

# Modeling Connectivity in Health and Disease: Examples from the Motor System

# 17

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## 17.1 Principles of Brain Organization

Elucidating the neural correlates underlying dysfunction in neurological or psychiatric disease is one of the major long-term goals in systems neuroscience research. Knowing pathophysiological mechanisms giving rise to complex disorders like schizophrenia or Parkinson's disease will, however, remain futile without understanding physiological brain organization. The human brain, like that of other mammals, is organized according to two fundamental principles: *functional segregation* and *functional integration* (Friston 2002). The former emphasizes that the human brain—and in particular the cerebral cortex—is not a homogenous entity but can be subdivided into regionally distinct *modules* such

as cortical areas or subcortical nuclei based on functional or microstructural properties. The idea of *functional integration*, conversely, is based on the observation that no brain region is by itself sufficient to perform any cognitive, sensory, or motor process. Rather, all of these mental capacities or *tasks* have to rely on a dynamic interplay and exchange of information between different regions sustaining different computational processes. Importantly, however, functional integration and functional segregation are not mutually exclusive but rather complementary concepts of brain organization as any interaction will need to take place between specialized regions, each performing a distinct computational sub-process (Friston 2002; Eickhoff et al. 2009).

### 17.1.1 Specialized Modules in the Brain: The Nodes of Connectivity Models

In particular invasive research in nonhuman primates with electrodes penetrating the cerebral cortex has demonstrated that the regional specialization of the brain, that is, the cognitive or sensory processes that are served by particular location of the cortex, is determined by both the intrinsic (structure) and extrinsic (connectivity) properties of a cortical area (Broca 1863; Brodmann 1909; Eickhoff et al. 2005; Schleicher et al. 2005; Grodzinsky and Santi 2008). In comparison to the fundamental distinction between functional segregation and functional integration

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outlined above, this evidence provides a slightly different focus as it suggests that specialization for a particular function or process is not necessarily an intrinsic property of a region independent of its connectivity. Rather, functional specialization of a cortical area is seen as a (potentially necessary) result of both its local anatomical and neurochemical features as well as its distinct pattern of inputs and outputs, that is, connectivity. A module of functional specialization may hence not be completely defined without its (potential) connectivity but is rather provided by the intersection of regionally specific architecture and connectivity patterns. Each cognitive, sensory or motor task, or mental capacity then relies on the coordinated activity and interaction of such modules.

Brain organization and disturbances thereof in neurological and psychiatric disorders might thus only be targeted by considering (i) the anatomical differentiation of the cerebral cortex into microstructurally distinct areas; (ii) the specific response properties or, more general, the pattern of recruitment of brain regions during the performance of various mental operations; and finally (iii) interaction with other brain regions. Research in nonhuman primates has a long tradition for such integrated analysis of regional brain organization (Kobbert et al. 2000; Le et al. 1986; Behrens et al. 2003; Friston 1994). Here, functional properties of a microstructurally distinct area (e.g., as determined by cytoarchitectonic, myeloarchitectonic, or receptorarchitectonic criteria) may be probed by recording single cells or local field potentials (LFPs). Axonal connectivity of the very same location may be revealed by injecting a tracing dye that is transported to interconnected brain regions. All of these techniques, however, ultimately entail sacrificing the examined animal and hence are not feasible in *humans*. Recent advances in neuroimaging techniques, however, have enabled not only the integration of structural and functional data on the organization of the human cerebral cortex but in particular also the modeling of functional interactions, thereby allowing a mechanistic insight into the dynamic interplay between cortical regions.

## 17.2 Structure-Function Relationships in the Brain

### 17.2.1 Regional Functional Specialization

Functional neuroimaging approaches such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are well established for the *in vivo* investigation of functional specialization in the human brain (Biswal et al. 1995; Fox and Raichle 2007; Greicius et al. 2003; Sporns et al. 2004; Buckner 2010). Based on the measurement of local changes in cerebral blood flow, glucose, or oxygen metabolism, these techniques allow the localization of regionally specific neural activation underlying a certain motor, sensory, or cognitive task. Although spatial precision in group activation studies is influenced by factors such as inter-individual variability, averaging effects, and imperfect spatial normalization (Eickhoff et al. 2009), group fMRI studies enable localizing specific response patterns and testing hypotheses about, for example, a functional differentiation between two regions or a dichotomy between the neural correlates of two processes in the range of a centimeter or less.

### 17.2.2 Regional Structural Specialization

The structural examination of the human brain, in particular the histological mapping of the cerebral cortex, has a long tradition in neuroscience (Brodmann 1909). These analyses rely on the investigation of human postmortem tissue, where cell bodies, myelinated fibers, or the presence of specific molecules may be visualized using cell staining, radioactive labeling, or *in situ* hybridization. More recently, high-field imaging methods also opened the possibility of assessing the microstructural properties of the human brain *in vivo* (Stephan et al. 2007a). However, currently, no *in vivo* imaging approach seems capable of providing a microstructural account of the human brain as precise as histological postmortem data.

Therefore, combining functional imaging and histological maps has been proposed for an integrated description of regional segregation (Eickhoff et al. 2005). The currently prevalent approach for analyzing the correspondence between structure and function in the human brain is thus to perform both analyses separately (evidently in two groups of subjects) and then to integrate the obtained data by means of probabilistic brain atlases (Friston et al. 2003; Kiebel et al. 2006; Stephan et al. 2008). These atlases may be generated on the basis of automated analyses of histological sections in micrometer resolution (Schleicher et al. 2005), which are then warped to a common reference brain, for example, the MNI brain, to describe the location and variability of cortical areas on the group level in standard space. In contrast to classical anatomical brain atlases that present the observer-dependent parcellation of one or a few brains as drawings or schematic surface views, probabilistic atlases thus allow the direct and quantitative assessment of structure-function correlations (Fig. 17.1; Eickhoff et al. 2005).

### 17.2.3 Regional Structure-Function Relationships

Advances in the mapping of regional specialization enable a description of the mental processes that recruit a specific, structurally defined area and have provided plenty of evidence that anatomical borders indeed constrain functional specialization (Friston et al. 2003). However, such a *localization approach* is not sufficient to describe brain function, as a single region may be *specialized* for a broad range of mental operations. For example, the inferior frontal gyrus hosts a distinct cytoarchitectonic area which Korbinian Brodmann coined *area 44* (Brodmann 1909). Pierre-Paul Broca already noticed that this part of the brain is strongly engaged in language production (Broca 1863). A number of neuroimaging studies, however, clearly showed that this region is not language specific but recruited by a broad range of tasks ranging from speech to working memory and motor production (Grodzinsky and

Santi 2008). Does this contradict the fundamental idea of functional specialization? Not necessarily, when assuming that BA 44 is specialized toward a particular computational process rather to sustain any particular (psychologically defined) mental operations. These basic computations, however, which may be sequencing or temporospatial updating like, would then be integral parts of many different task-specific recruited networks. Hence, a network perspective seems to be much closer to the neurobiology underlying human brain function under both physiological and pathological conditions.

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## 17.3 The Elusive Concept of Brain Connectivity

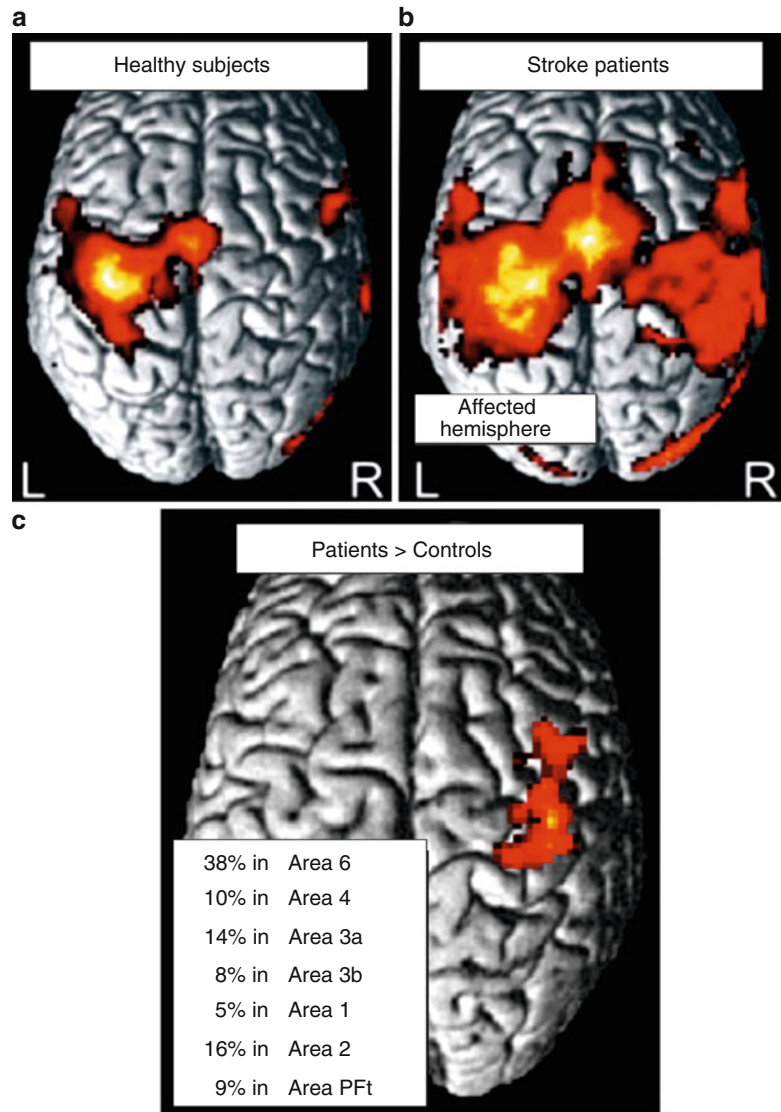
In spite of the pivotal role of connectivity analyses for the understanding of human brain organization, the concept of brain connectivity in itself has remained somewhat enigmatic. First, there is no such thing as *the* connectivity of a particular brain region. Rather, several conceptually different aspects of brain connectivity may be distinguished. In the following, we will provide a short outline of the major concepts and approaches, their strength and drawback, and then focus on explicit network modeling as an approach to a mechanical understanding of the context-dependent interactions in health and disease.

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## 17.4 Anatomical Connectivity

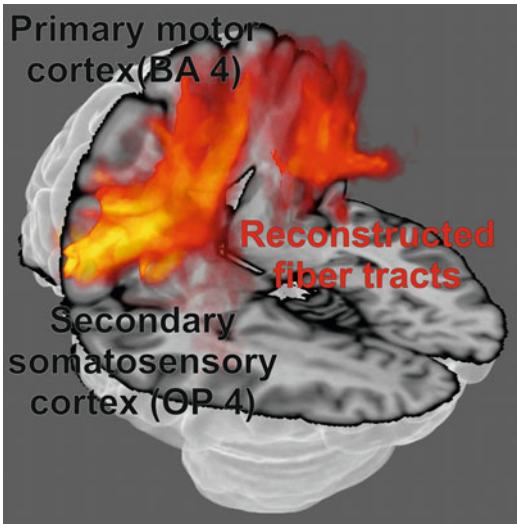
Anatomical connectivity in the strict sense denotes the presence of axonal connections between neurons in different brain regions. Several years ago, knowledge on the anatomical connectivity of the human brain was mostly based on postmortem dissection techniques or on extrapolations from invasive tract-tracing studies in nonhuman primates (Kobbert et al. 2000). The advent of diffusion-weighted imaging (DWI) and tractography approaches has more recently also enabled the *in vivo* explorations of anatomical connectivity in the human brain. DWI is based on the fact that in a

**Fig. 17.1** Blood oxygenation level-dependent (BOLD) activity during a simple motor task. **(a)** In healthy subjects, rhythmic fist closures of the right hand activate a left-lateralized network of areas in frontal and parietal cortex. **(b)** BOLD activity in patients with motor deficits of the right hand is more widespread and also found in the unaffected (here right) hemisphere. **(c)** Using a probabilistic cytoarchitectonic atlas, enhanced activity can be localized in distinct cortical areas such as BA 6 (premotor cortex), BA 4 (primary motor cortex), primary somatosensory cortex (BA 3a and 3b) and higher-order somatosensory areas (BA1, BA2, and PFt) (Adopted from Grefkes et al. 2008b)



structured tissue such as a fiber bundle, water does not diffuse isotropic but rather primarily along the direction of the fiber. By employing MR sequences sensitive to random motion of water molecules along a diffusion-encoding direction in a pulsed field gradient (Le et al. 1986), it becomes possible to characterize the diffusion characteristics and hence the fiber orientation in each voxel. From the fiber orientation directions in each voxel in combination with measures about diffusion uncertainty, it is possible to infer the course of a particular fiber tract in the brain. Such *tractography* (Fig. 17.2) may be deterministic (following the principal

diffusion direction at each voxel) or probabilistic (by repeated sampling of the possible diffusion directions in each voxel as reflected by the uncertainty on orientation distributions; Behrens et al. 2003). Although it should be noted that such approaches only delineate fiber tracts running from one region to another (rather than axonal connections between neurons in these regions), anatomical connectivity as revealed by diffusion imaging represents the structural scaffold, on which any functional interaction may be realized. It also represents a truly independent aspect of interregional integration and brain networks that is



**Fig. 17.2** Illustration of the fiber tracts running from area OP 4 of the secondary somatosensory cortex to the primary motor cortex, as delineated by probabilistic tractography based on diffusion-weighted imaging of 17 healthy subjects. Note that due to interindividual variability but also uncertainty about the fiber orientation in each voxel, there is a considerable variance in the data as demonstrated by the fact that only few voxels have high probabilities of belonging to this particular tract (coded in *bright yellow*)

not confounded by using the same source of data as investigations into functional specialization. Anatomical connectivity studies, however, do not allow any inference on information transfer and dynamics within the hereby defined networks.

## 17.5 Functional Connectivity

Functional connectivity is rather broadly defined as the temporal coincidence of spatially distant neurophysiological events (Friston 1994). That is, areas are presumed to be functionally coupled and hence components of the same network if their properties are consistently correlated. This definition already stresses a key aspect that must be considered when dealing with functional connectivity, that is, its correlative nature. Importantly, functional connectivity thus does not imply any causal relationship or a direct connection between functionally coupled areas. Rather, correlated activity in two regions may be mediated via additional structures relaying information from the

first area to the second, including cortical-subcortical loops involving, for example, the basal ganglia or the cerebellum, or a third area may induce correlated activation in two regions not having any direct interaction. An example for the latter situation would be the feed-forward of stimulus-driven activity in sensory areas that is forwarded to parietal sensory areas for perceptual analysis and, in parallel, to premotor cortex for response preparation.

### 17.5.1 Resting-State Functional Connectivity

To date functional connectivity in neuroimaging is mainly analyzed by assessing coherent low-frequency fluctuations in resting-state fMRI time series (Biswal et al. 1995). Given the richness of fMRI data, which usually consists of several hundred time points of voxel-wise data across the brain, this approach has the perspective to yield information on functional connectivity at the level of the entire brain. Resting-state fMRI time series are obtained while the subjects are scanned lying in the scanner without any imposed task. Given that raw MRI signal time courses are noisy due to scanner or motion-induced effects, there is an important need to reduce spurious correlations by multiple processing steps such as spatial and temporal filtering as well as removal of signal contributions from motion, physiological noise, and global signal fluctuations. A large number of different studies have used data-driven approaches, in particular, independent component analysis (ICA; Fox and Raichle 2007), to delineate large-scale systems of coherent MRI signal changes providing evidence for the existence of several distinct components (i.e., functional networks) in fMRI datasets obtained during a task-free, *resting* state in particular at lower frequencies (<0.1 Hz; Greicius et al. 2003). Most of these *resting-state networks* (RSNs) closely resemble networks that are commonly engaged in task-based fMRI studies (Fox and Raichle 2007). The relationship of these components to task-related networks, however, warrants further examination as intuitive associations may be

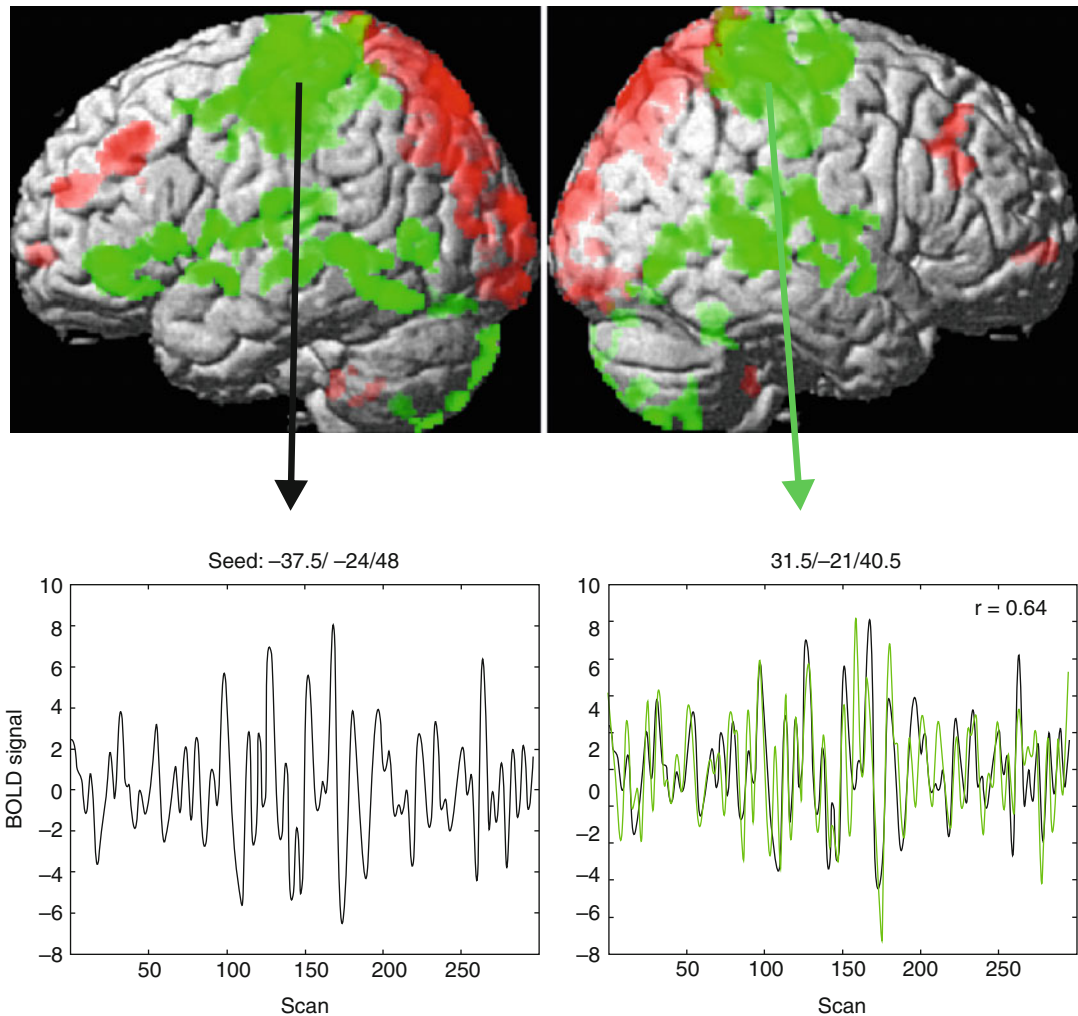
premature (Rehme et al. 2013). There is also an ongoing debate on the physiological basis of such correlations. They have been suggested to arise from intrinsic activity events constrained by anatomical connections between the respective areas (Sporns et al. 2004), that is, anatomical connectivity. Other RSNs, however, are poorly explained by anatomical connections and it remains unresolved what drives fluctuations of sufficient magnitude to propagate along anatomical connections (Buckner 2010). This has motivated a modified view, which de-emphasizes the *resting* aspect by assuming that the brain is never at *rest* (Fox and Raichle 2007). Rather, the *resting* state should reflect ongoing activity composed of a vast variety of mental functions such as bodily perception, memories, emotions, and explicit cognitive thoughts, including inner speech (Eickhoff and Grefkes 2011). That is, when lying in an MRI scanner without a specific task, subjects are not resting but rather performing all sorts of mental operations in succession or parallel. The correlation in the MR signal-time course between two regions should thus reflect the degree to which these jointly participate in the various mental networks (Laird et al. 2011a). *Resting-state* activity would hence consist of a, more or less random, sampling of all the different task-related networks that the brain is capable of. It has hence been proposed to refrain from the term *resting state* in favor of *endogenous, task-free functional connectivity* or *functional connectivity in the absence of a structured task set*.

### 17.5.2 Task-Based Functional Connectivity

The notion of functional connectivity in the absence of an structured task easily leads to the complementary aspect of *task-based* or *task-dependent* functional connectivity which may be inferred from correlation analysis between time series from different brain regions while performing a particular task (Rehme et al. 2013). In this case, however, inference is limited to the task at hand or, more precisely, the particular experiment rather than addressing the core question about

“which other regions does a particular area work with?” In other words, if a particular area is activated, which other brain regions are also co-activated more likely than chance? An answer to this question has emerged from the advent of large-scale databases on functional neuroimaging results (Fig 17.3), which enabled new approaches to task-based functional connectivity analysis (Eickhoff et al. 2010). Such resources, like the BrainMap database (<http://brainmap.org/>; Logothetis 2000; Friston et al. 2003), contain a summary of the results of several thousands of functional neuroimaging experiments. Given the high standardization when reporting neuroimaging data and the ubiquitous adherence to standard coordinate systems, the results reported in these studies can be readily integrated to assess co-activation probabilities. In practice, functional connectivity of a seed region is established by retrieving all experiments from a database that feature at least one focus of activation within this seed region of interest (Eickhoff et al. 2010; Laird et al. 2009a, 2009b). Coordinate-based meta-analysis is then performed over all activation foci reported in these experiments to test for significant convergence, which (outside the seed itself) reflects above-chance co-activation. In doing so, *meta-analytic connectivity mapping* (MACM) closely follows the definition of functional connectivity by testing for coincidences of neurophysiological events (Laird et al. 2011). In MACM, however, unit of observation is not a specific point in an acquired (e.g., resting-state fMRI) time series but a particular neuroimaging experiment. Thus, functional connectivity is not expressed as coherent fluctuation across time but rather as coherent activation across experiments (Eickhoff and Grefkes 2011; Fig. 17.4).

The fact that functional connectivity analyses are fundamentally correlative in nature represents both their major strength and mostly severe drawback. As noted above, a correlation between neuroimaging signals on any scale does not imply a direct interaction. Moreover, given the absence of a specific model on the nature of the interactions, functional connectivity analyses tend to be rather susceptible to various physiological confounds or epiphenomena. On the other hand, the fact that only minimal assumptions need to be made for



**Fig. 17.3** Demonstration of resting-state functional connectivity analysis, seeding from the left primary motor cortex. Following spatial (realignment, spatial normalization, smoothing) and temporal (confound removal, band-pass filtering for the range of 0.001–0.008 Hz) preprocessing, the fMRI time series of the seed is extracted as displayed in the *lower left*. Subsequently, the similarly

time series of all other voxels in the brain are correlated with the seed's time series. Significant correlations are shown in *green*, significant anti-correlations in *red*. The significantly correlated time series of the right motor cortex is displayed (*green*) on the seed time series (*black*) in the *lower right panel*

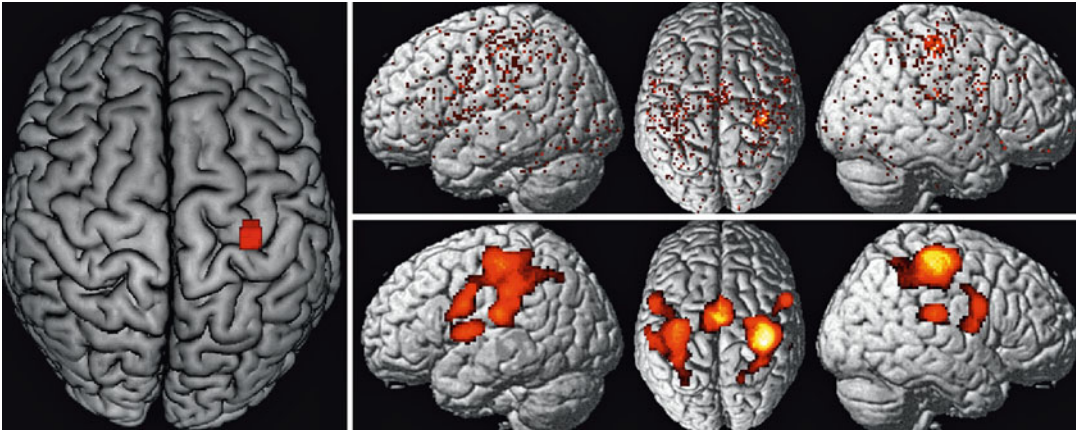
functional connectivity analyses also renders them a particularly unbiased and robust approach toward the mapping of interacting networks.

## 17.6 Effective Connectivity

Effective connectivity in the brain is defined as the causal influence one area exerts over another (Friston 1994), thus providing an approach

toward to understanding how different brain regions affect another. Importantly, in contrast to the correlative nature of functional connectivity analyses, effective connectivity measurements are based on explicit models, how influences between brain regions are mediated. Model parameters are then fitted using the measured fMRI signal.

In spite of the considerable differences between methods and concepts for effective



**Fig. 17.4** Task-based functional connectivity of the right primary motor cortex. The *left panel* illustrates the location of the seed region on the MNI single subject template. Subsequently, the BrainMap database was filtered to identify all those experiments that featured at least one activation within this region of interest. The location of all foci

of activation reported in the thus identified experiments is shown in the *upper-right panel*. By performing a quantitative meta-analysis over the identified experiments, locations where the reported foci significantly converge and which thus show significant above-chance co-activation likelihood with the seed may be identified

connectivity modeling, all approaches allow inference on directed influences. This has led to the common custom of representing effective connectivity analyses as directed graphs, where nodes represent the individual brain regions that were either included in the analysis or inferred from it (Bullmore and Sporns 2009). The directed edges of the graph then express the causal influences of one region on another, that is, effective connectivity. The dependency on an explicit model of interactions between areas is the major advantage of effective connectivity analyses. Since models reflect hypotheses about functional integration in the brain, the comparison of different models allows the comparison of competing hypotheses. Models of effective connectivity are thus hypothesis-driven investigations of how data are propagated and processed in and between different areas of the brain. However, the reliance on the explicit and implicit assumptions going into a particular model and its parameter estimation scheme has also been voiced as the most fundamental limitation of effective connectivity modeling. In particular, while model- and hypothesis-based analyses enable a mechanistic assessment of interaction processes, any inference drawn from these analyses crucially depends on the validity of the modeling

assumptions. Moreover, estimating effective connectivity from fMRI time presents a major challenge, since fMRI measurements do not reflect any neuronal signal directly but rather after its convolution with a hemodynamic response function (HRF; Logothetis 2000). Inference hence has to be based on a constrained approximation or inference of neuronal responses based on the measured time series rather than on the hemodynamic observation (David et al. 2008).

Above these fundamental aspects that must be considered for all approaches for assessing effective connectivity, there are also major lines of conceptual and practical distinctions between them. Some methods such as psycho-physiological interactions (PPI) or Granger causality mapping (GCM) enable spatial inference (Friston et al. 1997; Roebroeck et al. 2005). That is, given a particular seed region or a set of seed regions, areas showing functional connectivity with these, either by influencing the seed or being influenced by it, may be delineated. Other approaches, for example, dynamic causal modelling (DCM) or structural equation modeling (SEM), do not aim at localizing effects but rather model the interactions within a predefined network or regions (Friston et al. 2003; McIntosh and Gonzalez-Lima 1994; Stephan



2004). Models of effective connectivity also differ in whether external perturbations of a system are explicitly incorporated in a model, assumed to be stochastic, or in equilibrium. Examples for the former would be PPIs and DCM; the probably prime example for the latter is SEM. Finally, modeling schemes may also differ with respect to the level of hemodynamic modeling involved (David et al. 2008; Stephan et al. 2007b; Penny et al. 2004).

### 17.6.1 Dynamic Causal Modelling

In contrast to other methods, which are rooted in non-brain imaging applications, dynamic causal modelling (DCM) represents an approach to effective connectivity modeling that has been specifically designed for the analysis of fMRI time series (Friston et al. 2003). Given this conceptual specificity and the fact that it represents by far the most common approach to fMRI-based effective connectivity analysis, we will hence focus here on the theory and application of DCM while referring the reader to specialized literature on other approaches (Stephan et al. 2007a; Kiebel et al. 2006).

The key concept behind DCM is to consider the brain as a nonlinear dynamic system in which external perturbations (inputs, which consist of the experimental manipulations) cause changes in neuronal activity or interregional coupling strength, that is, connectivity. The ensuing changes in neuronal activity states, which are explicitly modeled in DCM, in turn then cause changes in the blood oxygen level-dependent (BOLD) signal observable with fMRI. That is, DCM considers a hidden level of neuronal dynamics (neuronal states) which are driven by the experimental inputs (sensory stimulation or contextual influences such as task settings). These dynamics are explicitly modeled by a set of differential equations but, however, cannot be directly observed, that is, measured by fMRI. Rather, these neuronal dynamics give rise to externally assessable outputs such as BOLD signal changes through the hemodynamic response that they evoke. In DCM, the effective

connectivity within the assessed dynamic neuronal system is, therefore, expressed in terms of coupling between unobservable brain states (e.g., the modeled neuronal activity in the different regions comprised in the model), rather than being inferred directly from the measured time series. It must be noted that the neuronal states, which are central to DCM as it is their dynamics and interactions that are at the heart of the model, do not directly correspond to a particular physiological quantity (Friston et al. 2003). Consequently, they do not represent multi-unit activity, spike rates, or local field potentials. Rather they represent the population dynamic of the represented area in an abstract form. The neuronal state of region  $k$  at a particular time  $t$  is given by  $z_{k(t)}$ . Aggregating the neuronal states of all modeled regions at a particular time then provides the neuronal state vector  $z_{(t)}$ , which describes the state of the entire system considered for a particular point in time. Key to the modeling is now to explain the change in the neuronal state variable of each region, which means the dynamic of activity as a function of (i) the influences other areas exert over it (ii) the modulations of these influences brought upon by the experimental manipulations, and (iii) the direct driving input of the latter. This is implemented by a set of differential equations that reflect the change of the neuronal state vector  $z$  over time as a function of its current state (via the exerted effective connectivity) and the experimental perturbations that act on the neuronal system. For the purpose of the model, experimental factors are represented by a set of input functions  $u$ , with  $u_j$  corresponding to the time course (denoting presence or absence) of the  $j$ th condition or manipulation. In the standard form of DCM for fMRI, changes in neuronal states over time are represented in the following equation forming the generative model of the neuronal level (Stephan et al. 2008):

$$\frac{dx}{dt} = \left( A + \sum_{j=1}^m u_j B^{(j)} + xD \right) x + Cu$$

In this formulation of effective connectivity architecture, the endogenous connectivity matrix

A (square matrix, whose size reflects the number of regions) represents the task- or process-independent component of interregional interactions, that is, the propagation of neuronal activity from one area to another expressed as the change of neuronal state as a function of the current state of the system. The task-dependent modulations in matrix B represent the changes in coupling strength brought upon by a particular stimulus or task. More specifically,  $B^{(i)}$  (of the same size as A) reflects the additive effect that is present when the respective context  $u_j$  is present. If the respective context is not present, as reflected by a value of 0 in the input function, the term  $i_j B^{(i)}$  becomes zero and only the remaining components of the effective connectivity model become expressed. Nonlinear effects are modeled in D which represents the modulatory influence of a particular region on the coupling strength between two other regions (i.e., gating). That is, the change of neuronal states is modeled as a nonlinear (multiplicative) interaction between the activity in two other regions such that the current state of region A only influences the change in the neuronal state of region B (exerting effective connectivity) when activity is also present in region C. Finally, the driving inputs C reflect direct effects of experimental conditions, again separated according to the individual input functions  $u_{(i)}$  on the different regions. These driving inputs are particularly relevant, as they inject activity into the system, which is then propagated between the different regions and returns back to baseline level due to negative self-coupling, that is, dampening of activity, within each region. In that context, it must be noted that while the driving inputs mostly reflect sensory stimuli, they are not limited to those. Rather, activity could also enter a particular *higher-order* brain region, like the SMA or the DLPFC, in a given endogenously driven context in the same manner that it could enter a sensory area in the case of an external, for example, visual stimulus.

The modeled neuronal dynamics are then linked to the observable changes in the BOLD response via a biophysically validated hemodynamic forward model translating neuronal states into predicted measurements (Friston et al.

2003). While this approach entails two separate layers of modeling, the neuronal and the hemodynamic, each of which has its own sets of parameters to be estimated, it has two major advantages. First, DCM allows building mechanistic models of neuronal dynamics, interactions, and causal effects at the neuronal level, which evidently is of primary interest. Second, by not de-convolving the observed MRI time series by a canonical hemodynamic response function but rather estimating the regionally specific HRF from the acquired data (under biological constraints), it may accommodate moderate deviations of the hemodynamic effects from their canonical form. The latter is in particular relevant in the application to clinical populations such as patient post-stroke, which may show generalized vascular changes that could impact the form of hemodynamic responses. In the conceptual framework of DCM, effective connectivity within a given brain network is inferred from the coupling parameters computed for the hidden neuronal states as detailed above. In this context, effects are deemed causal in the sense of control theory, describing how dynamics in one neuronal population cause dynamics in another and how such interactions are modulated by contextual manipulations. That is, rather than computing a measure of connectivity from the actual data, DCM fits a model of neuronal states; their interactions and evoked hemodynamics to the measured fMRI time series and effective connectivity in the modeled system are then given by the estimated parameters of the neuronal model.

### 17.6.1.1 Model Estimation

Estimation of the (in particular neuronal) model parameters and hence inference on effective connectivity is based on perturbing the system through experimental manipulation, for example, by engaging subjects with different tasks while measuring the evoked effects on the BOLD time series of the regions included in the model. The parameters of the model that best translate the input functions based on the experimental design into the measured time series may be estimated by Bayesian inversion. For the hemodynamic parameters, the use of a Bayesian framework has

the major advantage that it allows to incorporate prior knowledge about biophysically plausible ranges for the different parameters controlling the hemodynamic response such as vessel stiffness or transit time (Friston et al. 2003; Stephan et al. 2007a). For the neuronal parameters, in turn, shrinkage priors are employed, that is, the a priori expected effective connectivity for any connection in the model is zero. The precision of these shrinkage priors then determines how much the model is allowed to adapt the parameters to fit the observed data and plays a major role in ensuring model stability. In particular, the larger the model, that is, the more areas it contains, the higher the danger of activity *spiraling up* and the model becoming instable (Friston et al. 2003). Consequently, the precision of the shrinkage prior increases with model size, making the model more conservative as now the prior expectation of zero, that is, no connectivity, has a higher influence on the posterior parameter estimates.

#### 17.6.1.2 Model Comparison

Bayesian model inversion does not only provide estimates (posterior densities) for the model parameters but also an approximation to the log evidence of the model for the observed data. This log evidence can be used to compare alternative DCMs of the same data, that is, to decide between alternative hypotheses on the architecture of the neuronal interactions underlying an observed pattern of activation (Penny et al. 2004). This formal approach to comparing different hypothesis on the model structure has been conceptualized as one of the major advantages of DCM over other approaches to effective connectivity.

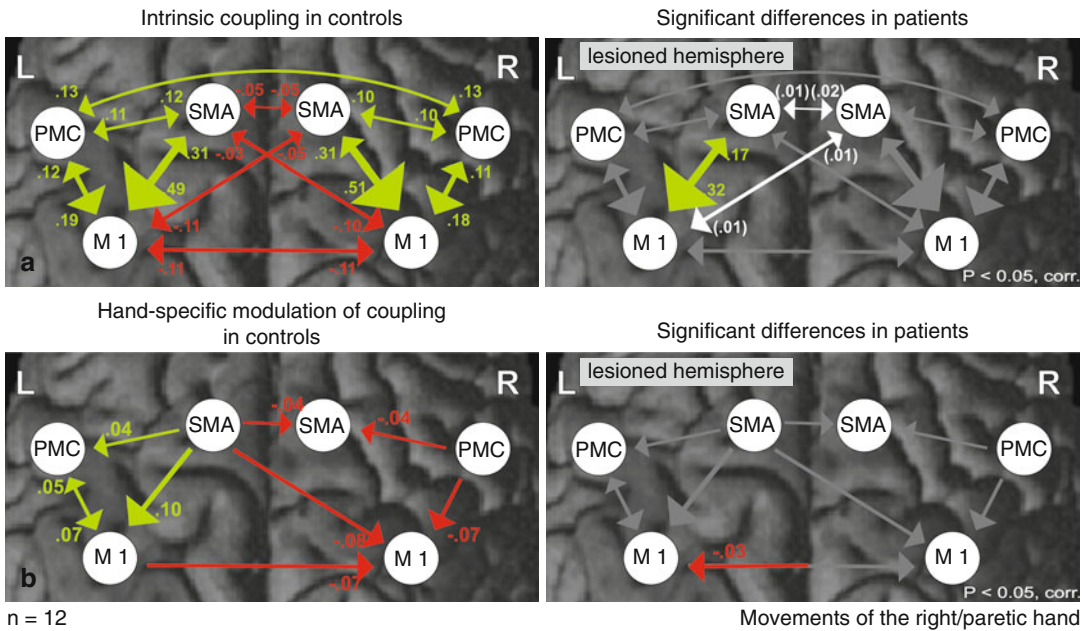
#### 17.6.1.3 Deterministic and Stochastic Models

As noted above, perturbation is especially important in the classical formulation of DCM (Friston et al. 2003), as here the modeled neuronal network is considered completely deterministic and only driven by external inputs without which it would remain idle. Without such driving input, however, the system would stay and remain at rest. More recent developments, however, have added stochastic behavior and may thus alleviate

the strong dependency of DCM analyses on the experimental manipulation and the assumption that neural population dynamics may be correctly captured from the modeled inputs (Daunizeau et al. 2009). In spite of these revisions, the mainstay of DCM analyses is still the modeling of task-specific contextual influences aiming at an interpretation of functional neuroimaging data in terms of the underlying connectivity patterns. As such, the model and its parameters obviously are strongly conditioned on the performed experimental task and its particular setup. DCM thus primarily represents as a tool providing an additional layer of insight into the causes of regionally specific activation patterns rather than revealing information about functional connectivity patterns that go beyond the particular experiment. In other words, DCM represents the most confirmative modeling approach currently available for effective connectivity modeling in healthy subjects and patients. However, it must be remembered that confirmatory models of connectivity like DCM strongly depend on a priori assumptions, for example, on the included regions, the assessed model space and finally the assumptions underlying the modeling approach itself such as the form of the hemodynamic priors.

#### 17.6.1.4 Application: Modeling Effective Connectivity in the Motor System

Models of effective connectivity like DCM can be used to explain activation patterns observed in conventional fMRI analyses. As shown in Fig. 17.1, simple unilateral hand movements elicit a typical lateralized activation pattern with highest BOLD activity in contralateral primary motor cortex (M1). Patients with motor deficits due to a brain lesion resulting from stroke show several changes in neural activity during movements of the affected hand, especially in the unaffected hemisphere. Applying DCM to the dataset of healthy subjects reveals that neural coupling among key motor areas is symmetrically organized (Fig. 17.5a). Estimating the constant part of connectivity, that is, coupling irrespective of moving the left or right hand (DCM A matrix), reveals that motor areas such



**Fig. 17.5** Connectivity among motor regions in healthy subjects and patients with hemiparesis caused by subcortical stroke. Coupling parameters (rate constants in 1/s) indicate connection strength, which is also coded in the size and color of the *arrows* representing effective connectivity. Positive (*green*) values represent facilitatory, negative (*red*) values inhibitory influences on neuronal activity. The greater the absolute value, the more predominant the effect one area has over another. (a) Neural coupling in healthy subjects: In healthy subjects, the intrinsic coupling of motor areas is well balanced within and across hemispheres, while movements of the right hand induce a hemispheric-specific modulation of interregional coupling.

as the supplementary motor area (SMA), lateral premotor cortex (PMC), and primary motor cortex (M1) show a strong positive coupling with each other, especially between SMA and M1 (Grefkes et al. 2008a). The interhemispheric coupling parameters between left and right M1 are negative, suggesting mutual inhibition in the absence of a particular hand movement (Fig. 17.5a). In contrast, moving the left or the right hand induces a side-specific modulation of interregional connectivity. Neural coupling is strongly enhanced in the hemisphere contralateral to the moving hand, while ipsilateral areas, especially ipsilateral M1, are inhibited (Fig. 17.5b). Patients suffering from stroke-induced motor deficits in the subacute phase (i.e., in the first few weeks and months poststroke)

(b) Significant changes of coupling parameters in stroke patients. *Gray arrows* denote no significant difference to healthy control subjects, while *white arrows* indicate a loss of coupling in the patient group. Patients with subcortical stroke show a significant reduction in intrinsic SMA-M1 coupling in the lesioned hemisphere and a decoupling of ipsilesional areas from contralesional SMA (*white arrows*). Movements of the paretic hand are associated with a pathological inhibition of ipsilesional M1 exerted by contralesional M1, which does not occur in healthy subjects and correlate with the motor deficit of the paretic hand (adapted from Grefkes et al. 2008b, with permission)

show several changes in this pattern of “normal” cortical connectivity within and across hemispheres (Grefkes et al. 2008b). Especially endogenous (i.e., movement-independent) coupling between ipsilesional SMA and ipsilesional M1 is significantly reduced compared to healthy control subjects (Fig. 17.5a, right panel). Importantly, the amount of *hypoconnectivity* between SMA and M1 correlates with the individual motor deficit, suggesting that reduced motor performance may—at least to some extent—be caused by ineffective processing between ipsilesional SMA and M1. Likewise, the negative coupling with contralesional SMA is significantly reduced in the group of stroke patients (Fig. 17.5a, right panel). As these disturbances in effective connectivity are independent from which hand was

moved by the patients, they might explain the finding that the unaffected hand of stroke patients often shows subtle motor deficits when compared to healthy control subjects (Nowak et al. 2007). Apart from changes in movement-independent coupling, the DCM analysis also revealed significant changes in the modulation of interregional coupling evoked by moving the paretic or non-paretic hand. While in healthy subjects contralateral M1 exerts an inhibitory influence on M1 activity ipsilateral to the moving hand, stroke patients show an additional inhibitory influence on ipsilesional M1 originating from contralesional M1, which is not present in healthy subjects or when patients move their unaffected hand (Fig. 17.5b, right panel). Importantly, the strength of this pathological inhibition from contralesional M1 correlates with the motor impairment of the paretic hand (Grefkes et al. 2008b). This means that especially in patients with stronger motor deficits, ipsilesional M1 activity is negatively influenced by contralesional M1 which exerts a detrimental effect upon motor performance of the paretic hand. Reducing contralesional M1 excitability by means of repetitive transcranial magnetic stimulation (rTMS) is associated with a significant reduction of pathological coupling between contralesional and ipsilesional M1 compared to an rTMS control stimulation site (Grefkes et al. 2010). In addition, intrinsic neural coupling between ipsilesional SMA and ipsilesional M1 is significantly enhanced after rTMS applied over contralesional M1, and the increase in coupling correlates with the increase in motor performance of the paretic hand (Grefkes et al. 2010). Hence, a focal stimulation by means of TMS does not only alter connectivity of the region stimulated but also of areas distant to the stimulation site. This also implies that behavioral effects evolving after stimulation are based on a remodeling of the whole network rather than being caused by excitability changes of a single motor region. In particular, a more effective integration of ipsilesional M1 into the motor network architecture might constitute a key factor for improving motor performance of stroke patients by means of rTMS (Grefkes et al. 2010).

## 17.7 Conclusion

A connectivity-based approach of analyzing functional imaging data allows hypothesis-driven investigations of the interactions among brain regions under physiological and pathological conditions. In contrast to *classical* voxel-wise analyses of fMRI data aimed at localizing neural activity, models of connectivity make use of a network perspective in which the change of neural activity of a given brain region is explained by interactions with other brain regions. In this context, it is important to underline that there is no such thing as *the* connectivity in the brain, but rather several different characteristics may be assessed. Structural, task-based and task-independent functional as well as effective connectivity all focus on different properties and aspects of network properties and may hence inform our knowledge on the physiological and pathological organization of the human brain.

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