half their segment length.

One element $C_{ij}$ of the cross spectral matrix consists of the cross spectral densities of signals $i$ and $j$. Therefore, $C$ contains

Abbreviations: DICS, dynamic imaging of coherent sources; MEG, magnetoencephalography; EEG, electroencephalography; pSM, power statistical parametric map; EMG, electromyography; FDI, flexor digitorum superficialis; SNR, signal-to-noise ratio; PWIM, full width at half maximum; PM, premotor cortex.

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The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. §1734 solely to indicate this fact.
Here, we characterize real-time neural connectivity during reading. We determine the network nodes directly from interactions among whole-head MEG data, without prior assumptions of specific areas or network structure, and estimate both synchronization and direction of information flow between the nodes. Thus, we directly assess the question of “how” distinct brain areas work together to support cognitive behavior.

Our analysis method is based on a beamformer technique optimized for the frequency domain, Dynamic Imaging of Coherent Sources (DICS), that was originally adapted for analysis of the motor system, with EMG as reference signal (Gross and others 2001, 2002). Here, we have developed DICS to allow identification of initial reference areas in the brain and, further, entire networks without need for non-brain reference signals.
Direction of information flow can be assessed for each node in the network using an analysis technique known as \textit{Granger Causality}. 
Top-Down Control Versus Bottom-Up ‘Drive’
Studies of Visuo-spatial attention
Anticipatory Biasing of Visuospacial Attention Indexed by Retinotopically Specific $\alpha$-Band Electroencephalography Increases over Occipital Cortex

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$\alpha$-Band (8–14 Hz) oscillatory EEG activity was examined with high-density scalp electrical recording during the cue–stimulus interval of an endogenous spatial cueing paradigm. In different blocks, cued spatial locations (left or right) were in either the upper or lower visual field, and attended stimuli were either oriented Ts or moving dots. Distractor stimuli were equally likely in the uncued hemifield. Sustained focal increases of $\alpha$-band activity were seen over occipital cortex contralateral to the direction of the to-be-ignored location (ipsilateral to the cued direction of attention) before onset of the to-be-attended stimulus. The focus of $\alpha$-band activity also moved depending on whether cued locations were in the upper or lower field. Results are consistent with active gating of uncued spatial locations.

Key words: alpha; attention; ERP; cueing; oscillations; gating
Figure 2. $\alpha$-Band oscillatory activity is selectively modulated by spatially directing visual attention. A, Top view (nose at the top) of the concentric layout of the electrodes that are used to plot the topographic maps in Figure 3. Electrodes used for statistical analysis are shown in red. B, C, ERPs to the lower left and right cues (collapsed across motion and orientation trials) for two occipital electrode sites, averaged over 10 subjects. Data for attend lower left are plotted in green, and data for attend lower right are plotted in red. D, E, Corresponding $\alpha$-band (8–14 Hz) TSE waveforms for the same electrodes. A sustained divergence in TSE amplitude is seen starting at $\sim$500 msec, which depends on both the cued direction of attention and the side of recording. TSE amplitudes are larger over occipital cortex ipsilateral to the direction of attention.
In the pre-cue period, directing attention to the left:

*Reduces* Alpha oscillatory power on the right compared to the left.

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**Figure 2.** $\alpha$-Band oscillatory activity is selectively modulated by spatially directing visual attention. *A*, Top view (nose at the top) of the concentric layout of the electrodes that are used to plot the topographic maps in Figure 3. Electrodes used for statistical analysis are shown in red. *B*, *C*, ERPs to the lower left and right cues (collapsed across motion and orientation trials) for two occipital electrode sites, averaged over 10 subjects. Data for attend lower left are plotted in green, and data for attend lower right are plotted in red. *D*, *E*, Corresponding $\alpha$-band (8–14 Hz) TSE waveforms for the same electrodes. A sustained divergence in TSE amplitude is seen starting at $\sim$500 msec, which depends on both the cued direction of attention and the side of recording. TSE amplitudes are larger over occipital cortex ipsilateral to the direction of attention.
In the pre-cue period, directing attention to the right: *Reduces* Alpha oscillatory power on the left compared to the right.

Figure 2. α-Band oscillatory activity is selectively modulated by spatially directing visual attention. A, Top view (nose at the top) of the concentric layout of the electrodes that are used to plot the topographic maps in Figure 3. Electrodes used for statistical analysis are shown in red. B, C, ERPs to the lower left and right cues (collapsed across motion and orientation trials) for two occipital electrode sites, averaged over 10 subjects. Data for attend lower left are plotted in green, and data for attend lower right are plotted in red. D, E, Corresponding α-band (8–14 Hz) TSE waveforms for the same electrodes. A sustained divergence in TSE amplitude is seen starting at ~500 msec, which depends on both the cued direction of attention and the side of recording. TSE amplitudes are larger over occipital cortex ipsilateral to the direction of attention.
In order to understand the working brain as a network, it is essential to identify the mechanisms by which information is gated between regions. We here propose that information is gated by inhibiting task-irrelevant regions, thus routing information to task-relevant regions. The functional inhibition is reflected in oscillatory activity in the alpha band (8–13 Hz). From a physiological perspective the alpha activity provides pulsed inhibition reducing the processing capabilities of a given area. Active processing in the engaged areas is reflected by neuronal synchronization in the gamma band (30–100 Hz) accompanied by an alpha band decrease. According to this framework the brain could be studied as a network by investigating cross-frequency interactions between gamma and alpha activity. Specifically the framework predicts that optimal task performance will correlate with alpha activity in task-irrelevant areas. In this review we will discuss the empirical support for this framework. Given that alpha activity is by far the strongest signal recorded by EEG and MEG, we propose that a major part of the electrophysiological activity detected from the working brain reflects gating by inhibition.

Keywords: magnetoencephalography, electroencephalography, alpha, gamma, functional connectivity, effective connectivity
Neuronal Synchronization along the Dorsal Visual Pathway Reflects the Focus of Spatial Attention

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Neuron 60, 709–719, November 26, 2008
Main posterior effects....(sensor space)

cue period

stim period

Neuron 60, 709–719, November 26, 2008
Alpha/Beta effects (beamformer)
High- and Low- Gamma effects

Delay Interval
Attend left - Attend right

Stimulus Interval
Attend left - Attend right

Low gamma (35-60 Hz)

High gamma (60-100 Hz)

z score
-4.6  ± 1.96  3.4
-8.5  ± 1.96  5.8
-7.5  ± 1.96  6.1

Neuron 60, 709–719, November 26, 2008
Cholinergic Enhancement of Visual Attention and Neural Oscillations in the Human Brain

Markus Bauer,1,2,* Christian Kluge,1,2,3 Dominik Bach,1 David Bradbury,1 Hans Jochen Heinze,3 Raymond J. Dolan,1 and Jon Driver1,2

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Oscillations in general, the neurochemical pathways supporting these spectral changes are unknown but theoretical proposals suggest that an enhancement in high-frequency gamma oscillations is driven by cholinergic activity [17–19]. However, alpha oscillations are also known to be influenced by cholinergic neuromodulation [24–27].

Here we tested the impact of a cholinergic pharmacological intervention on brain oscillations during an attentional task in humans. Specifically, we recorded magnetoencephalography (MEG) while participants performed a spatial visual attention task (Figure 1), either under treatment with physostigmine...
Alpha Modulated by Attention - in cue period i.e. prestimulus
...these are boosted by physostigimine
Stimulus induced occipital gamma activity

gamma not visibly modulated by drug
Extra-striate (but not V1) gamma modulated by attention
primary visual cortex - V1
extrastriate visual cortex

fMRI

MEG - Gamma
A

Fixation
(3 s)

Stationary
(2 s)

Rotation
(10 s)
Increased during attention
Unchanged during attention
Suppression deepened by attention
1. Narrow-band gamma -> Mostly driven by stimulus parameters.

2. Broadband gamma -> top-down modulated by spatial attention
Correlated with firing rates

Not-correlated with firing rates
Consistent with an ECoG study in epilepsy patients from 2013...
Oscillatory resting-state networks
The fMRI community has gone resting-state crazy…

**Functional connectomics from resting-state fMRI**

Stephen M. Smith¹, Diego Vidaserre², Christian F. Beckmann³,⁴,¹, Matthew F. Glasser⁵, Mark Jenkinson⁶, Karla L. Miller⁶, Thomas E. Nichols⁷,⁸, Emma C. Robinson⁹, Gholamreza Salimi-Khorshidi⁹, Mark W. Woolrich⁴,¹, Deanna M. Barch¹, Kamil Ugurbil¹, and David C. Van Essen¹

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**Large-scale “gross networks” - extended spatial maps**

(A) Seed-based correlation map

(B) Low-dimensional ICA: one component out of 30

**Detailed decomposition into hundreds of network nodes**

(C) Hard parcellation of all grey matter into hundreds of parcels (network nodes)

(D) High-dimensional ICA: 5 components (network nodes) out of 300

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**Node 94**

**Node 31**

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**Predicted fluid intelligence vs Measured fluid intelligence**

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*Review*
ICA Analysis of resting-state data
Comparison with fMRI equivalent
Most networks in Alpha/Beta frequency bands
DMN
Alpha Band
Frontoparietal Beta Band
Primary Visual Beta Band
Multi-scale (dys)connectivity
Oscillatory fingerprinting in health and disease

Local (columnar ~ 1mm) scale
• Narrow-band gamma (bottom-up). Layer 2/3
• Broadband gamma (top-down, firing rates?). All layers
• Beta oscillations: Deep layers (5)

Inter-regional (e.g. V1 to V2) scale
• Narrow-band gamma (??) e.g. Fries’ recent paper.
• Alpha/Beta Oscillations - gated via thalamus? Active inhibition?

Global i.e. whole-brain networks
• No evidence (animal or human) for long-range gamma?
• Resting-state networks
• Mostly expressed in Alpha/Beta range
MEG: Standard oscillatory protocols

**Vision:** 5 mins

- Gamma spike
- Sustained gamma

**Motor:** 5 mins

- Motor Gamma, beta ERD and beta rebound

**Eyes Open/Closed:** 5 mins

- Thalamo-cortical alpha reactivity

**Resting-state networks:** 10 mins

- Extended network connectivity
Take Home Messages

1. There is no such thing as “neural activity”.

2. There are multiple task-related increases/decreases in various evoked and induced oscillatory measures, all at the same location.

3. MEG, using beamformer source-localisation, reveals phenomenology that is very similar to invasive LFP recordings in cat and macaque.

4. Oscillatory dynamics can be quantified/characterised at multiple spatial scales, indexing different levels of (dys)connectivity.

5. MEG studies of oscillatory parameters may provide a new window onto layer-specific synaptic physiology e.g. the cortical excitation/inhibition (GABA) balance.

6. Attentional manipulations modify multiple oscillatory signals (Alpha and Gamma)

7. Narrow-band induced visual gamma appears to be bottom-up driven by stimulus parameters. More broadband visual gamma (from the same location) is more sensitive to top-down control e.g. visuospatial attention.

8. MEG measured oscillations may be useful as a new metric in pharma studies

9. Oscillatory markers may be useful in studies of individual variability in health and disease e.g. probing GABA or Glutamate disease-related impairments.
Thanks for listening...