www.elsevier.com/locate/euroneuro

REVIEW

Exploring the brain network: A review on resting-state fMRI functional connectivity

Martijn P. van den Heuvel *, Hilleke E. Hulshoff Pol

Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Neuroimaging Division, The Netherlands

Abstract

Our brain is a network. It consists of spatially distributed, but functionally linked regions that continuously share information with each other. Interestingly, recent advances in the acquisition and analysis of functional neuroimaging data have catalyzed the exploration of functional connectivity in the human brain. Functional connectivity is defined as the temporal dependency of neuronal activation patterns of anatomically separated brain regions and in the past years an increasing body of neuroimaging studies has started to explore functional connectivity by measuring the level of co-activation of resting-state fMRI time-series between brain regions. These studies have revealed interesting new findings about the functional connections of specific brain regions and local networks, as well as important new insights in the overall organization of functional communication in the brain network. Here we present an overview of these new methods and discuss how they have led to new insights in core aspects of the human brain, providing an overview of these novel imaging techniques and their implication to neuroscience. We discuss the use of spontaneous resting-state fMRI in determining functional connectivity, discuss suggested origins of these signals, how functional connections tend to be related to structural connections in the brain network and how functional brain communication may form a key role in cognitive performance. Furthermore, we will discuss the upcoming field of examining functional connectivity patterns using graph theory, focusing on the overall organization of the functional brain network. Specifically, we will discuss the value of these new functional connectivity tools in examining believed connectivity diseases, like Alzheimer's disease, dementia, schizophrenia and multiple sclerosis.
© 2010 Elsevier B.V. and ECNP. All rights reserved.

1. Introduction

Our brain is a network. A very efficient network to be precise. It is a network of a large number of different brain regions that each have their own task and function, but who are continuously sharing information with each other. As such, they form a complex integrative network in which information

* Corresponding author. Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Heidelberglaan 100, 3508 GA Utrecht, PO BOX 85500, The Netherlands. Tel.: +31 88 75 58244; fax: +31 88 75 55443.
E-mail address: M.P.vandenheuvel@umcutrecht.nl (M.P. van den Heuvel).

is continuously processed and transported between structurally and functionally linked brain regions: the brain network.

In the past three decades, a rich history of structural and functional neuroimaging studies have provided an incredible amount of knowledge about the primate and human brain, especially about the role and function of each brain region. Interestingly, recent advances in functional neuroimaging have provided new tools to measure and examine functional interactions between brain regions, catalyzing the examination of functional connectivity in the human brain. Functional connectivity is defined as the temporal dependence of neuronal activity patterns of anatomically separated brain regions (Aertsen et al., 1989; Friston et al., 1993) and studies have been shown the feasibility of examining functional connectivity between brain regions as the level of co-activation of functional MRI time-series measured during rest (Lowe et al., 2000).

Examining the human brain as an integrative network of functionally interacting brain regions can provide new insights about large-scale neuronal communication in the human brain. It provides a platform to examine how functional connectivity and information integration relates to human behavior and how this organization may be altered in neurodegenerative diseases (Bullmore and Sporns, 2009; Greicius, 2008). In the past few years, novel neuroimaging techniques and analysis methods have enabled the examination of whole-brain functional connectivity patterns, enabling the *in vivo* examination of functional connectivity on a whole-brain scale. These studies have examined the level of co-activation between the functional time-series of anatomically separated brain regions during rest, using so-called resting-state functional Magnetic Resonance Imaging, believed to reflect functional communication between brain regions (Biswal et al., 1995; Damoiseaux et al., 2006; Greicius et al., 2003; Salvador et al., 2005a). This review provides an overview of these new imaging and analysis techniques and their implication to neuroscience. We discuss the most commonly used resting-state fMRI acquisition and analysis techniques, discuss how functional connections are likely to relate to white matter structural tracts and how these resting-state fMRI techniques can be used to examine specific as well as whole-brain functional connectivity patterns. Furthermore, we will discuss the upcoming field of applied graph analytical approaches of resting-state data, enabling the exploration of the overall organization of functional communication channels within the brain network. We discuss how the efficiency of functional communication between brain regions might form a new framework to examine complex behavior in the human brain, reviewing recent studies on a direct link between overall functional communication efficiency and cognitive ability. Furthermore, we discuss how resting-state functional connectivity can be used to examine hypothesized disconnectivity effects in neurodegenerative and psychiatric brain diseases.

2. Functional connectivity: resting-state fMRI

Our brain is a complex network of functionally and structurally interconnected regions. Functional communication between brain regions is likely to play a key role in complex cognitive processes, thriving on the continuous

integration of information across different regions of the brain. This makes the examination of functional connectivity in the human brain of high importance, providing new important insights in the core organization of the human brain. Functional connectivity is defined as the temporal dependency between spatially remote neurophysiological events (Aertsen et al., 1989; Friston et al., 1993). In the context of functional neuroimaging, functional connectivity is suggested to describe the relationship between the neuronal activation patterns of anatomically separated brain regions, reflecting the level of functional communication between regions. Interestingly, around 15 years after the invention of fMRI, studies started to examine the possibility of measuring functional connectivity between brain regions as the level of co-activation of spontaneous functional MRI time-series, recorded during rest (Biswal et al., 1997; Greicius et al., 2003; Lowe et al., 2000). During these resting-state experiments, volunteers were instructed to relax and not to think of something in particular, while their level of spontaneous brain activity was measured throughout the period of the experiment. Biswal and colleagues were the first to demonstrate that during rest the left and right hemispheric regions of the primary motor network are not silent, but show a high correlation between their fMRI BOLD time-series (Biswal et al., 1995; Biswal et al., 1997), suggesting ongoing information processing and ongoing functional connectivity between these regions during rest (Biswal et al., 1997; Cordes et al., 2000; Greicius et al., 2003; Lowe et al., 2000). In their study (schematically illustrated in Fig. 1), the resting-state time-series of a voxel in the motor network was correlated with the resting-state time-series of all other brain voxels, revealing a high correlation between the spontaneous neuronal activation patterns of these regions. Several studies have replicated these pioneering results, showing a high level of functional connectivity between the left and right hemispheric motor cortex, but also between regions of other known functional networks, like the primary visual network, auditory network and higher order cognitive networks (Biswal et al., 1997; Cordes et al., 2002; Cordes et al., 2000; Damoiseaux et al., 2006; De Luca et al., 2005; Fox and Raichle, 2007; Greicius et al., 2003; Lowe et al., 2000; Lowe et al., 1998; Van den Heuvel et al., 2008a; Xiong et al., 1999). These studies mark that during rest the brain network is not idle, but rather shows a vast amount of spontaneous activity that is highly correlated between multiple brain regions (Buckner et al., 2008; Buckner and Vincent, 2007; Greicius, 2008). To summarize, resting-state fMRI experiments are focused on mapping functional communication channels between brain regions by measuring the level of correlated dynamics of fMRI time-series.

3. Origin of spontaneous resting-state fMRI signals

Of special interest are the low frequency oscillations (~0.01–0.1 Hz) of resting-state fMRI time-series (Biswal et al., 1995; Biswal et al., 1997; Cordes et al., 2001; Lowe et al., 2000; Lowe et al., 1996). The true neuronal basis of these low frequency resting-state fMRI oscillations is not yet fully understood and in the past years there has been an ongoing debate on whether these resting-state BOLD signals result from physiological processes, like respiratory and
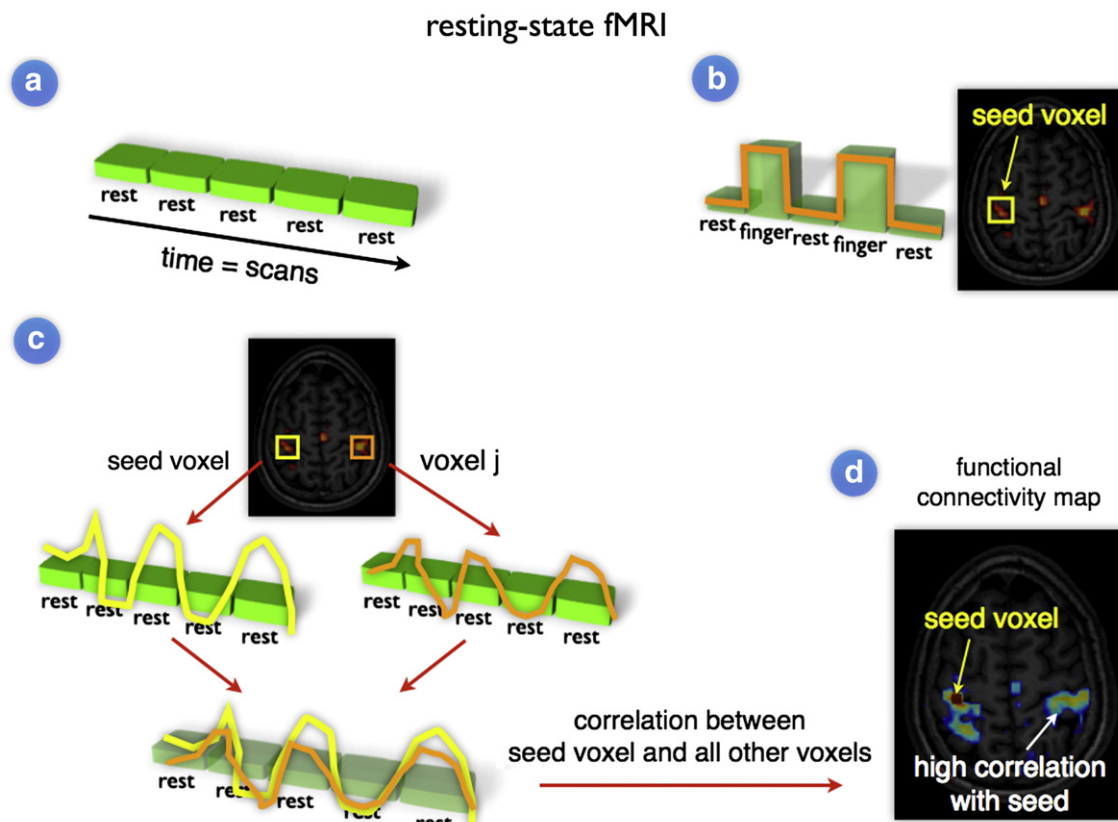
resting-state fMRI

Figure 1   Resting-state fMRI studies are focused on measuring the correlation between spontaneous activation patterns of brain regions. Within a resting-state experiment, subjects are placed into the scanner and asked to close their eyes and to think of nothing in particular, without falling asleep. Similar to conventional task-related fMRI, the BOLD fMRI signal is measured throughout the experiment (*panel a*). Conventional task-dependent fMRI can be used to select a seed region of interest (*panel b*). To examine the level of functional connectivity between the selected seed voxel i and a second brain region j (for example a region in the contralateral motor cortex), the resting-state time-series of the seed voxel is correlated with the resting-state time-series of region j (*panel c*). A high correlation between the time-series of voxel i and voxel j is reflecting a high level of functional connectivity between these regions. Furthermore, to map out all functional connections of the selected seed region, the time-series of the seed voxel i can be correlated with the time-series of all other voxels in the brain, resulting in a functional connectivity map that reflects the regions that show a high level of functional connectivity with the selected seed region (*panel d*).

cardiac oscillations (Birn et al., 2006; Birn et al., 2008; Chang et al., 2009; Shmueli et al., 2007; Wise et al., 2004) or whether these correlations originate from co-activation in the underlying spontaneous neuronal activation patterns of these regions, measured through a hemodynamic response function (Buckner and Vincent, 2007; Greicius et al., 2003; Gusnard et al., 2001). Typically, fMRI protocols have a low temporal resolution (common acquisition rate of 2–3 s per scan, i.e. 0.5 Hz), causing high frequent respiratory and cardiac oscillations to be aliased back into the lower resting-state frequencies (0.01–0.1 Hz). As a result, these higher frequent cardiac and respiratory patterns might shape the BOLD time-series of anatomically separate brain regions in a similar way, introducing artificial correlations between the time-series of these regions (Birn et al., 2006; Birn et al., 2008; Chang et al., 2009; Shmueli et al., 2007; van Buuren et al., 2009; Wise et al., 2004). However, support for a possible neuronal basis of resting-state fMRI signals comes from the observation that most of the resting-state patters tend to occur between brain regions that overlap in both function and neuroanatomy, for example regions of the motor, visual

and auditory network (Biswal et al., 1995; Damoiseaux et al., 2006; De Luca et al., 2005; Lowe et al., 2000; Salvador et al., 2005a; Van den Heuvel et al., 2008a). This observation suggests that brain regions that often have to work together form a functional network during rest, with a high level of ongoing spontaneous neuronal activity that is strongly correlated between the anatomically separated regions that form the network. Further support for a neuronal basis of resting-state fMRI signals comes from studies who report that the observed spontaneous BOLD signals are mainly dominated by lower frequencies (< 0.1 Hz) with only a minimal contribution of higher frequent cardiac and respiratory oscillations (> 0.3 Hz) (Cordes et al., 2001; Cordes et al., 2000). Cardiac and respiratory oscillations have been reported to have a different frequency pattern and therefore a different frequency related influence on resting-state correlations than the low frequencies of interest in (0.01–0.1 Hz) (Cordes et al., 2001; Cordes et al., 2000). Furthermore, support for a neuronal basis of resting-state fMRI recordings comes from studies reporting on an (indirect) association between the amplitude profiles of resting-state

fMRI correlations and electrophysiological recordings of neuronal firing (Nir et al., 2008) and from studies showing a strong association between spontaneous BOLD fluctuations and simultaneous measured fluctuations in neuronal spiking (Shmuel and Leopold, 2008; Shmuel et al., 2002). Taken together, more and more studies are in support of a neuronal basis of the resting-state fMRI signal. As a result, the general discussion tends to shift to *to what extent* resting-state fMRI patterns are confounded by non-neural oscillations, like cardiac and respiratory oscillations, rather than if resting-state fMRI patterns reflect ongoing neuronal activation and functional connectivity *at all*. However, this does not mean that resting-state fMRI time-series are solely reflecting co-activation of brain regions during rest. Influences of non-neuronal patterns can still influence and corrupt the resting-state signal and methods to reduce the influence of these signals are becoming more and more standard in the preprocessing of resting-state fMRI signals (Birn et al., 2008; Chang et al., 2009; van Buuren et al., 2009). These methods include the subtraction of physiological signals out of the resting-state fMRI signal by monitoring physiological patterns during scanning and/or regressing non-gray matter signals out of the fMRI signal (Weissenbacher et al., 2009), as well as the use of high sampling rates to prevent aliasing of high frequencies into the lower resting-state frequencies of interest (Cordes et al., 2001; Cordes et al., 2000; Van den Heuvel et al., 2008a,b,c).

In general, a fast growing body of neuroimaging studies support the notion that resting-state BOLD fluctuations of cortical and sub-cortical regions originate, at least in part, from spontaneous neuronal activity and that the observed temporal correlation between fMRI time-series of anatomically separated regions is reflecting a level of ongoing functional connectivity between brain regions during rest (Buckner and Vincent, 2007; Greicius et al., 2003; Gusnard et al., 2001). This makes spontaneous resting-state fMRI oscillations a robust measure to examine functional connections between brain regions on a whole-brain scale.

4. How to process resting-state fMRI data

Several methods to process resting-state fMRI data, examining the existence and extent of functional connections between brain regions, have been proposed, including seed methods (Andrews-Hanna et al., 2007; Biswal et al., 1995; Cordes et al., 2000; Fransson, 2005; Larson-Prior et al., 2009; Song et al., 2008), principal component analysis (PCA) (Friston et al., 1993), singular value decomposition (Worsley et al., 2005), independent component analysis (Beckmann et al., 2005; Calhoun et al., 2001; van de Ven et al., 2004) and clustering (Cordes et al., 2002; Salvador et al., 2005a; Thirion et al., 2006; Van den Heuvel et al., 2008a). Roughly, resting-state fMRI methods can be placed into two groups: model-dependent and model-free methods.

4.1. Model-dependent methods: seed method

The most straightforward way to examine the functional connections of a particular brain region is to correlate the resting-state time-series of the depicted brain region against the time-series of all other regions, resulting in a functional connectivity map (fcMap) defining the functional connections of the predefined brain region (Fig. 1) (Biswal et al., 1997; Cordes et al., 2000; Jiang et al., 2004). This region of interest is typically called *seed*. A seed can be *a priori* defined region or it can be selected from a traditional task-dependent activation map acquired in a separate fMRI experiment, pinpointing a specific region of interest. For example, if the focus of interest is on examining the functional connections of the left primary motor cortex, one can use a task-dependent fMRI experiment (Fig. 1) in which the volunteers are instructed to move their right hand, selecting the most activated voxels along the left precentral gyrus as the seed area. Next, resting-state time-series of the selected seed region can be correlated with the resting-state time-series of all other voxels (Fig. 1), resulting in a *functional connectivity map* (fcMap). The resulting fcMap provides information about with which regions the selected primary motor seed region is functionally linked and to what extent. The relative simplicity of this analysis forms a strong advantage of seed-dependent methods, together with the straight forwardness of the results (Buckner and Vincent, 2007). Functional connectivity maps provide a clear view of with which regions the seed region is functionally connected, making it an elegant way of examining functional connectivity in the human brain. However, the information of a fcMap is limited to the functional connections of the selected seed region, making it difficult to examine functional connections patterns on a whole-brain scale.

4.2. Model-free methods

To examine whole-brain connectivity patterns, model-free methods have been introduced, enabling the exploration of connectivity patterns without the need of defining an *a priori* seed region. In contrast to seed-based methods, model-free methods are designed to look for general patterns of (unique) connectivity across brain regions. Several model-free methods have been suggested and successfully applied to resting-state time-series, including principal component analysis (PCA) (Friston, 1998), independent component analysis (ICA) (Beckmann et al., 2005; Calhoun et al., 2001; De Luca et al., 2006; van de Ven et al., 2004) and hierarchical (Cordes et al., 2002; Salvador et al., 2005a), Laplacian (Thirion et al., 2006) and normalized cut clustering (Van den Heuvel et al., 2008a). ICA-based methods (Beckmann et al., 2005; Calhoun et al., 2001; De Luca et al., 2006; van de Ven et al., 2004) are perhaps the most commonly used and have been reported to show a high level of consistency (Damoiseaux et al., 2006). ICA methods are designed to search for a mixture of underlying sources that can explain the resting-state patterns, looking for the existence of spatial sources of resting-state signals that are maximally independent from each other. ICA methods for resting-state fMRI are powerful methods as they can be applied to whole-brain voxel-wise data and as the temporal signals of the independent resting-state components can be easily selected for further examination of possible group differences between healthy controls and patients. A possible disadvantage of ICA methods might include that the independent components are often perceived as more difficult to understand than traditional seed-dependent fcMaps, as they contain a more

complex representation of the data, which could complicate the translation of between-group results to clinical relevance (Fox and Raichle, 2007). In addition to ICA-based approaches, a number of clustering strategies have been applied to resting-state fMRI time-series. Clustering involves the grouping of datapoints into a sub-group that show a high level of similarity and grouping datapoints into different subsets that show a low level of similarity (Salvador et al., 2005a; Van den Heuvel et al., 2008a). Clustering is aimed at maximizing the level of similarity between datapoints, grouping connected points into non-overlapping sub-clusters. As such, clustering results may be more comparable to traditional fcMap results, as they more directly reflect functional connections between brain regions. On the other hand, ICA has the strong advantage of enabling direct comparison between subject groups, while clustering methods generally need additional seed-like processing steps to compare functional connectivity between patients and healthy volunteers. Nevertheless, although all having their advantages and disadvantages, ICA, clustering and seed methods tend to show a high level of overlap (Fig. 2). For example, group ICA resting-state fMRI studies have consistently reported the formation of the so-called default mode network during rest (Beckmann et al., 2005; Damoiseaux et al., 2007; Damoiseaux et al., 2006), which have been extensively confirmed by both seed-based (Greicius et al., 2003; Whitfield-Gabrieli et al., 2009) and clustering approaches (Van den Heuvel et al., 2008a,b). Furthermore, ongoing functional connectivity in the primary motor network, originally revealed by seed-based analysis (Biswal et al., 1995; Cordes et al., 2001; Xiong et al., 1999), have been extensively verified by ICA and clustering methods (Beckmann et al., 2005; Damoiseaux et al., 2006; Salvador et al., 2005b; Van den Heuvel et al., 2008a). Similarly, intrinsic functional connectivity between primary visual and auditory regions has been found by all three methods, as well functional connectivity between regions of well known frontal-parietal attentional networks. Taken together, seed-based, ICA-based and clustering-based methods all tend to show strong overlap between their results, supporting the notion of the robust formation of multiple functionally linked networks in the human brain during resting-state.

5. Functionally linked brain regions: resting-state networks

Group resting-state studies have reported the formation of strongly functionally linked sub-networks during rest, networks that are often referred to as *resting-state networks*
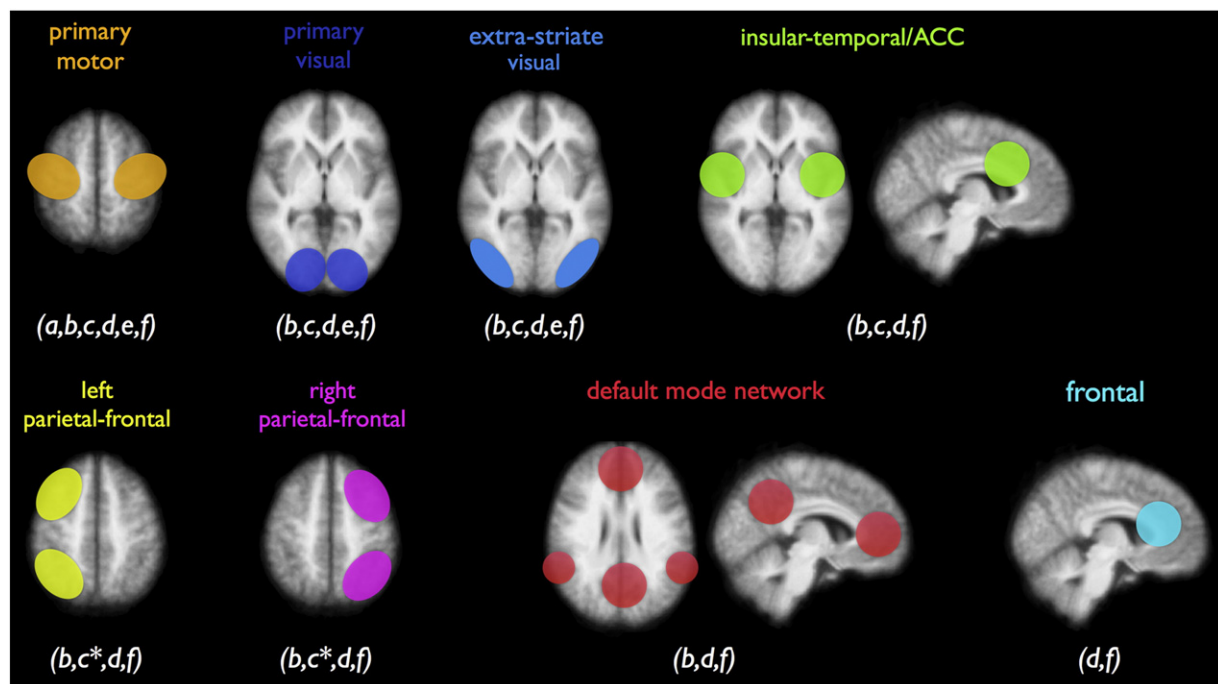
Figure 2 Resting-state networks. A number of group resting-state studies have consistently reported the formation of functionally linked resting-state networks during rest. These studies, although all using different groups of subjects, different methods (e.g. seed, ICA or clustering) (Beckmann et al., 2005; Biswal et al., 1995; Damoiseaux et al., 2006; De Luca et al., 2006; Salvador et al., 2005a; Van den Heuvel et al., 2008a) and different types of MR acquisition protocols, show large overlap between their results, indicating the robust formation of functionally linked resting-state networks in the brain during rest. This figure shows the most consistent reported resting-state networks across these studies, including the primary sensorimotor network, the primary visual and extra-striate visual network, a network consisting of bilateral temporal/insular and anterior cingulate cortex regions, left and right lateralized networks consisting of superior parietal and superior frontal regions (*reported as one single network) and the so-called *default mode network consisting of precuneus, medial frontal, inferior parietal cortical regions and medial temporal lobe*. The figure illustrates resting-state networks reported by the following studies: (a) Biswal et al. (1995), (b) Beckmann et al. (2005), (c) De Luca et al. (2006), (d) Damoiseaux et al. (2006), (e) Salvador et al. (2005a), and (f) Van den Heuvel et al. (2008a).

(Beckmann et al., 2005; Damoiseaux et al., 2006; Fox and Raichle, 2007; Fox et al., 2005). These resting-state networks consist of anatomically separated, but functionally linked brain regions that show a high level of ongoing functional connectivity during rest. Up until now, neuroimaging studies have identified around eight functionally linked sub-networks (Beckmann et al., 2005; Damoiseaux et al., 2006; De Luca et al., 2006; Fransson, 2005; Salvador et al., 2005a; van de Ven et al., 2004; Van den Heuvel et al., 2008a). Fig. 2 illustrates the most often reported resting-state networks, describing networks of anatomically separated brain regions that show a high level of functionally connectivity during rest. These networks include the motor network, the visual network, two lateralized networks consisting of superior parietal and superior frontal regions, the so-called default mode network consisting of precuneus, medial frontal and inferior parietal and temporal regions (Buckner and Vincent, 2007; Fox and Raichle, 2007; Fox et al., 2005; Fransson, 2005; Greicius et al., 2003; Gusnard et al., 2001; Raichle et al., 2001; Raichle and Snyder, 2007) and a network consisting of bilateral temporal/insular and anterior cingulate cortex regions (Fig. 2). Although using a variety of MR scanners (multiple vendors, multiple field strengths 1.5, 3 T, 4 T) and analysis techniques (seed methods, independent component analysis, clustering) these studies show large overlap between their reported networks, demonstrating the robust formation of resting-state networks during rest (Fig. 2).

Interestingly, most of these resting-state networks tend to represent known functional networks, overlapping regions that are known to share a common function, supporting the functional relevance of these networks. They overlap the primary motor regions, the primary visual regions and parietal–frontal networks involved in attention processing (Biswal et al., 1995; Cordes et al., 2000; De Luca et al., 2006) (Damoiseaux et al., 2006; Fox et al., 2005). Interestingly, recently studies have suggested that not only wide-scale functional networks are formed, but that resting-state networks may show an internal topology that is strongly organized to their sub-functions. Whole-brain voxel-wise analysis have distinguished the formation of sub-networks within the full visual network, separating a sub-network overlapping primary visual regions from a sub-network overlapping extra-striate visual regions (Beckmann et al., 2005; Damoiseaux et al., 2006; Van den Heuvel et al., 2008a). Furthermore, the functional connections within the primary motor resting-state network have been reported to be ordered according to the somatotopic organization of the precentral gyrus, suggesting the formation of functionally linked somatotopic sub-networks within the primary motor network (Van den Heuvel and Hulshoff Pol, 2010). Together these findings tend to suggest that, at least one class of functional connectivity during rest may indicate ongoing connectivity between regions that have an overlapping function. Neurons are well known to show a high level of spontaneous firing in the absence of performing a task, continuously transporting information to other neurons. In this context, it may be reasonable to speculate about the idea that functional connectivity may aid to keep functional systems in an active state, helping to improve performance and their reaction time whenever functional connectivity is needed. Indeed, recent studies have suggested that long

term motor training may significantly increase resting-state activity within primary motor regions (Xiong et al., 2008).

Of special interest is the so-called *default mode network*, a network consisting of functionally linked posterior cingulate cortex/precuneus, medial frontal and inferior parietal regions (Fig. 2). In contrast to the other resting-state networks, the regions of the *default mode network* are known to show an elevated level of neuronal activity during rest, in comparison to when (cognitive) tasks are performed, suggesting that activity of this network is reflecting a *default state* of neuronal activity of the human brain (Gusnard et al., 2001; Raichle et al., 2001; Raichle and Snyder, 2007). Furthermore, these increased levels of neuronal activity tend to be strongly correlated during rest, forming one integrative functionally interconnected resting-state network (Greicius et al., 2003). Activity and connectivity of the default mode network have been linked to core process of human cognition, including the integration of cognitive and emotional processing (Greicius et al., 2003), monitoring the world around us (Gusnard et al., 2001) and mind-wandering (Mason et al., 2007). This makes default mode activation and connectivity of special interest in examining cognitive disfunctioning in neurologic and psychiatric brain disorders (Bullmore and Sporns, 2009; Greicius, 2008) (Harrison et al., 2007; Rombouts et al., 2005) (Garrity et al., 2007; Lowe et al., 2008; Mohammadi et al., 2009; Whitfield-Gabrieli et al., 2009; Zhou et al., 2007b).

6. Functional versus structural connectivity: a structural core of resting-state connectivity

What is supporting this ongoing functional connectivity between these anatomically separated brain regions during rest? Most resting-state networks, like the default mode network and the lateralized attentional parietal-frontal networks, but also the primary motor and visual networks, consist of anatomically separated cortical regions. But how are these anatomically separated brain regions able to stay functionally connected? If resting-state fluctuations truly reflect ongoing neuronal activity and communication between brain regions, one would at least expect the existence of structural connections between these functionally linked brain regions to support the ongoing communication. When we are talking about structural connections in the brain we refer to white matter tracts, describing the bundles of millions of long-distance axons that directly interconnect large groups of spatially separated neurons. White matter tracts are the information highways of the brain, enabling transport of large amount of functional data between spatially separated regions. In this context, when correlation of resting-state fMRI time-series of anatomically separated brain regions is indeed reflecting ongoing interregional functional communication, there should be a structural core of white matter connections facilitating this neuronal communication (Damoiseaux and Greicius, 2009). Recently, a number of studies have indeed suggested a direct association between functional and structural connectivity in the human brain by combining resting-state fMRI with structural diffusion tensor imaging measurements (DTI). DTI is a MRI technique that enables the reconstruction of white matter tracts in the human brain. DTI measures the diffusion profile of free water molecules in brain tissue, which are known to diffuse along a strong preferred

direction in white matter tracts due to the compact layout of axonal bundles. Indeed, concerning a general relationship between functional and structural connectivity, local regions on either side of a sulcus that are structurally connected by short-range fibers were found to also show a high level of functional connectivity (Koch et al., 2002). Furthermore, also on a global whole-brain scale, regions with a higher level of structural connectivity have been reported to show a higher level of functional connectivity (Hagmann et al., 2008; Honey et al., 2007; Honey et al., 2009). Focusing on the default mode network, specific white matter tracts have been suggested to structurally interconnected the functionally linked regions of this network (Greicius et al., 2008). Combining resting-state fMRI recordings with DTI data identified an important role for the cingulum tract in interconnecting the key regions of the default mode network, verifying the direct structural axonal connections between the posterior cingulate cortex and medial frontal cortex known from animal studies (Lawes et al., 2008; Schmahmann et al., 2007; Wakana et al., 2004). Moreover, the microstructural organization of these white matter tracts was found to be directly related to the level of functional connectivity between these regions (Van den Heuvel et al., 2008b). Besides suggesting an important role for the cingulum in the default mode network, also the medial temporal lobe and posterior cingulate cortex, other regions of the default mode network have been found to be interconnected by structural white matter tracts, suggesting a more general link between structural and functional connectivity within the default mode network and resting-state networks in general (Greicius et al., 2008). Indeed, a recent study showed that almost all functionally linked regions of the most often reported resting-state networks are structurally interconnected by known white matter tracts (Van den Heuvel et al., 2009). This suggests the existence of a general structural core of resting-state networks, supporting the notion of an overall link between structural and functional connectivity on a whole-brain scale (Damoiseaux and Greicius, 2009; Hagmann et al., 2008; Honey et al., 2009). However, although the functional and structural organization of the brain network are likely to be linked, we by no means try to suggest that it is a one-to-one relationship; their exact relationship remains unknown (Bullmore and Sporns, 2009). The structural brain network needs to facilitate a vast amount of functional configurations, but how this is achieved remains unknown. This calls for future structural and functional network studies to examine how the structural brain network is able to support fast changing functional activation patterns of functional networks (Bullmore and Sporns, 2009).

# 7. Examining the organization of the brain network

7.1. Graph analysis

Up until now the main focus of this review has been on the examination of *specific* functional connections between *specific* cortical regions. However, recently, new advances in resting-state analysis techniques have shown the possibility of examining the overall structure of the brain network, still with a high level of spatial detail, using graph analytical methods. Interestingly, these studies have shown that,

besides the formation of multiple resting-state networks, the human brain forms one integrative complex network, linking all brain regions and sub-networks together into one complex system. Examining the overall organization of this network can provide new valuable insights in how the human brain operates. How are the functional connections between brain regions organized? How efficiently can the brain integrate information between different sub-systems? And are there brain regions that have a specialized role in this efficient communication? Graph theory provides a theoretical framework in which the topology of complex networks can be examined, and can reveal important information about both the local and global organization of functional brain networks (Bullmore and Sporns, 2009; Sporns et al., 2004; Stam et al., 2009; Stam and Reijneveld, 2007).

Using graph theory, functional brain networks can be defined as a graph $G = (V,E)$, with V the collection of *nodes* reflecting the brain regions, and E the functional *connections* between these brain regions. Fig. 3 provides a schematic figure of a graph representation of the functional brain network. Within such a graph theoretical framework, the nodes of the brain network can be represented as (sub)cortical regions, which can be a small number of large-scale brain regions based on a predefined cortical template (e.g. Brodmann template) or fMRI voxels, or a hybrid approach somewhere in between. Second, the level of functional connectivity between two regions is computed as the level of correlation between the time-series of the two brain regions (Fig. 3b). Computing the level of functional connectivity between all possible node-pairs and determining the existence of a functional connection by using a predefined cut-off threshold or by using a weighted approach, results in a graph representation of the functional brain network and allows for the examination of its organization using graph theory (Fig. 3c).

Graph theory has been extensively used to examine the properties of complex networks like the internet, aircraft flight patterns and biological systems, collecting key information about their organization. Fig. 4 explains the notion of a graph and some of its key graph properties, including the clustering-coefficient, characteristic path length, node degree and degree distribution, centrality and modularity (Reijneveld et al., 2007; Sporns et al., 2004; Stam and Reijneveld, 2007). The clustering-coefficient of a graph provides information about the level of local neighborhood clustering within a graph, expressing how close the neighbors of node are connected themselves. This indicates the level of local connectedness of a graph (Fig. 4b). Furthermore, the characteristic path length of a graph describes how close on average a node of the network is connected to every other node in the network, providing information about the level of global connectivity of the network and about how efficient information can be integrated between different systems (Fig. 4c). The degree of a node describes the number of connections of a node (Fig. 4d) and provides information about the existence of highly connected *hub nodes* in the brain network. Important additional information of the formation of *hubs* in networks comes from centrality measures, indicating how many of the shortest travel routes within a network pass through a specific node of the network. If a node has a high level of centrality , it facilitates a large number of shortest routes in the network, indicating
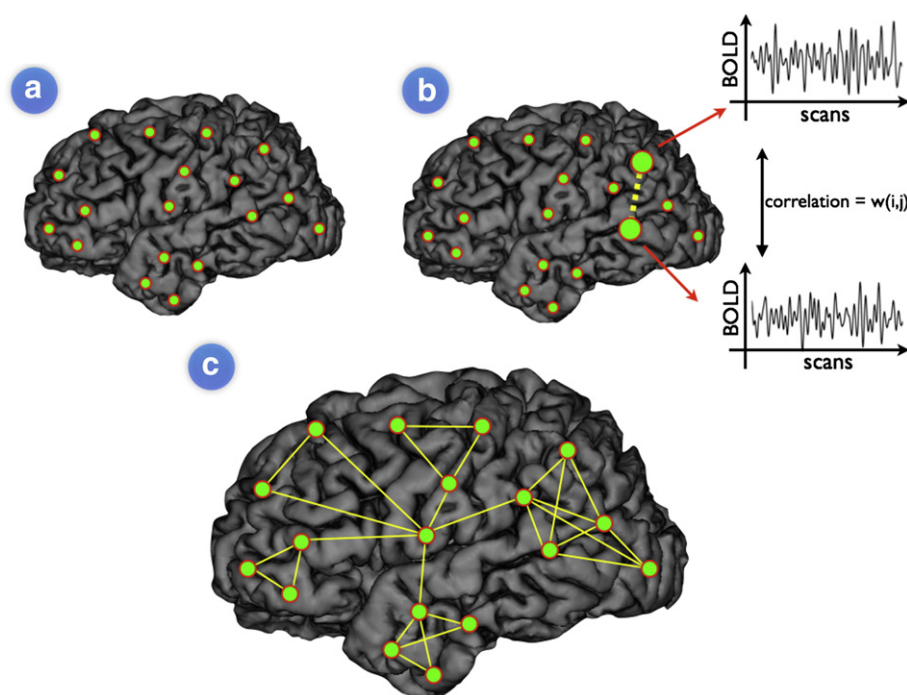
Figure 3   Modeling the functional brain network. The functional connected brain network can be represented as a graph, consisting of nodes, and edges (or connections) between regions that are functionally linked. First, the collection of nodes is defined. These can be brain regions, defined by a preselected template of brain regions, for example the Brodmann Areas (*panel a*). Second, the existence of functional connections between the nodes in the network needs to be defined, indicating the level of interaction between the nodes of the network. Within resting-state fMRI studies, the level of co-activation between brain regions is used as a measure of connectivity, defined by the level of correlation between the resting-state fMRI time-series. Within a graph approach, the level of functional connectivity between each possible pair of nodes in the network is computed (i.e. between all possible regions or voxel pairs), resulting in a connectivity matrix (*panel b*). Finally, the existence of a connection between two points can be defined as whether their level of functional connectivity exceeds a certain predefined threshold. This results in modeling the brain as a functional network with connections between regions that are functionally linked (*panel c*).

that it has a key role in the overall communication efficiency of a network. Furthermore, the level of modularity (Fig. 4e) of a graph describes to which extent groups of nodes in the graph are connected to the members of their own group, indicating the formation of sub-networks within the full network. All together, these graph values provide important information about the structure of a network and may mark a specific organization, like a small-world, scale-free and/or modular organization (see Fig. 5). The use of graph theory on neuroimaging data is an upcoming field and more and more graph organizational measures are designed and tested for their potential use in examining the functional and structural connectome of the brain (Rubinov and Sporns, 2009) (Bullmore and Sporns, 2009).

7.2. Applying graph analysis to resting-state fMRI: exploring the functional brain network

A number of pioneering studies have applied advanced graph analysis techniques to resting-state fMRI data (Achard and Bullmore, 2007; Achard et al., 2006; Eguiluz et al., 2005; Liu et al., 2008; Salvador et al., 2005b; Van den Heuvel et al., 2008c; van den Heuvel et al., 2009), revealing new insights about the general organization of functional brain networks. These resting-state fMRI studies have indicated a very

efficient organization of functional connectivity during rest (Achard et al., 2006; Watts and Strogatz 1998), supporting the findings of MEG and EEG studies (Bassett et al., 2006; Micheloyannis et al., 2006a; Stam, 2004). Together, these studies show that the brain network is organized according to an efficient *small-world* organization (Fig. 5a). Small-world networks are known for their high level of local connectedness, but still with a very short average travel distance (i.e. low path length) between the nodes of the network. As such, this organization combines a high level local efficiency with a high level of global efficiency. Recent studies have supported these findings, showing an efficient organization of the human brain network on both a regional (Achard and Bullmore, 2007; Liu et al., 2008) as well as on a voxel-scale (Eguiluz et al., 2005; Van den Heuvel et al., 2008c). Furthermore, it has also been suggested that connectivity distribution of the functional brain network is different from that of a random network, suggesting that within the functional brain network some nodes (i.e. brain regions) have many more connections than other nodes. Regional studies, using a predefined anatomical template to define the nodes of the network as brain regions, have indicated that the probability of a node having k connections follows an exponential truncated power-law (Achard et al., 2006; Liu et al., 2008). Moreover, voxel-based studies, defining the brain network as a detailed network of voxels, have even
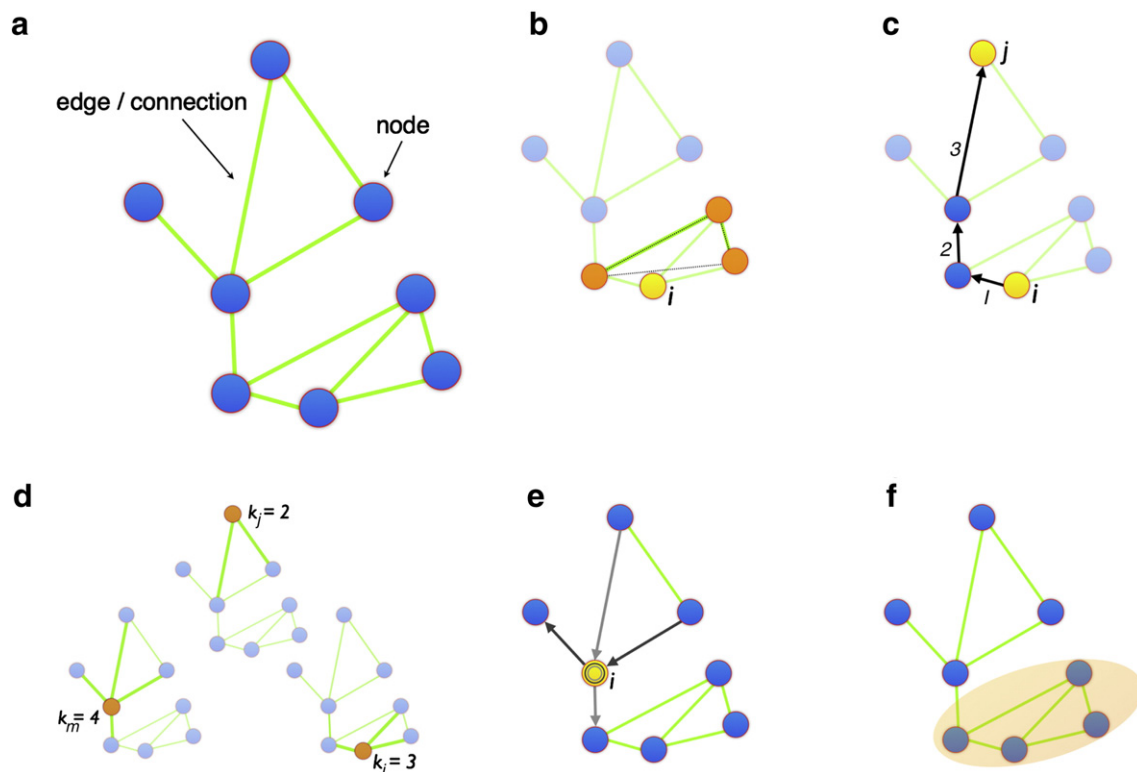
Figure 4 Graph characteristics: a graph, clustering-coefficient, characteristic path length, connectivity degree, centrality and modularity. A graph (*panel a*). Complex dynamic systems can be represented as graph $G = (V,E)$, with V the collection of nodes and E the collection of edges (connections), describing the interactions between the nodes. *Clustering-coefficient (panel b)*. The clustering-coefficient of node i provides information about the level of local connectedness in the graph and is given by the ratio of the number of connections between the direct neighbors of node i and the maximum number of possible connections between the neighbors of node i. The clustering-coefficient provides information about the level of local connectedness of the graph. *Characteristic path length (panel c)*. The characteristic path length of node i provides information about how close node i is connected to all other nodes in the network and is given by the distance $d(i,j)$ between node i and all other nodes j in the network. Distance $d(i,j)$ can be defined as the number of connections that have to be crossed to travel from node i to node j in the graph. Path length L provides important information about the level of global communication efficiency of a network. *Centrality (panel d)*. The level of (betweenness) centrality of a node i indicates how many of the shortest paths between the nodes of the network pass through node i. A high betweenness centrality indicates that this node is important in interconnecting the nodes of the network, marking a potential hub role of this node in the overall network. *Node degree (panel e)*. The degree of node i is defined as its total number of connections. The degree probability distribution $P(k)$ describes the probability that a node is connected to k other nodes in the network. *Modularity (panel f)*. The modularity of a graph describes the possible formation of communities in the network, indicating how strong groups of nodes form relative isolated sub-networks within the full network.

suggested a possible power-law function of the connectivity distribution, marking a possible scale-free organization of functional brain networks (Fig. 5b) (Eguiluz et al., 2005; Fraiman et al., 2009; Van den Heuvel et al., 2008c). Scale-free networks and exponentially truncated power-law networks are known for their high level of resilience against random attack, indicating a very robust network organization, making them an interesting model for the functional brain network (Barabasi and Albert, 1999; Barabasi and Bonabeau, 2003). However, a scale-free organization is vulnerable to specialized attacks on the connected hub nodes. This suggests a possible specialized attack on hub nodes in brain connectivity diseases. Graph analysis of resting-state fMRI data have revealed a number of highly connected hub-regions in the human brain and it has been hypothesized that these specialized hub nodes may be affected in Alzheimer's disease, resulting in decreased functional brain efficiency in these patients (Buckner et al., 2009). Indeed, recent MEG results have suggested that specialized attack on brain hub nodes may result in reduced network efficiency as observed in Alzheimer's patients (Stam et al., 2009). Taken together, graph analysis of resting-state time-series have suggested an efficient organization of functional communication in the brain network, indicating that the human brain is not just a random network, but one with an organization optimized towards a high level of local and global efficiency.

8. Linking functional connectivity to cognition

A number of recent studies have suggested a direct link between resting-state functional connectivity patterns and
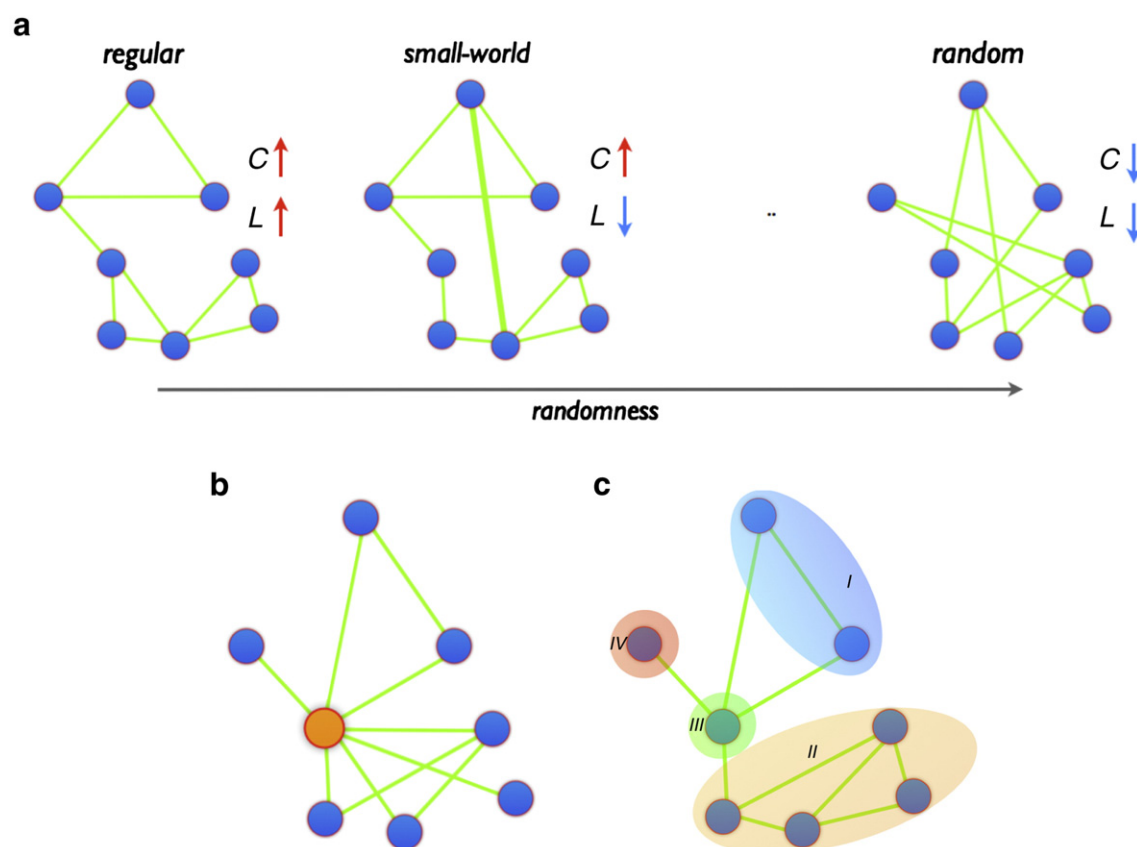
Figure 5 Network topologies: regular, random, small-world, scale-free and modular networks. The organizational characteristics of a graph provide important information about the organization of a network. A regular network (*panel a, left*) has a rather local character, characterized by a high clustering-coefficient C (Fig. 4a) and a high path length L (Fig. 4b), taking a large number of steps to travel from a specific node to a node on the other end of the graph. However, distributing all connections randomly across the network results in a graph with a random organization (*panel a, right*). In contrast to the local character of the regular network, a random network has a more global character, with a low C and a much shorter path length L than the regular network. Interestingly, Watts and Strogatz (1998) showed that with a low probability p of randomly reconnecting a connection in the regular network, a so-called small-world organization arises, with both a high C and a low L, combining a high level of local clustering with still a short average travel distance in the overall network. Small-world networks mark a special topology as they are shown to be very robust and combine a high level of local and global efficiency. Many networks in nature have been marked as small-world, including the internet, protein-networks, social networks and recent studies have also indicated such an efficient organization of the functional and structural brain network, combining a high level of segregation with a high level of global information integration. In addition, Barabasi et al. showed that networks can have a heavy tailed connectivity distribution, in contrast to random networks in which the nodes roughly all have the same number of connections (Barabasi and Albert, 1999; Barabasi and Bonabeau, 2003). Scale-free networks are characterized by a degree probability distribution that follows a power-law function, indicating that on average a node has only a few connections, but with the exception of a small number of nodes that are heavily connected (*panel b*). These nodes are often referred to as hub nodes and they play a central role in the level of efficiency of the network, as they are responsible for keeping the overall travel distance in the network to a minimal. As these hub nodes play a key role in the organization of the network, scale-free networks tend to be vulnerable to specialized attack on the hub nodes. In addition, networks can show the formation of so-called communities, consisting of a subset of nodes that are mostly connected to their direct neighbors in their community and to a lesser extend to the other nodes in the network. Such networks are referred to as modular networks (*panel c*) and are characterized by a high level of modularity of the nodes (Fig. 4, *panel f*).

human cognition. The main focus of these studies has been on the examination of cognitive behavior in relation to specific resting-state networks, mostly the default mode network. Activity and connectivity of the default mode network has been suggested to be involved in the integration of cognitive and emotional processing (Greicius et al., 2003) and monitoring the world around us (Gusnard et al., 2001). Furthermore, higher levels of activity of the default mode network has been linked to an increased occurrence of stimulus independent thoughts (Mason et al., 2007). The default mode network is likely to be related to a wide range of high order cognitive functions and several possible functions of the default mode network have been suggested, often based on functional properties of the network in combination with its specific structural network structure of linked associative brain regions (Buckner et al., 2008; Buckner and Vincent, 2007). Suggested functions of the default mode network include the support of internal mental

processing detached from the external world, linking stored personal experiences with thinking about future events and evaluating alternative perspectives for the present and a special role in monitoring the external world (Gusnard et al., 2001) (Buckner et al., 2008; Buckner and Vincent, 2007).

Furthermore, in addition to linking functional activity and functional connectivity of the default mode network to cognitive behavior, recent studies have explored the relationship between the overall topology of functional brain networks and cognitive ability, using a graph theoretical approach (see section 7). The organization of a network is directly related to its efficiency, as the topology defines its level of robustness, capability to integrate information and communication capacity (Achard and Bullmore, 2007; Bullmore and Sporns, 2009; Buzsaki and Draguhn, 2004; Chen et al., 2006; Grigorov, 2005; Latora and Marchiori, 2001; Mathias and Gopal, 2001). Indeed, recent studies have suggested a link between the efficient organization of the brain network and intellectual performance. Focusing on specific functional connections, the level of functional connectivity of the dorsolateral prefrontal cortex has been found to be predicative for intellectual performance (Song et al., 2008). Furthermore, supporting a neural efficiency hypothesis of intellectual performance, a recent study has suggested a positive relationship between the level of efficiency of functional brain networks and IQ, showing that the most efficient organized brain networks belonged to the most intelligent people (van den Heuvel et al., 2009). Interestingly, as these studies were based on resting-state fMRI recordings, and not acquired during the performance of a task that enters into the IQ score, this may mark functional connectivity patterns as a powerful predictor for cognitive performance. Indeed, supporting an information integration efficiency hypothesis of intelligence (Jung and Haier, 2007; Neubauer and Fink, 2009; van den Heuvel et al., 2009), EEG findings have indicated that higher educated participants have on average a shorter path length than lower educated subjects (Micheloyannis et al., 2006b). Further support comes from structural studies, showing that the quality of white matter tracts between associative brain regions is associated with intellectual performance (Chiang et al., 2009), as well as the level of overall organization of white matter tracts between brain regions (Li et al., 2009). Taken together, although it is too early to be conclusive, these preliminary studies support the notion that the efficiency of functional and structural connectivity patterns in the human brain may be related to cognitive performance. Interestingly, the critical role of a short path length in cortical networks has been noted before, showing that structural cortical networks are optimized towards a short average travel distance, due to the existence of important long-distance projections (Kaiser and Hilgetag, 2006). This suggests that the human brain is optimized towards a high level of information integration, possibly leading towards to a high IQ (van den Heuvel et al., 2009). In conclusion, graph theoretical studies of functional resting-state fMRI data have marked that the human brain is organized according to a highly efficient and cost-effective small-world topology with an optimization towards an high level of information processing and information integration across the different sub-systems of the brain network.

9. Functional connectivity and neurological and psychiatric brain disorders

A growing body of studies are exploring the use of resting-state fMRI techniques in examining possible functional disconnectivity effects in neurologic and psychiatric brain disorders, including Alzheimer's disease (Greicius et al., 2004; Rombouts et al., 2005), depression (Greicius et al., 2007), dementia (Rombouts et al., 2009) and schizophrenia (Liu et al., 2008; Whitfield-Gabrieli et al., 2009; Bluhm et al., 2007; Garrity et al., 2007). Most of these studies have been focused on the default mode network, but recent studies have started to examine the overall organization of the functional brain network using graph analysis techniques. Furthermore, also altered levels of functional connectivity in other neurogenerative brain diseases, like multiple sclerosis (MS) (Lowe et al., 2008) and amyotrophic lateral sclerosis (ALS) (Mohammadi et al., 2009) have been reported, reporting changed functional connectivity in default mode network as well as in other resting-state networks. Together, these studies suggest that neurodegenerative diseases are targeting interconnected cortical networks, rather than single regions (Seeley et al., 2009).

Alzheimer's disease has been linked to decreased default mode functional connectivity. Using an ICA approach, studies have shown decreased resting-state activity in the PCC and hippocampus, suggesting a decreased participation of these regions in the default mode network in Alzheimer's patients (Greicius et al., 2004). In support, Alzheimer's patients have been reported to show decreased deactivation of the default mode network in the processing of attentional information, suggesting decreased resting-state activity and decreased adaptation of the default mode network in comparison to healthy controls (Rombouts et al., 2005). Furthermore, a resting-state fMRI graph analysis study revealed a decreased overall clustering of the brain network of Alzheimer's patients in comparison to age-matched healthy controls, suggesting decreased efficiency of local information processing in Alzheimer's disease (Supekar et al., 2008). These findings are in support of resting-state functional connectivity MEG studies, reporting on decreased brain network integrity and efficiency in Alzheimer's disease (de Haan et al., 2008; Stam et al., 2009).

From almost the beginning of its definition, schizophrenia has been marked as a potential disconnection disease (Bleuler, 1911; Kraepelin, 1919). Schizophrenia is a severe psychiatric disease that is characterized by delusions and hallucinations, loss of emotion and disrupted thinking. Widespread functional disconnectivity between brain regions has been suggested to underlie these symptoms (Andreasen et al., 1998; Friston, 1998; Friston and Frith, 1995). Schizophrenia is known to have aberrant effects on gray and white matter, with the most strong effects in frontal and parietal regions (Hulshoff Pol et al., 2004; Hulshoff Pol et al., 2001; van Haren et al., 2007), regions that overlap with the regions of the default mode network. Therefore, examining the default state and the organization of the functional brain network of schizophrenic patients can provide new insights in impaired brain communication and functional connectivity in schizophrenia (Bassett et al., 2008; Bluhm et al., 2007; Kim et al., 2005; Kim et al., 2003;

Zhou et al., 2007a; Garrity et al., 2007). Indeed, recent studies have indicated aberrant default mode functional connectivity in schizophrenic patients, reporting on a decrease in functional connectivity between medial frontal cortex and precuneus, key regions of this network (Bluhm et al., 2007; Whitfield-Gabrieli et al., 2009). Interestingly, also altered levels of white matter integrity have been reported in schizophrenia (Kubicki et al., 2007; Kubicki et al., 2005; Mandl et al., 2008), including decreased levels of micro-structural organization in the cingulum tract (Nestor et al., 2007; Sun et al., 2003). In particular, as the white matter cingulum tract is known to interconnect the MFC and PCC regions of the default mode network (Greicius et al., 2008; Van den Heuvel et al., 2008b), changed levels of default mode functional connectivity and altered integrity of the cingulum could play an interactive role in schizophrenia. Furthermore, studies have also marked spatial differences in the default mode network in schizophrenia patients together with significant higher frequency fluctuations in default mode regions (Garrity et al., 2007), as well as hyperactivity and hyperconnectivity of the default mode network in patients in the early phase of schizophrenia (Whitfield-Gabrieli et al., 2009). These studies suggest an important role for the default mode network in the pathophysiology of schizophrenia (Whitfield-Gabrieli et al., 2009). Functional disconnectivity in schizophrenia could be expressed in altered connectivity of specific functional connections and/or functional networks, but it could also be related to a changed organization of the functional brain network. Indeed, schizophrenia patients have been suggested to show a decreased level of overall brain network efficiency, suggesting aberrant information integration between regions of the brain network in schizophrenic patients (Liang et al., 2006; Liu et al., 2008; Micheloyannis et al., 2006a). These studies have marked an important role for graph analysis in the examination of brain network alterations in schizophrenia. Especially, examining the brain network in high spatial detail could provide new insights in which brain regions have a differentiating role in the overall network organization in schizophrenic patients in comparison to healthy controls.

As mentioned, also in other degenerative brain diseases altered functional connectivity patterns have been reported. Examining the link between functional and structural connectivity in multiple sclerosis (MS) indicated a direct link between decreased resting-state functional connectivity of regions of the primary motor network and decreased microstructural organization of the interconnecting callosal white matter tracts (Lowe et al., 2008). This marks that decreases in white matter integrity can directly have an effect on functional connectivity within the primary motor network. Furthermore, using ICA analysis, studies have suggested decreased functional connectivity in patients with amyotrophic lateral sclerosis (ALS) (Mohammadi et al., 2009).

These studies, aimed at either specific networks or overall functional connectivity organization, suggest that altered resting-state functional connectivity patterns occur in a wide variety of neurodegenerative diseases. These studies show the importance of examining neurodegenerative diseases as conditions that target large-scale interconnected functional and structural brain networks, rather than separate brain regions (Seeley et al., 2009).

10. Conclusion

Our brain is a complex integrative network of functionally linked brain regions. Multiple spatially distributed, but functionally linked brain regions continuously share information with each other, together forming interconnected resting-state communities. With the use of resting-state fMRI we can explore the functional connections of the brain network, using seed-based, ICA-based and/or cluster-based methods. Recent studies have shown that functional communication within the human brain is not just random, but organized according to an efficient topology that combines efficient local information processing with efficient global information integration. This integration of information may be facilitated by important hub-regions, as suggested by the observed heavy tailed connectivity distributions of functional brain networks. Interestingly, most pronounced functional connections are found between regions that are known to share a common function, suggesting that resting-state fMRI oscillations may reflect ongoing functional communication between brain regions during rest. Around eight resting-state networks have been consistently reported, overlapping the primary motor, visual and auditory network, the default mode network and known higher order attention networks. Functional connections of resting-state networks tend to be strongly related to structural white matter connections, suggesting the existence of an underlying structural core of functional connectivity networks in the human brain. Recently, the use of graph theory in combination with resting-state fMRI has provided a new platform to explore the overall structure of local and global functional connectivity in the human brain. In conclusion, recent resting-state fMRI studies examining functional connectivity between brain regions have revealed new fundamental insights in the organization of the human brain and provide a new and promising platform to examine hypothesized disconnectivity effects in neurologic and psychiatric brain diseases.

Role of the funding source

Contributors

MP and HE designed and wrote the manuscript.

Conflict of interest

The authors have no conflict of interest to report

References

Achard, S., Bullmore, E., 2007. Efficiency and cost of economical brain functional networks. PLoS Comput. Biol. 3 (2), e17.

Achard, S., Salvador, R., Whitcher, B., Suckling, J., Bullmore, E., 2006. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. J. Neurosci. 26 (1), 63–72.

Aertsen, A.M., Gerstein, G.L., Habib, M.K., Palm, G., 1989. Dynamics of neuronal firing correlation: modulation of "effective connectivity". J. Neurophysiol. 61 (5), 900–917.

Andreasen, N.C., Paradiso, S., O'Leary, D.S., 1998. "Cognitive dysmetria" as an integrative theory of schizophrenia: a dysfunction in cortical–subcortical–cerebellar circuitry? Schizophr. Bull. 24 (2), 203–218.

Andrews-Hanna, J.R., Snyder, A.Z., Vincent, J.L., Lustig, C., Head, D., Raichle, M.E., Buckner, R.L., 2007. Disruption of large-scale brain systems in advanced aging. Neuron 56 (5), 924–935.

Barabasi, A.L., Albert, R., 1999. Emergence of scaling in random networks. Science 286 (5439), 509–512.

Barabasi, A.L., Bonabeau, E., 2003. Scale-free networks. Sci. Am. 288 (5), 60–69.

Bassett, D.S., Meyer-Lindenberg, A., Achard, S., Duke, T., Bullmore, E., 2006. Adaptive reconfiguration of fractal small-world human brain functional networks. Proc. Natl. Acad. Sci. U. S. A. 103 (51), 19,518–19,523.

Bassett, D.S., Bullmore, E., Verchinski, B.A., Mattay, V.S., Weinberger, D.R., Meyer-Lindenberg, A., 2008. Hierarchical organization of human cortical networks in health and schizophrenia. J. Neurosci. 28 (37), 9239–9248.

Beckmann, C.F., DeLuca, M., Devlin, J.T., Smith, S.M., 2005. Investigations into resting-state connectivity using independent component analysis. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 360 (1457), 1001–1013.

Birn, R.M., Diamond, J.B., Smith, M.A., Bandettini, P.A., 2006. Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. Neuroimage 31 (4), 1536–1548.

Birn, R.M., Smith, M.A., Jones, T.B., Bandettini, P.A., 2008. The respiration response function: the temporal dynamics of fMRI signal fluctuations related to changes in respiration. Neuroimage 40 (2), 644–654.

Biswal, B., Yetkin, F.Z., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. 34 (4), 537–541.

Biswal, B.B., Van Kylen, J., Hyde, J.S., 1997. Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. NMR Biomed. 10 (4–5), 165–170.

Bleuler, 1911. Dementia Praecox or the Group of Schizophrenias. International Universities Press, New York.

Bluhm, R.L., Miller, J., Lanius, R.A., Osuch, E.A., Boksman, K., Neufeld, R., Theberge, J., Schaefer, B., Williamson, P., 2007. Spontaneous low-frequency fluctuations in the BOLD signal in schizophrenic patients: anomalies in the default network. Schizophr. Bull. 33, 1004–1012.

Buckner, R.L., Vincent, J.L., 2007. Unrest at rest: default activity and spontaneous network correlations. Neuroimage 37 (4), 1091–1096.

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann. N. Y. Acad. Sci. 1124, 1–38.

Buckner, R.L., Sepulcre, J., Talukdar, T., Krienen, F.M., Liu, H., Hedden, T., Andrews-Hanna, J.R., Sperling, R.A., Johnson, K.A., 2009. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. J. Neurosci. 29 (6), 1860–1873.

Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat. Rev. Neurosci. 10 (3), 186–198.

Buzsaki, G., Draguhn, A., 2004. Neuronal oscillations in cortical networks. Science 304 (5679), 1926–1929.

Calhoun, V.D., Adali, T., Pearlson, G.D., Pekar, J.J., 2001. A method for making group inferences from functional MRI data using independent component analysis. Hum. Brain Mapp. 14 (3), 140–151.

Chang, C., Cunningham, J.P., Glover, G.H., 2009. Influence of heart rate on the BOLD signal: the cardiac response function. Neuroimage 44 (3), 857–869.

Chen, B.L., Hall, D.H., Chklovskii, D.B., 2006. Wiring optimization can relate neuronal structure and function. Proc. Natl. Acad. Sci. U. S. A. 103 (12), 4723–4728.

Chiang, M.C., Barysheva, M., Shattuck, D.W., Lee, A.D., Madsen, S. K., Avedissian, C., Klunder, A.D., Toga, A.W., McMahon, K.L., de Zubicaray, G.I., et al., 2009. Genetics of brain fiber architecture and intellectual performance. J. Neurosci. 29 (7), 2212–2224.

Cordes, D., Haughton, V.M., Arfanakis, K., Wendt, G.J., Turski, P.A., Moritz, C.H., Quigley, M.A., Meyerand, M.E., 2000. Mapping functionally related regions of brain with functional connectivity MR imaging. AJNR Am. J. Neuroradiol. 21 (9), 1636–1644.

Cordes, D., Haughton, V.M., Arfanakis, K., Carew, J.D., Turski, P.A., Moritz, C.H., Quigley, M.A., Meyerand, M.E., 2001. Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. AJNR Am. J. Neuroradiol. 22 (7), 1326–1333.

Cordes, D., Haughton, V., Carew, J.D., Arfanakis, K., Maravilla, K., 2002. Hierarchical clustering to measure connectivity in fMRI resting-state data. Magn. Reson. Imaging 20 (4), 305–317.

Damoiseaux, J.S., Greicius, M.D., 2009. Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. Brain Struct. Funct. 213 (6), 525–533 (Epub 2009 Jun 30).

Damoiseaux, J.S., Rombouts, S.A., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F., 2006. Consistent resting-state networks across healthy subjects. Proc. Natl. Acad. Sci. U. S. A. 103 (37), 13,848–13,853.

Damoiseaux, J.S., Beckmann, C.F., Arigita, E.J., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Rombouts, S.A., 2007. Reduced resting-state brain activity in the "default network" in normal aging. Cereb. Cortex 18 (8), 1856–1864 (Epub 2007 Dec 5).

de Haan, W., Stam, C.J., Jones, B.F., Zuiderwijk, I.M., van Dijk, B. W., Scheltens, P., 2008. Resting-state oscillatory brain dynamics in Alzheimer disease. J. Clin. Neurophysiol. 25 (4), 187–193.

De Luca, M., Smith, S., De Stefano, N., Federico, A., Matthews, P.M., 2005. Blood oxygenation level dependent contrast resting state networks are relevant to functional activity in the neocortical sensorimotor system. Exp. Brain Res. 167 (4), 587–594.

De Luca, M., Beckmann, C.F., De Stefano, N., Matthews, P.M., Smith, S.M., 2006. fMRI resting state networks define distinct modes of long-distance interactions in the human brain. Neuroimage 29 (4), 1359–1367.

Eguiluz, V.M., Chialvo, D.R., Cecchi, G.A., Baliki, M., Apkarian, A.V., 2005. Scale-free brain functional networks. Phys. Rev. Lett. 94 (1), 018102.

Fox, M.D., Raichle, M.E., 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat. Rev. Neurosci. 8 (9), 700–711.

Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D. C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U. S. A. 102 (27), 9673–9678.

Fraiman, D., Balenzuela, P., Foss, J., Chialvo, D.R., 2009. Ising-like dynamics in large-scale functional brain networks. Phys. Rev. E Stat. Nonlin. Soft Matter. Phys. 79 (6 Pt 1), 061922.

Fransson, P., 2005. Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum. Brain Mapp. 26 (1), 15–29.

Friston, K.J., 1998. The disconnection hypothesis. Schizophr. Res. 30 (2), 115–125.

Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome? Clin. Neurosci. 3 (2), 89–97.

Friston, K.J., Frith, C.D., Liddle, P.F., Frackowiak, R.S., 1993. Functional connectivity: the principal-component analysis of large (PET) data sets. J. Cereb. Blood Flow Metab. 13 (1), 5–14.

Garrity, A.G., Pearlson, G.D., McKiernan, K., Lloyd, D., Kiehl, K.A., Calhoun, V.D., 2007. Aberrant "default mode" functional connectivity in schizophrenia. Am. J. Psychiatry 164 (3), 450–457.

Greicius, M., 2008. Resting-state functional connectivity in neuropsychiatric disorders. Curr. Opin. Neurol. 21 (4), 424–430.

Greicius, M.D., Krasnow, B., Reiss, A.L., Menon, V., 2003. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc. Natl. Acad. Sci. U. S. A. 100 (1), 253–258.

Greicius, M.D., Srivastava, G., Reiss, A.L., Menon, V., 2004. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc. Natl. Acad. Sci. U. S. A. 101 (13), 4637–4642.

Greicius, M.D., Flores, B.H., Menon, V., Glover, G.H., Solvason, H. B., Kenna, H., Reiss, A.L., Schatzberg, A.F., 2007. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol. Psychiatry 62, 429–437.

Greicius, M.D., Supekar, K., Menon, V., Dougherty, R.F., 2008. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb. Cortex 19 (1), 72–78 (Epub 2008 Apr 9).

Grigorov, M.G., 2005. Global properties of biological networks. Drug Discov. Today 10 (5), 365–372.

Gusnard, D.A., Raichle, M.E., Raichle, M.E., 2001. Searching for a baseline: functional imaging and the resting human brain. Nat. Rev. Neurosci. 2 (10), 685–694.

Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C.J., Wedeen, V.J., Sporns, O., 2008. Mapping the structural core of human cerebral cortex. PLoS Biol. 6 (7), e159.

Harrison, B.J., Yucel, M., Pujol, J., Pantelis, C., 2007. Task-induced deactivation of midline cortical regions in schizophrenia assessed with fMRI. Schizophr. Res. 91 (1–3), 82–86 (Epub 2007 Feb 16).

Honey, C.J., Kotter, R., Breakspear, M., Sporns, O., 2007. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. Proc. Natl. Acad. Sci. U. S. A. 104 (24), 10,240–10,245.

Honey, C.J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.P., Meuli, R., Hagmann, P., 2009. Predicting human resting-state functional connectivity from structural connectivity. Proc. Natl. Acad. Sci. U. S. A. 106 (6), 2035–2040.

Hulshoff Pol, H.E., Schnack, H.G., Mandl, R.C., van Haren, N.E., Koning, H., Collins, D.L., Evans, A.C., Kahn, R.S., 2001. Focal gray matter density changes in schizophrenia. Arch. Gen. Psychiatry 58 (12), 1118–1125.

Hulshoff Pol, H.E., Schnack, H.G., Mandl, R.C., Cahn, W., Collins, D. L., Evans, A.C., Kahn, R.S., 2004. Focal white matter density changes in schizophrenia: reduced inter-hemispheric connectivity. Neuroimage 21 (1), 27–35.

Jiang, T., He, Y., Zang, Y., Weng, X., 2004. Modulation of functional connectivity during the resting state and the motor task. Hum. Brain Mapp. 22 (1), 63–71.

Jung, R.E., Haier, R.J., 2007. The Parieto-Frontal Integration Theory (P-FIT) of intelligence: converging neuroimaging evidence. Behav. Brain Sci. 30 (2), 135–154 Discussion 154-87.

Kaiser, M., Hilgetag, C.C., 2006. Nonoptimal component placement, but short processing paths, due to long-distance projections in neural systems. PLoS Comput. Biol. 2 (7), e95.

Kim, J.J., Kwon, J.S., Park, H.J., Youn, T., Kang, D.H., Kim, M.S., Lee, D.S., Lee, M.C., 2003. Functional disconnection between the prefrontal and parietal cortices during working memory processing in schizophrenia: a [15(O)]H2O PET study. Am. J. Psychiatry 160 (5), 919–923.

Kim, J.J., Ho Seok, J., Park, H.J., Soo Lee, D., Chul Lee, M., Kwon, J. S., 2005. Functional disconnection of the semantic networks in schizophrenia. Neuroreport 16 (4), 355–359.

Koch, M.A., Norris, D.G., Hund-Georgiadis, M., 2002. An investigation of functional and anatomical connectivity using magnetic resonance imaging. Neuroimage 16 (1), 241–250.

Kraepelin, 1919. Dementia Praecox and Paraphrenia. Livingstone, Edinburgh.

Kubicki, M., McCarley, R.W., Shenton, M.E., 2005. Evidence for white matter abnormalities in schizophrenia. Curr. Opin. Psychiatry 18 (2), 121–134.

Kubicki, M., McCarley, R., Westin, C.F., Park, H.J., Maier, S., Kikinis, R., Jolesz, F.A., Shenton, M.E., 2007. A review of diffusion tensor imaging studies in schizophrenia. J. Psychiatr Res. 41 (1–2), 15–30.

Larson-Prior, L.J., Zempel, J.M., Nolan, T.S., Prior, F.W., Snyder, A.Z., Raichle, M.E., 2009. Cortical network functional connectivity in the descent to sleep. Proc. Natl. Acad. Sci. U. S. A. 106 (11), 4489–4494.

Latora, V., Marchiori, M., 2001. Efficient behavior of small-world networks. Phys. Rev. Lett. 87 (19), 198,701.

Lawes, I.N., Barrick, T.R., Murugam, V., Spierings, N., Evans, D.R., Song, M., Clark, C.A., 2008. Atlas-based segmentation of white matter tracts of the human brain using diffusion tensor tractography and comparison with classical dissection. Neuroimage 39 (1), 62–79.

Li, Y., Liu, Y., Li, J., Qin, W., Li, K., Yu, C., Jiang, T., 2009. Brain anatomical network and intelligence. PLoS Comput. Biol. 5 (5), e1000395.

Liang, M., Zhou, Y., Jiang, T., Liu, Z., Tian, L., Liu, H., Hao, Y., 2006. Widespread functional disconnectivity in schizophrenia with resting-state functional magnetic resonance imaging. Neuroreport 17 (2), 209–213.

Liu, Y., Liang, M., Zhou, Y., He, Y., Hao, Y., Song, M., Yu, C., Liu, H., Liu, Z., Jiang, T., 2008. Disrupted small-world networks in schizophrenia. Brain 131 (4), 945.

Lowe, M.J., Mock, B.J., Sorenson, J.A., 1996. Resting state fMRI signal correlations in multi-slice EPI. Neuroimage 3 (S257).

Lowe, M.J., Mock, B.J., Sorenson, J.A., 1998. Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations. Neuroimage 7 (2), 119–132.

Lowe, M.J., Dzemidzic, M., Lurito, J.T., Mathews, V.P., Phillips, M. D., 2000. Correlations in low-frequency BOLD fluctuations reflect cortico–cortical connections. Neuroimage 12 (5), 582–587.

Lowe, M.J., Beall, E.B., Sakaie, K.E., Koenig, K.A., Stone, L., Marrie, R.A., Phillips, M.D., 2008. Resting state sensorimotor functional connectivity in multiple sclerosis inversely correlates with transcallosal motor pathway transverse diffusivity. Hum. Brain Mapp. 29 (7), 818–827.

Mandl, R.C., Schnack, H.G., Luigjes, J., van den Heuvel, M.P., Cahn, W., Kahn, R.S., Hulshoff Pol, H.E., 2008. Tract-based analysis of magnetization transfer ratio and diffusion tensor imaging of the frontal and frontotemporal connections in schizophrenia. Schizophr. Bull. (2008 November 27, Electronic publication ahead of print).

Mason, M.F., Norton, M.I., Van Horn, J.D., Wegner, D.M., Grafton, S.T., Macrae, C.N., 2007. Wandering minds: the default network and stimulus-independent thought. Science 315 (5810), 393–395.

Mathias, N., Gopal, V., 2001. Small worlds: how and why. Phys. Rev. E Stat. Nonlin. Soft Matter. Phys. 63 (2 Pt 1), 021117.

Micheloyannis, S., Pachou, E., Stam, C.J., Breakspear, M., Bitsios, P., Vourkas, M., Erimaki, S., Zervakis, M., 2006a. Small-world networks and disturbed functional connectivity in schizophrenia. Schizophr. Res. 87 (1–3), 60–66.

Micheloyannis, S., Pachou, E., Stam, C.J., Vourkas, M., Erimaki, S., Tsirka, V., 2006b. Using graph theoretical analysis of multi channel EEG to evaluate the neural efficiency hypothesis. Neurosci. Lett. 402 (3), 273–277.

Mohammadi, B., Kollewe, K., Samii, A., Krampfl, K., Dengler, R., Munte, T.F., 2009. Changes of resting state brain networks in amyotrophic lateral sclerosis. Exp. Neurol. 217 (1), 147–153.

Nestor, P.G., Kubicki, M., Spencer, K.M., Niznikiewicz, M., McCarley, R.W., Shenton, M.E., 2007. Attentional networks and cingulum bundle in chronic schizophrenia. Schizophr. Res. 90 (1–3), 308–315.

Neubauer, A.C., Fink, A., 2009. Intelligence and neural efficiency. Neurosci. Biobehav. Rev. 33 (7), 1004–1023.

Nir, Y., Mukamel, R., Dinstein, I., Privman, E., Harel, M., Fisch, L., Gelbard-Sagiv, H., Kipervasser, S., Andelman, F., Neufeld, M.Y., et al., 2008. Interhemispheric correlations of slow spontaneous neuronal fluctuations revealed in human sensory cortex. Nat. Neurosci. 11 (9), 8.

Raichle, M.E., Snyder, A.Z., 2007. A default mode of brain function: a brief history of an evolving idea. Neuroimage 37 (4), 1083–1090.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proc. Natl. Acad. Sci. U. S. A. 98 (2), 676–682.

Reijneveld, J.C., Ponten, S.C., Berendse, H.W., Stam, C.J., 2007. The application of graph theoretical analysis to complex networks in the brain. Clin. Neurophysiol. 118, 2317–2331.

Rombouts, S.A., Barkhof, F., Goekoop, R., Stam, C.J., Scheltens, P., 2005. Altered resting state networks in mild cognitive impairment and mild Alzheimer's disease: an fMRI study. Hum. Brain Mapp. 26 (4), 231–239.

Rombouts, S.A., Damoiseaux, J.S., Goekoop, R., Barkhof, F., Scheltens, P., Smith, S.M., Beckmann, C.F., 2009. Model-free group analysis shows altered BOLD FMRI networks in dementia. Hum. Brain Mapp. 30 (1), 256–266.

Rubinov, M., Sporns, O., 2009. Complex network measures of brain connectivity: uses and interpretations. Neuroimage (2009 October 9, Electronic publication ahead of print).

Salvador, R., Suckling, J., Coleman, M.R., Pickard, J.D., Menon, D., Bullmore, E., 2005a. Neurophysiological architecture of functional magnetic resonance images of human brain. Cereb. Cortex 15 (9), 1332–1342.

Salvador, R., Suckling, J., Schwarzbauer, C., Bullmore, E., 2005b. Undirected graphs of frequency-dependent functional connectivity in whole brain networks. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 360 (1457), 937–946.

Schmahmann, J.D., Pandya, D.N., Wang, R., Dai, G., D'Arceuil, H.E., de Crespigny, A.J., Wedeen, V.J., 2007. Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. Brain 130 (Pt 3), 630–653.

Seeley, W.W., Crawford, R.K., Zhou, J., Miller, B.L., Greicius, M.D., 2009. Neurodegenerative diseases target large-scale human brain networks. Neuron 62 (1), 42–52.

Shmuel, A., Leopold, D.A., 2008. Neuronal correlates of spontaneous fluctuations in fMRI signals in monkey visual cortex: implications for functional connectivity at rest. Hum. Brain Mapp. 29 (7), 751–761.

Shmuel, A., Yacoub, E., Pfeuffer, J., Van de Moortele, P.F., Adriany, G., Hu, X., Ugurbil, K., 2002. Sustained negative BOLD, blood flow and oxygen consumption response and its coupling to the positive response in the human brain. Neuron 36 (6), 1195–1210.

Shmueli, K., van Gelderen, P., de Zwart, J.A., Horovitz, S.G., Fukunaga, M., Jansma, J.M., Duyn, J.H., 2007. Low-frequency fluctuations in the cardiac rate as a source of variance in the resting-state fMRI BOLD signal. Neuroimage 38 (2), 306–320.

Song, M., Zhou, Y., Li, J., Liu, Y., Tian, L., Yu, C., Jiang, T., 2008. Brain spontaneous functional connectivity and intelligence. Neuroimage 41 (3), 1168–1176.

Sporns, O., Chialvo, D.R., Kaiser, M., Hilgetag, C.C., 2004. Organization, development and function of complex brain networks. Trends Cogn. Sci. 8 (9), 418–425.

Stam, C.J., 2004. Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network? Neurosci. Lett. 355 (1–2), 25–28.

Stam, C.J., Reijneveld, J.C., 2007. Graph theoretical analysis of complex networks in the brain. Nonlinear Biomed. Phys. 1 (1), 3.

Stam, C.J., de Haan, W., Daffertshofer, A., Jones, B.F., Manshanden, I., van Cappellen van Walsum, A.M., Montez, T., Verbunt, J.P., de Munck, J.C., van Dijk, B.W., et al., 2009. Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer's disease. Brain 132 (Pt 1), 213–224.

Sun, Z., Wang, F., Cui, L., Breeze, J., Du, X., Wang, X., Cong, Z., Zhang, H., Li, B., Hong, N., et al., 2003. Abnormal anterior cingulum in patients with schizophrenia: a diffusion tensor imaging study. Neuroreport 14 (14), 1833–1836.

Supekar, K., Menon, V., Rubin, D., Musen, M., Greicius, M.D., 2008. Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. PLoS Comput. Biol. 4 (6), e1000100.

Thirion, B., Dodel, S., Poline, J.B., 2006. Detection of signal synchronizations in resting-state fMRI datasets. Neuroimage 29 (1), 321–327.

van Buuren, M., Gladwin, T.E., Zandbelt, B.B., van den Heuvel, M., Ramsey, N.F., Kahn, R.S., Vink, M., 2009. Cardiorespiratory effects on default-mode network activity as measured with fMRI. Hum. Brain Mapp. 30 (9), 3031–3042.

van de Ven, V.G., Formisano, E., Prvulovic, D., Roeder, C.H., Linden, D.E., 2004. Functional connectivity as revealed by spatial independent component analysis of fMRI measurements during rest. Hum. Brain Mapp. 22 (3), 165–178.

Van den Heuvel, M.P., Hulshoff Pol, H.E., 2010. Specific somatotopic organization of functional connections of the primary motor network during resting-state. Hum. Brain Mapp. 31 (4), 631–644.

Van den Heuvel, M.P., Mandl, R.C., Hulshoff Pol, H.E., 2008a. Normalized group clustering of resting-state fMRI data. PLoS ONE 3 (4), e2001.

Van den Heuvel, M.P., Mandl, R.C., Luigjes, J., Hulshoff Pol, H.E., 2008b. Microstructural organization of the cingulum tract and the level of default mode functional connectivity. J. Neurosci. 43 (28), 7.

Van den Heuvel, M.P., Stam, C.J., Boersma, M., Hulshoff Pol, H.E., 2008c. Small-world and scale-free organization of voxel based resting-state functional connectivity in the human brain. Neuroimage 43 (3), 11.

van den Heuvel, M.P., Stam, C.J., Kahn, R.S., Hulshoff Pol, H.E., 2009. Efficiency of functional brain networks and intellectual performance. J. Neurosci. 29 (23), 7619–7624.

Van den Heuvel, M.P., Mandl, R.C.W., Kahn, R.S., Hulshoff Pol, H.E., 2009. Functionally linked resting state networks reflect the underlying structural connectivity architecture of the human brain. Hum. Brain Mapp. 30 (10), 3127–3141.

van Haren, N.E., Hulshoff Pol, H.E., Schnack, H.G., Cahn, W., Mandl, R.C., Collins, D.L., Evans, A.C., Kahn, R.S., 2007. Focal gray matter changes in schizophrenia across the course of the illness: a 5-year follow-up study. Neuropsychopharmacology 32 (10), 2057–2066.

Wakana, S., Jiang, H., Nagae-Poetscher, L.M., van Zijl, P.C., Mori, S., 2004. Fiber tract-based atlas of human white matter anatomy. Radiology 230 (1), 77–87.

Watts, D.J., Strogatz, S.H., 1998. Collective dynamics of 'small-world' networks. Nature 393 (6684), 440–442.

Weissenbacher, A., Kasess, C., Gerstl, F., Lanzenberger, R., Moser, E., Windischberger, C., 2009. Correlations and anticorrelations in resting-state functional connectivity MRI: a quantitative comparison of preprocessing strategies. Neuroimage 47 (4), 1408–1416.

Whitfield-Gabrieli, S., Thermenos, H.W., Milanovic, S., Tsuang, M.T., Faraone, S.V., McCarley, R.W., Shenton, M.E., Green, A.I., Nieto-Castanon, A., Laviolette, P., et al., 2009. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. Proc. Natl. Acad. Sci. U. S. A 106 (4), 1279–1284.

Wise, R.G., Ide, K., Poulin, M.J., Tracey, I., 2004. Resting fluctuations in arterial carbon dioxide induce significant low frequency variations in BOLD signal. Neuroimage 21 (4), 1652–1664.

Worsley, K.J., Chen, J.I., Lerch, J., Evans, A.C., 2005. Comparing functional connectivity via thresholding correlations and singular

value decomposition. Philos. Trans. R. Soc. Lond. B. Biol. Sci. 360 (1457), 913–920.

Xiong, J., Parsons, L.M., Gao, J.H., Fox, P.T., 1999. Interregional connectivity to primary motor cortex revealed using MRI resting state images. Hum. Brain Mapp. 8 (2–3), 151–156.

Xiong, J., Ma, L., Wang, B., Narayana, S., Duff, E.P., Egan, G.F., Fox, P.T., 2008. Long-term motor training induced changes in regional cerebral blood flow in both task and resting states. Neuroimage 45 (1), 75–82.

Zhou, Y., Liang, M., Jiang, T., Tian, L., Liu, Y., Liu, Z., Liu, H., Kuang, F., 2007a. Functional dysconnectivity of the dorsolateral prefrontal cortex in first-episode schizophrenia using resting-state fMRI. Neurosci. Lett. 417 (3), 297–302.

Zhou, Y., Liang, M., Tian, L., Wang, K., Hao, Y., Liu, H., Liu, Z., Jiang, T., 2007b. Functional disintegration in paranoid schizophrenia using resting-state fMRI. Schizophr. Res. 97 (1–3), 194–205.