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# fMRI for the Assessment of Functional Connectivity

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## 1. Introduction

The advantage of modern brain imaging techniques is the ability to non-invasively investigate human brain function during mental work. Therefore, most functional neuroimaging studies have investigated brain activity evoked by certain types of stimulation or tasks. Related brain function is then localized by contrasting task-states, or often, with a baseline-state acquired during rest. However, in wakeful human subjects this resting condition cannot be associated with neutral brain activity, in part, because there is always a relatively high level of neuronal background activity. Thus, the question arises whether spontaneous fluctuations of resting brain activity can be dismissed as stochastic noise, or whether they contain functionally relevant information.

In the past decade, numerous studies have investigated brain activity during the resting state. Background activity has been shown to fluctuate spontaneously, i.e. unrelated to any obvious task, and that these fluctuations are not random. Rather, this spontaneous activity is characterized by several distinct pattern of correlated brain activity, so called: "resting state networks". Network activity, usually derived from temporal correlation of neuronal activity measured in different brain regions ("functional connectivity"), describes the functional relationship between brain regions. Functional connectivity networks have been identified by different methods, such as positron emission tomography (PET), optical imaging, magneto- and electroencephalography (M/EEG), whereas by far most studies made use of functional magnetic resonance imaging (fMRI) data. Traditionally, functional connectivity measures rely on correlation analyses, however in recent years the analytic tools for describing the functional organization of the brain has increased dramatically.

This chapter will provide insight into different ways to assess functional connectivity from resting-state fMRI data and describe applications of functional connectivity analyses to specific scientific questions. We will start with a description of the BOLD-effect, the underlying neurophysiological parameter in resting-state fMRI, followed by a résumé of the use of BOLD in functional neuroimaging, stating its history from simple "baseline-task-contrasts" to the nowadays widely-used concept of functional connectivity. In the following sub-chapters, we will briefly describe analytic categories as applied to resting-state fMRI data, including "seed-based functional connectivity", "independent component analysis (ICA)", "clustering", "multivariate pattern analysis (MVPA)", "graph theory" and "centrality". Finally, we will discuss two specific applications of functional connectivity analyses: (1) investigation of anatomy, and (2) investigation of dynamics using simultaneous EEG-fMRI measurements.

## 2. History of BOLD in functional neuroimaging, and the beginnings of functional connectivity in both task-states and rest

fMRI is the most widely used imaging technique in modern cognitive neuroscience. It allows for non-invasive (albeit indirect) studying of neuronal processes in the brain with excellent spatial resolution. While the first functional MRI experiment was performed with an exogenous contrast agent (Belliveau et al., 1991), fortunately another method was developed using magnetic properties of blood itself, so that such a contrast agent was no longer required for functional imaging (Bandettini et al., 1992; Frahm et al., 1992; Kwong et al., 1992; Ogawa et al., 1992). The fMRI signal depends on the vascular response to functional brain activation and is typically implemented by imaging of the blood oxygenation-level dependent (BOLD) contrast.

### 2.1 The BOLD-effect

The use of the BOLD effect for imaging brain activation relies on the fact that changes in neuronal activity are associated with changes in energy consumption and cerebral blood flow (Roy & Sherrington, 1890; Villringer & Dirnagl, 1995)[1]. Since changes in oxygen consumption and blood flow are associated with changes in haemoglobin oxygenation, the latter can also be used as an indirect measure of neuronal activity, assuming that activated neuronal circuits have an increased metabolic demand.

The magnetic susceptibility of blood depends on the magnetic properties of haemoglobin, the molecule carrying the oxygen necessary for aerobic cellular metabolism. During brain activation, blood focally changes its oxygenation level, which depends on the proportion of oxygenated haemoglobin ([oxy-Hb]) and deoxygenated haemoglobin ([deoxy-Hb]). [oxy-Hb] is a diamagnetic molecule, whereas [deoxy-Hb] is paramagnetic. The presence of [deoxy-Hb] causes local field inhomogeneities, which are responsible for a dephasing of the local transversal magnetization[2], leading to a reduction in the transverse relaxation time $T_2$.

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[1] Although fMRI is widely used in scientific and clinical approaches, the complex mechanism describing the coupling of neuronal activity and metabolic demand ("neurovascular coupling") is not yet fully understood. Not only the role of the different mediators dealing with neurovascular coupling is under debate, also the formation of the vascular response obtained with fMRI is unclear (Buxton et al. 1998; Steinbrink et al. 2006; Villringer & Dirnagl 1995).

[2] In medicine, the MR signal is usually based on the magnetic dipole moment of hydrogen nuclei (protons) in water, by far the most abundant nuclei in the human body. In a static magnetic field $B_0$, these magnetic dipole moments generate a magnetisation vector $M_L$ longitudinal oriented to $B_0$. Applying an adequate radio frequency pulse induces an additional magnetic field $B_1$, that flips M into the plane perpendicular to $B_0$. According to classical mechanics, this transversal magnetisation vector $M_T$ starts rotating about the direction of $B_0$, inducing a voltage in a receiver coil proportional to the proton density. In the absence of B1, however, the excited magnetic spins will return to equilibrium. This relaxation is characterised by (1) a re-growth of $M_L$ with the time constant $T_1$, and (2) by a decay of $M_T$ with the time constant $T_2$. The values of T1 and T2 depend on tissue composition, structure and surroundings. The setting of a long echo time TE, that is the time between excitation and read-out, produces $T_2$-weighted images, because only tissue with a long $T_2$ decay constant will contribute to the signal intensity.

As a diamagnetic molecule, [oxy-Hb] does not produce the same dephasing. Thus, changes in [deoxy-Hb] can be observed as the BOLD contrast in $T_2$-weighted MR-images, serving as an indirect measure of neuronal activity. Since neuronal activation is accompanied by a focal increase in oxygenated blood, overshooting the actual metabolic demand, activated brain areas are characterised by positive BOLD responses in fMRI measurements.

### 2.2 From 'baseline' to 'resting' to 'intrinsic' dynamics

For functional investigations of the human brain, typically, a task or a stimulus is administered to a subject in a block or event-related experimental design and the resulting changes in neuronal activity are detected by contrasting a “task-state” and a “control- or baseline-state”. The term "baseline-state" thereby cannot be associated with "zero brain activity", since even during so called “rest conditions”, there is always some neuronal activity (spikes, synaptic activity) associated with a relatively high level of (baseline) cerebral blood flow and oxygen consumption (Clarke & Sokoloff, 1999; Sokoloff et al., 1955 for a review Raichle, 2010). Such task-state contrasts are by far the most used data analysis approach in fMRI assuming more or less constant baseline activity to be independent from task- or stimulation-evoked activity.

Given that baseline activity is not zero, the question arises whether spontaneous fluctuations of resting brain activity are stochastic (“noise”) and thus can be simply attenuated by averaging procedures. Furthermore, it is of relevance whether fluctuations of the baseline influence the shape and amplitude of task-evoked activity during the stimulation period. In recent years, the issue of “physiological noise” and brain activity during resting states has become accessible for investigation. Numerous studies have been published examining spontaneous fluctuations of baseline activity (i.e. unrelated to any obvious task) in the low-frequency range <0.1 Hz (Biswal et al., 1995; Fox et al., 2005). These fluctuations contain important function-related information and it has been shown that “resting states” are characterized by several distinct patterns of correlated intrinsic brain activity, so called “resting state networks”, describing intrinsic functional connectivity (Gusnard & Raichle, 2001). Resting state activity has been identified by different methods, such as fMRI, PET, Optical Imaging, EEG, and MEG, and in several instances simultaneous combinations of methods such as EEG/fMRI have been particularly useful. In addition, numerous studies have addressed the influence of ongoing activity on behavioural responses and the relationship between ongoing activity and evoked activity (Becker et al., 2011; Scheeringa et al., 2011; for a review Nierhaus et al., 2009; Sadaghiani et al., 2010).

#### 2.2.1 Task-state contrasts (evoked brain activity)

Despite the fact that vascular responses are only indirectly related to changes in brain activity and that they develop with time constants of several seconds to the underlying neuronal activity, vascular methods, in particular fMRI, have become the most widely used method for the assessment of evoked brain activity. Stimuli or tasks are organized either in an event-related design, a block design, or a mixture of those two. Data analysis typically employs a general linear model of evoked brain activity (Friston et al., 1995). By contrasting the “activated state” with the “control state”, changes in brain activity due to task or stimulation are visualized. Figure 1 shows a typical fMRI response for a somatosensory stimulation paradigm, where subjects received 4-Hz electrical stimulation of the left middle finger at amplitude twice of the sensory perception threshold.

Alternating stimulation blocks with resting periods allowed for contrasting two activation states, revealing a positive BOLD signal change in the contralateral primary somatosensory cortex, whereas the secondary somatosensory cortices are bilaterally activated (Fig.1A). The time course of the activated region shows a high correlation with the stimulation, and the peak of the hemodynamic response occurs with a delay of several seconds. This approach of contrasting rest- and task-state assumes fluctuations of baseline activity to appear merely stochastic and independent from evoked activity, thus vanishing in the averaging process.

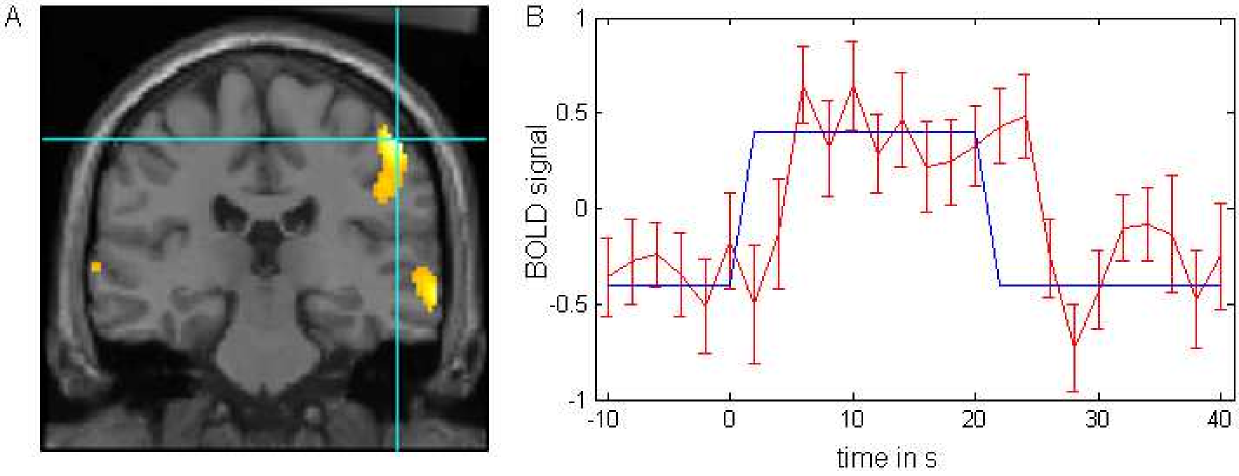

Fig. 1. Evoked brain activity. BOLD fMRI response on 4 Hz electrical stimulation of the left middle finger (adapted from Taskin et al., 2006). Stimulation was applied in blocks of 20 s alternating with periods of rest of the same duration. (A) The activation map generated by contrasting stimulation- with resting-periods (statistical T-maps, n=6, p<0.05 corrected for multiple comparisons). (B) BOLD dynamics as average time course over 30 blocks (red, mean+ S.E.M.) of the labelled region in A and stimulation paradigm (blue).

### 2.2.2 Resting state (ongoing brain activity)

The apparent "noise" in the BOLD signal was quite early assessed to have neuronal components, however, only in recent years has its investigation become a wide-spread research endeavour. Bharat Biswal and colleagues at the Medical College of Wisconsin demonstrated in 1995 that low frequency fluctuations of baseline (resting state) fMRI contain information about background neuronal activity (Biswal et al., 1995), which was subsequently elaborated by other groups (Fox et al., 2005; Greicius et al., 2003). Such correlations in the patterns of spontaneous activity specifically within the low-frequency band (<0.1 Hz) have given rise to the study of "resting state networks", an example of which is depicted in Figure 2.

The approach of measuring BOLD signal independent of any task makes the method independent of any differences of performance between sessions and/or subjects. Therefore, resting-state fMRI can be easily employed in patients with potentially limited ability for participation in task paradigms. Indeed it has been successfully applied in many clinical populations e.g., with Alzheimer disease (Greicius et al., 2004; Sorg et al., 2007), schizophrenia (Calhoun et al., 2009), stroke (van Meer et al., 2010), and different age-groups (Madden et al., 2010).

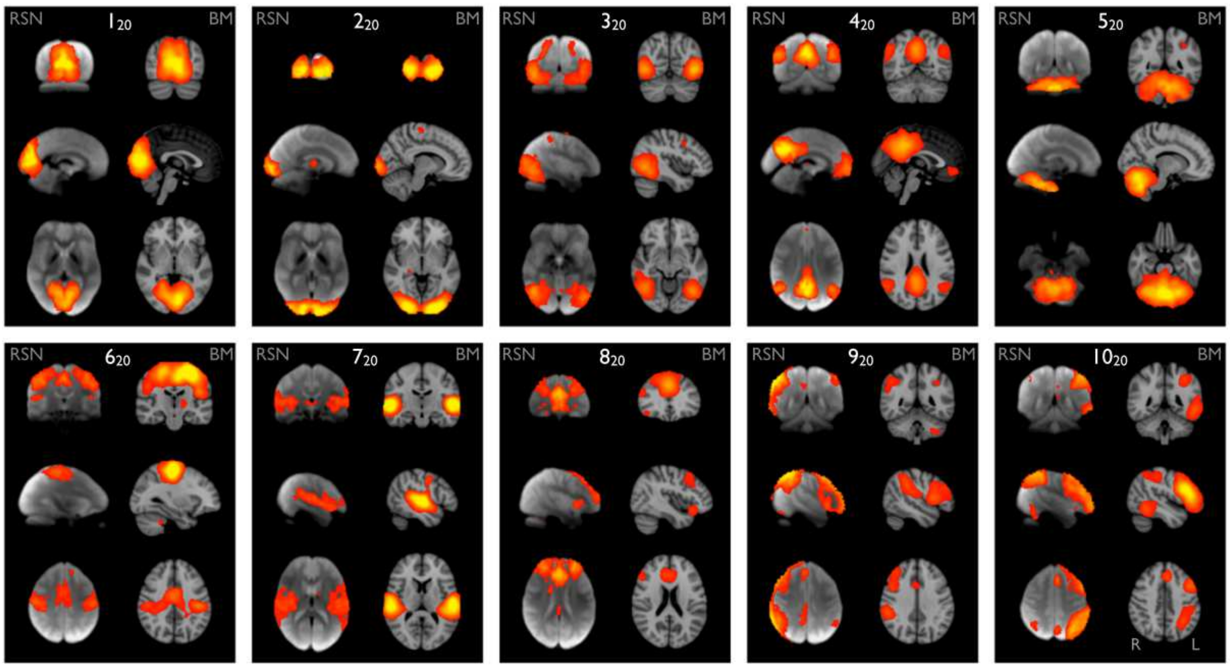

Fig. 2. Figure from Smith et al. (2009) depicting similarity between 'resting-state network' (left) and task-coactivation derived networks (right).

Many questions remain open regarding the mechanisms underlying the coherence of these spatially-distributed, low-frequency fluctuations. However, the rapid employment of these techniques by the imaging community over the past decade is due, in part, to both the ease of data acquisition and the similarity of results to previous finding using task-induced approaches. Since the methods for analysing resting-state activity are not limited to data acquired during 'rest', the term 'functional connectivity' has gained popularity, describing functional interplay of spatially distinct brain regions.

## 3. A brief overview of analytic methods to assess functional connectivity

Different post-processing techniques can be used for identifying spatial patterns of coherent BOLD activity in fMRI data, allowing for interpretation regarding functional connectivity[3] between spatially distributed brain areas. Since the following subchapters will explain only very briefly the idea and theoretical presuppositions of each analytic tool, for a more detailed description, we refer to a recent review by our group (Margulies et al., 2010).

### 3.1 Seed-based functional connectivity

This technique makes use of correlation from an *a priori* region-of-interest (ROI) or "seed region". In its simplest form, an averaged ROI time series is correlated with the time series of

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[3] Functional Connectivity is often described in contrast to Effective Connectivity. While the former describes different brain regions which are functionally connected, the latter addresses the direction of these neuronal interactions. Causality models, such as Dynamic Causal Modelling, Structural Equation Modelling or Granger Causality are used to estimate effective connectivity from neuroimaging data. Assuming that better prediction is an indication of influence, the common idea is to determine whether activity in one brain region can be predicted by the dynamics in other brain regions.

all the other voxels in the brain, or with the average time series of several distributed ROIs. The resulting matrix of correlation coefficients then can be interpreted as the functional connectivity of the selected seed region, where a high correlation coefficient indicates strong functional connectivity to the respective area. From such correlation maps, a number of different functional networks have been derived, e.g. a motor network, a visual network, the default-mode network and others. Seed-based functional connectivity analysis was initially applied to resting-state data by Biswal et al. (1995), showing motor cortex functional connectivity being similar to motor task activity patterns. Mapping the default-mode network - which is implicitly linked to the brains resting state - was much later achieved (Greicius et al., 2003).

*Correlation of time series* implies quantifying the relation of two signals in the time-domain (such as 'covariance' or 'cross-correlation'). Of course, different mathematical methods can be used to quantify the relationship between the seed region time series and the time series of other voxels or ROIs. While 'coherence' operates equivalently in the frequency-domain (Sun et al., 2004), another approach would be to explore the 'phase-spectrum delay' between regions (Sun et al., 2005). Thus, the choice of the proper mathematical method, and the selection, size and shape of the *a priori* defined seed region are critical variables for assessing functional connectivity with the seed-based method (Van Dijk et al., 2010).

### 3.2 Independent Component Analysis (ICA)

One of the features of resting-state analysis is that there is no stimulation paradigm for researchers to be dependent on. Therefore, many data-driven solutions have been employed for identification of low-frequency resting state patterns (Beckmann et al., 2005; Fox & Raichle, 2007). The most widely used approach is Independent Component Analysis (ICA). By using blind source separation techniques[4], ICA methods decompose the entire BOLD data set into statistically independent components (Hyvärinen & Oja, 2000) without any hypothesis paradigms, i.e. prior seed definition is not required any more. Researchers found that several separated spatial components could accurately represent specific functional networks during resting state. Many neuroimaging studies have demonstrated that ICA is a productive tool for investigating resting-state fMRI data. Some widely studied functional networks e.g., the default mode network and motor network, show consistency across subjects (Damoiseaux et al., 2006; Zuo et al., 2010). ICA has also been successfully applied to demonstrate significant differences in connectivity patterns between patients and healthy controls (Calhoun et al., 2009; Greicius et al., 2004; Sorg et al., 2007). In addition to identifying functionally relevant networks, ICA also enables automatic separation of artificial and physiological noise sources from fMRI data (De Martino et al., 2007; Tohka et al., 2008).

Still, two controversial issues should be considered: specifying the number of components and selecting those that are functionally meaningful. The number of independent

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[4] Blind source separation techniques underlie the assumption that the measured signal is a linear mixture of independent signals from a number of spatially distributed sources. Decomposition algorithms separate multi-channel data into a set of such independent spatial or temporal components. Temporal decomposition is widely used in EEG research, generating sources, each given by a time course of its activity and a weighting-vector, describing its contribution to the signal recorded in each sensor. As fMRI data usually consists of more spatial than temporal data points, spatial decomposition is more widely applied.

components appropriate to resting-state data is an issue of ongoing debate, and several data driven approaches for optimising the selection of this number have been developed (Beckmann & Smith, 2004; Li et al., 2007). However, it is worthwhile to consider that due to the multiple scales of functional organisation in the brain, determining the number of functionally relevant components is also a product of the spatial scale of interest. Thus, even with data driven approaches like ICA, certain assumptions about brain organization are still required. Selecting components that are of functional relevance is another challenging issue with ICA. While automatic rejection of artefact components can be implemented rather easily (through assessing the frequency spectrum or high spatial scattering), the most commonly used method for identifying functionally relevant components, such as the default-mode network, remains visual inspection by an expert—though several automated network selection approaches have also been proposed (Greicius et al., 2004; De Martino et al., 2007).

### 3.3 Multivariate Pattern Analysis (MVPA)

In recent years the use of pattern-classification algorithms has gained increasing importance in fMRI data analysis (for reviews Haynes & Rees, 2006; Norman et al., 2006). In general, these algorithms use specific features of objects to identify classes to which they belong. In fMRI data, spatially distributed brain activation or connectivity patterns are used as features to classify different brain or cognitive states. Applying this technique requires in the beginning a training of the classification algorithm with the features and the prespecified classes. Thereby a subset of the data (training-set) must be used to attune the classifier on the relationship between features and classes, before the rest of the data (testing-set) can be used to verify the classifiers capability for new/unknown data.

Feature selection and the choice of a proper classifier are critical issues to achieve good results. While mathematical methods allow for a data driven, automated selection of discriminative features, a manual selection method can be beneficial for designing application specific features. For pattern classification, usually supervised[5] machine learning algorithms, such as support vector machines (SVM), neural networks, or linear discriminant analysis (LDA), are used. Knowledge about the relationship between features and classes (i.e. a linear or non-linear relation is assumed) should be taken into account for classifier selection.

Revealing disease-related differences in resting-state functional connectivity, MVPA has been successfully used for disease-state prediction, discriminating patients and healthy controls (Craddock et al., 2009; Shen et al., 2010; Zhu et al., 2008).

### 3.4 Clustering

Similar to MVPA, clustering is a family of mathematical techniques that can be applied to fMRI data to search for characteristic patterns. However, clustering algorithms tend to find patterns without specific knowledge about classes. This means that data is partitioned (classified) into subsets (clusters) in an unsupervised manner, such that observations assigned to the same cluster are similar. Different clustering algorithms[6] have been applied

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[5] Unsupervised algorithms, such as clustering, tend to find pattern without prior knowledge about the desired classes, inevitably increasing uncertainty of the whole procedure.

[6] Different clustering approaches are e.g. 'hierarchical clustering', 'partitional clustering', 'spectral clustering' or 'non-metric clustering', and the development and improvement of clustering methods is an intense research field (Margulies et al., 2010).

to fMRI data in several studies deriving clusters of voxels or regions that represent known functional or anatomical subdivisions in the brain (Bellec et al., 2010; van den Heuvel et al., 2008; Salvador et al., 2005). Another approach is division of the data into functional units by clustering voxels that have similar pattern of functional connectivity (Cohen et al., 2008).

Although a model-free approach (in this sense similar to ICA) which finds specific pattern without prior assumptions (as e.g. seed selection in model based approaches), clustering still involves human judgement. Usually, the user has to define a number of clusters in which the data should be partitioned, and the clustering results need comparison with known functional networks.

### 3.5 Graph theory

Characterising aspects of network structure is a common mathematical problem in which graphs represent mathematical structures describing pairwise relations between objects in a certain network. A graph consists of a collection of *vertices* or *nodes*, and a collection of *edges* connecting pairs of vertices. A *path* in a graph is a sequence of vertices which are connected by edges, and the *distance* between two vertices is the shortest path connecting them. The *degree* of a vertex is the number of terminating edges. Vertices with very high degrees are termed *hubs*. Translated to fMRI data, a voxel or ROI constitute a vertex and their connections are represented by edges. Thus, the theoretical framework of graph theory can be used to analyse brain networks obtained from imaging data (for a review see Bullmore & Sporns, 2009). Given a functional connectivity map, a graph representation can be derived either by assigning an edge if the correlation between two vertices exceeds a certain threshold, or the correlation coefficients themselves can be used to weight each edge.

Numerous tools can be used for characterising such network organisation, which can be conceptually divided into 'local' measures (characterising vertices individually) and 'global' measures (characterising the whole graph). The latter is e.g. realised by the degree distribution $P(k)$, that represents the probability that a randomly chosen vertex has the degree $k$ (Achard et al., 2006; Eguíluz et al., 2005; Nakamura et al., 2009). It also offers information about the number of *hubs* in a graph - obviously regions of special interest for connectivity analyses (Buckner et al., 2009). The ability to separate a network into clusters with high internal connectivity is described by *modularity*, whereas the degree of integration of a graph can be described by the *average path length*. Combining these measures brings up the fundamental approach of the brain being characterised as a *small-world network,* supporting both modular processing of information by high clustering and distributed information processing via short wiring distances (Bassett & Bullmore, 2006).

### 3.6 Centrality

One of the graph-based approaches is the centrality measure. The centrality of a node within a network is an estimation of the relative importance of that node within a network.

Eigenvector centrality mapping (ECM) was recently implemented to estimate the centrality of human brain regions with fMRI data (Lohmann et al., 2010). In their study, the linear correlation was proposed to generate a network of every voxel within the entire brain. Then centrality of each voxel was estimated within its own brain network. They found that some brain regions, e.g. precuneus, cerebellum, showed higher centrality than other brain regions during resting state scan. In addition, by comparing centrality between a hungry and sated condition, the results showed that the precuneus has higher centrality in a hungry state than in a sated state.

The ECM analysis is a data-driven method and therefore it is an appropriate tool for data analysis of “resting-state” studies. There are only few studies on centrality of brain regions but if validity is confirmed, centrality measures will probably be of wide interest for many studies on the human brain in experimental and clinical settings.

## 4. Applications of functional connectivity analyses to specific scientific questions

As we have just described, functional connectivity provides a means of investigating underlying organization of functional systems in the brain. While each of these methodologies allows for the description of specific aspects of network structure, interaction, and organization, the research question we are now stuck with is how to meaningfully apply such techniques. We will here describe two main avenues of research, broadly categorized by anatomical and dynamical lines of investigation. More specifically, anatomical questions will relate to spatial aspects of brain organization, how regions connect to one another, and how those patterns differ between mental states, or between patients and healthy control populations. Dynamical aspects address the interactions in time between brain regions, and can likewise be evaluated for the aforementioned categorical differences. We consider the anatomical/dynamical distinction valuable because each set of research questions brackets a different set of analytic tools. For instance, in evaluating neuroanatomy, the relation between two regions can be quantified using a variety of correlation-based metrics, however, the aim of such analyses lies predominantly in the resulting spatial maps.

### 4.1.1 Investigation of anatomy

Brain mapping is mostly based on anatomical structures, e.g., Brodmann areas. Numerous schemas have been proposed over the past century for describing subdivisions in various areas of the cortex and subcortical regions. Among them, cytoarchitectonics, the mapping of the cellular structure within the cortical layers, has maintained popularity as a method for describing cortical areas within the functional neuroimaging literature. However, cytoarchitectonic mapping has the disadvantage of only being discernable using histological techniques, making it difficult to subsequently conduct functional imaging studies on the same research subjects. Function-based brain mapping is strongly demanded because of the value of precisely localizing functional areas in the brain. Intrinsic functional connectivity approaches, a synonym of resting-state functional connectivity, however, take advantage of a primary characteristic of the brain: namely, its connectivity. Connectivity has previously been applied extensively in the macaque monkey using axonal labelling tract-tracing techniques. The success of this approach in the macaque suggests that a non-invasive approach in humans also holds great promise.

In humans, resting-state functional connectivity has been successfully used to map divisions with complex structures such as the anterior cingulate (Margulies et al., 2007), precuneus (Margulies et al., 2009), striatum (Di Martino et al., 2008), lateral parietal lobule (Cohen et al., 2008; Mars et al., 2011; Nelson et al., 2010), motor cortex (Cauda et al., 2010; van den Heuvel & Hulshoff Pol, 2010), to name a few examples. In addition, functional connectivity has been demonstrated to map closely to anatomical connectivity methods, such as diffusion tensor imaging (DTI) tractography (Greicius et al., 2009; Skudlarski et al., 2008) and tract tracing studies in the macaque monkey (Margulies et al., 2009; Mars et al., 2011; Vincent et al., 2007). Therefore, several studies have begun to use functional networks to find functional areas within some anatomical brain regions. For instance, precuneus has been found to show similar sub-regions distribution in human and monkey (Margulies et al., 2009). In addition, supplementary motor area has been demonstrated to be organized into two functional anterior-posterior structures based on their respective functional networks (Kim et al., 2010), and a lateral-medial structure has been found in anterior bank of central gyrus (Long et al., 2010). These findings strongly suggest that functional network is a useful approach to delineating functionally unique brain regions. Underlying the strength of this approach is the hypothesis that differential functional connectivity is associated with differentiable functional roles.

### 4.1.2 Methods for investigating neuroanatomy

As previously described, the seed-based correlation approach creates a spatial map for an individual seed. These spatial maps can then be used as features to distinguish seed regions from one another. This can be done through both visual inspection, direct contrasts of the respective functional connectivity maps, and also through computationally based clustering techniques (e.g., Cohen et al., 2008; Kelly et al., 2010)

As the seed-based functional connectivity approach aims to describe the connectivity of a single region-of-interest, regions can also be delineated as whole networks (or 'functional systems'). The ICA approach previously described aims to pull out whole networks simultaneously using a multivariate approach. The primary advantage of this approach is that it can describe independent systems without a priori hypotheses about the spatial location of such systems. Notable early examples of this approach aimed to characterize the number of unique "resting-state networks" throughout the brain (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Smith et al., 2009). Discriminating the appropriate number of networks is still a challenge to the community, as the number of networks derived using ICA requires a priori assumptions. However, this data-driven approach also offers the advantage of not requiring prior assumptions about the location of networks.

### 4.2.1 Investigation of dynamics: simultaneous EEG-fMRI

Although fMRI is widely used in clinical and scientific approaches, many fundamental questions are still unknown; most notably, the precise relationship to the underlying neuronal activity. Despite significant progress in understanding this relationship (Lauritzen & Gold, 2003; Logothetis et al., 2001; Shibasaki, 2008), based on BOLD signal alone, the underlying neuronal activity cannot be recovered unambiguously ("Inverse Problem of fMRI"). This is not only due to the poor temporal resolution of the vascular response but also due to the fact that different types of neuronal (and non-neuronal) events such as excitatory/inhibitory postsynaptic potentials (EPSP/IPSP), action potentials, glia-activity, etc., are being translated into only a one-dimensional variable of "more or less" BOLD signal. Additional sources of information are frequently needed for further clarification of the underlying processes in the respective brain areas. Particularly, the combination of fMRI with electrophysiological methods such as EEG may be useful for this purpose. Simultaneous EEG-fMRI approaches allow for investigation of the link between changes in

EEG patterns and changes in the vascular signal. For functional connectivity studies, investigating intrinsic brain activity at rest, the EEG signal then can be used as independent variable, classifying brain states in the absence of any stimulation or task paradigm.

Of special interest for the investigation of intrinsic brain activity is spectral analysis of the ongoing EEG. Many perceptual and cognitive processes emerge from recurrent network interactions, which are induced by, but not necessarily phased-locked to external events. Analysis of event-related potentials (ERP)[7] excludes these non-phase-locked signal components from investigation. Different background rhythms in a large range of frequency bands have been described, not only recorded during 'rest', but also with relation to various cognitive states, mental activity, and showing specific temporal pattern following external events (for a review see Nierhaus et al., 2009). Since different sensory networks were found to exhibit distinct background rhythms[8], resting rhythmic activity denotes a network specific attribute, describing network activity from a different angle. Thus, investigating the relationship of spectral EEG phenomena and functional connectivity maps derived from fMRI data is an obvious and promising challenge.

#### 4.2.2 Associating EEG rhythms and resting-state networks

Simultaneous EEG-fMRI measurements have been applied to investigate the relationship of electrophysiological background rhythms and BOLD signal fluctuations (for reviews see Laufs 2008; Ritter & Villringer 2006). Most of these studies show an inverse correlation of the background rhythm strength with the spontaneous BOLD signal fluctuations in the cortical sensory area generating the respective rhythm. However, positive correlations between subcortical, i.e., thalamic BOLD signals and occipital EEG alpha power have also been reported. Investigation of stimulus driven responses revealed a close coupling between gamma-band (40-100 Hz) activity and BOLD signal of sensory cortical regions, demonstrated using intracranial recordings in human (Lachaux et al., 2007; Mukamel et al., 2005) and in animals (Logothetis et al., 2001; Niessing et al., 2005). Since gamma-band activity is associated with sensory information processing, further investigation with simultaneous EEG-fMRI should allow for a better understanding of resting-state network behaviour during mental work. First attempts of such investigations were recently performed using direct intracerebral recordings in the default-mode network (Jerbi et al., 2010). Execution of attention-demanding tasks were shown to suppress gamma power accompanied by BOLD deactivation.

The default-mode network (DMN) has also been investigated in several EEG-fMRI studies. Using the power of spontaneous EEG oscillations, a positive correlation of the *beta* frequency band with the DMN was shown (Laufs et al., 2003). The DMN activity has also been found to be negatively correlated to frontal theta power derived using ICA on the EEG data in a

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[7] Repeated measures of external events with subsequent averaging enables investigation of the isolated neural response phase-locked to the event.

[8] Most prominent is the occipital *alpha* rhythm with a frequency between 8-12 Hz. Since occipital alpha is strongest in the absence of visual input, it is referred to as the "idle rhythm" of the visual system. Such inverse relationship of rhythm strength and sensory input is also found for pericentral rhythms, with peak frequencies around 12 Hz (*mu*) and 20 Hz (*beta*), which are known to desynchronise following motor activation or somatosensory stimulation. Oscillations with a frequency of 3-8 Hz are termed *theta,* which are most prominent in hippocampus and frontal cortex and are associated with the neural basis of learning and memory. *Delta* oscillations (1-3 Hz) are a characteristic feature of deeper sleep stages.

resting state experiment (Scheeringa et al., 2008) and, in a second study, even at the single trial level increases of frontal theta power induced by a working memory task were correlated to decreased DMN activity (Scheeringa et al., 2009).

Mantini et al. used ICA to identify resting-state networks in fMRI data and then correlated the time courses of these networks with the power of five specific EEG frequency bands (*delta, theta, alpha, beta, gamma*), averaged across the entire scalp (Mantini et al., 2007). Four of six networks, including a dorsal attention network and a somatomotor network, showed exclusively negative correlations with EEG frequency band power. Again, the DMN showed a positive correlation with *beta* activity, and here additionally with *alpha* power. Also gamma power was found to be positively correlated with one network, well in line with the previous described invasive findings. Improved results could be expected from EEG source separation with direct correlation of source and network activity.

A common way to integrate EEG data into fMRI analyses is to take EEG frequency band power as a regressor in a general linear model, thus, investigating how well fMRI data is explained by certain features of the EEG. Vice versa it would be interesting if the EEG data can be explained by fMRI activity pattern. To address this question, MVPA might be a helpful technique: brain activation or connectivity pattern could be used as features to train a classifier, which capability then would be verified using EEG data.

Also "centrality mapping" could be a promising approach for analysing simultaneous acquired EEG-fMRI data. Therefor, the average time course of regions indicated by high centrality must be correlated with the time course of frequency band power of EEG source activity. The results would show whether regions of high "hubness" are also involved in EEG rhythm generation.

## 5. Conclusion

In the past decades the view on background fluctuations in brain activity, which were previously assumed to reflect (stochastic) “physiological noise”, has changed dramatically: Spontaneous fluctuations have been identified to contain important information reflecting brain function. Specifically, it has been shown that the brain ‘at rest' is characterised by several distinct pattern of correlated brain activity – resting state networks – and that changes in network activity can be associated with cognitive states, mental activity and pathophysiological conditions.

Numerous techniques can be applied to fMRI data for investigating functional connectivity, each with different weaknesses and strengths, depending on the experimental design and the kind of research question/hypothesis. Although described very briefly, we endeavoured to provide insight into each of the various options for investigating functional brain organisation with fMRI data. Further, two main research fields were broadly categorized by anatomical and dynamical lines of investigation, covering meaningful applications of the aforementioned analysis techniques.

The use of functional connectivity to investigate spatial aspects of brain organization is based on the assumption that brain areas with different functional roles exhibit differential functional connectivity pattern. Parcellating brain regions by their functional network patterns allows for a more precise localisation of brain function and there is no doubt that a well-investigated function-based human mapping will be created in future studies.

Investigating dynamical changes using EEG and fMRI indicate that EEG background rhythms and fMRI-based resting state measures are closely related, revealing network specific attributes from different angles. Furthermore, simultaneous EEG/fMRI provides insights into the spatio-temporal organization of intrinsic signal fluctuations, whether measured at rest or during stimulation or task. Thereby, the interplay of these rhythmic fluctuations measured with different modalities at rest can be analysed in a straightforward manner. However, tasks involving perception and cognition are accompanied by fast changes in EEG signals, and it is still a major challenge for cognitive neuroscience to link these transient EEG features to measures of functional connectivity. A proper combination of the aforementioned analytic tools will help to further understand this link with task-based approaches, and will enable future investigation of the interaction between ongoing dynamical changes and transient activations evoked by task or stimulation.

## 6. Acknowledgment

The authors would like to thank The Neuro Bureau (www.neurobureau.org) and its affiliated team of researchers for continued creative support.

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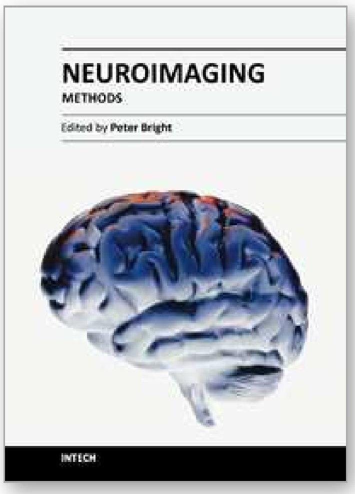

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Edited by Prof. Peter Bright

ISBN 978-953-51-0097-3
Hard cover, 358 pages
**Publisher** InTech

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Till Nierhaus, Daniel Margulies, Xiangyu Long and Arno Villringer (2012). fMRI for the Assessment of Functional Connectivity, Neuroimaging - Methods, Prof. Peter Bright (Ed.), ISBN: 978-953-51-0097-3, InTech, Available from: http://www.intechopen.com/books/neuroimaging-methods/fmri-for-the-assessment-of-functional-connectivity

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