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

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Introduction

- **Functional connectivity** is defined as the temporal dependence of neuronal activity patterns of anatomically separated brain regions.
- 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.

Functional connectivity: resting-state fMRI

- 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.
- Several studies have showed a high level of functional connectivity between the left and right hemispheric motor cortex, primary visual network, auditory network and higher order cognitive networks.

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.
- 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).
- Support for a possible neuronal basis comes from (1) the observation that most of the resting-state patters tend to occur between brain regions that overlap in both function and neuroanatomy, and (2) that the observed spontaneous BOLD signals are mainly dominated by lower frequencies (< 0.1 Hz).

Origin of spontaneous resting-state fMRI signals

- Furthermore, Shmuel and Leopold (2008) showed a strong association between spontaneous BOLD fluctuations and simultaneous measured fluctuations in neuronal spiking.
- 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.
- High sampling rates to prevent aliasing of high frequencies into the lower resting-state frequencies of interest.

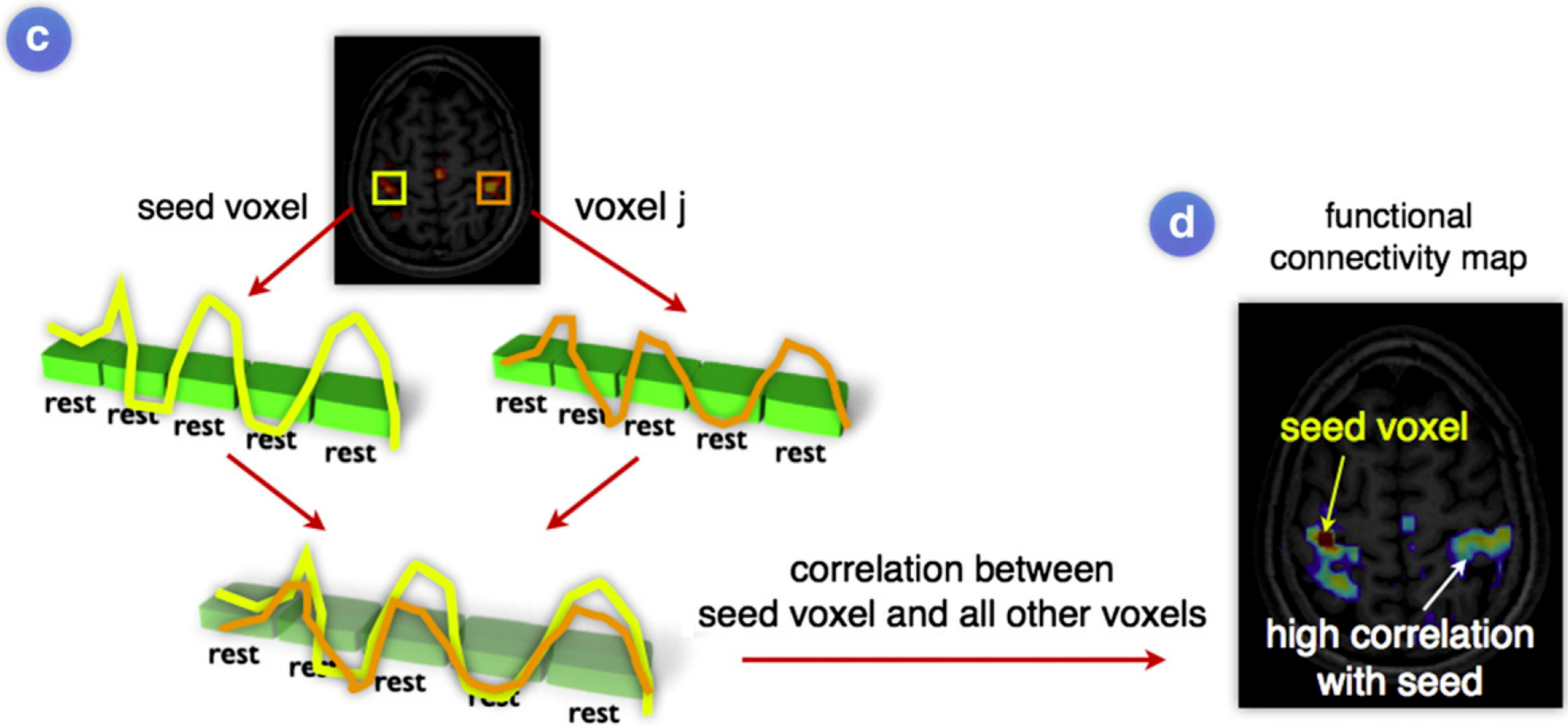
How to process resting-state fMRI data

- Model-dependent methods: seed method
- Model-free methods

Model-dependent methods: seed method

- 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)**.
- This region of interest is typically called **seed**. (Figure 1)
- 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.
- 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.

Figure 1


c
seed voxel
voxel j
rest
rest
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d
functional
connectivity map
correlation between
seed voxel and all other voxels
seed voxel
high correlation
with seed

Model-free methods

- Without the need of defining an a priori seed region.
- Several model- free methods have been suggested and successfully applied to resting-state time-series, including **principal component analysis (PCA), independent component analysis (ICA), hierarchical, Laplacian** and **normalized cut clustering**.
- ICA methods looks for the existence of spatial sources of resting-state signals that are maximally independent from each other and can be applied to **whole-brain voxel-wise** data.
- ICA could complicate the translation of between-group results to clinical relevance.
- Clustering results may be more comparable to traditional fcMap results.
- ICA has the strong advantage of enabling direct comparison between subject groups, while clustering methods generally need additional seed-like processing steps.

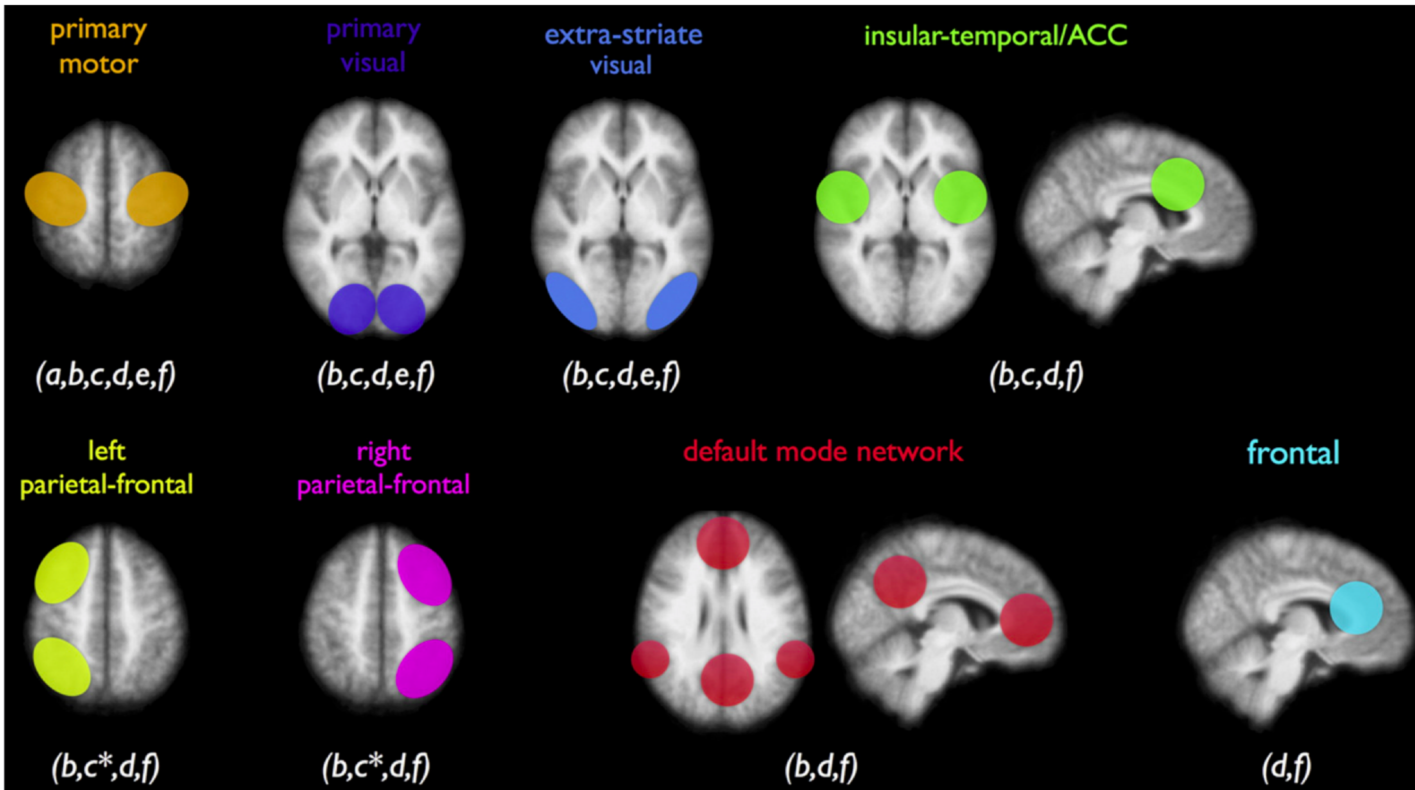
Functionally linked brain regions: resting-state networks

- 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**.
- Up until 2010, neuroimaging studies have identified around eight functionally linked sub-networks. (Figure 2)
- The so-called **default mode network** consists of precuneus, medial frontal and inferior parietal and temporal regions.
- 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.

Functionally linked brain regions: resting-state networks

- Resting-state networks may show an internal topology that is strongly organized to their sub-functions.
- 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.
- The regions of the default mode network are known to show an elevated level of neuronal activity during rest.

Figure 2


primary
motor
(a,b,c,d,e,f)
primary
visual
(b,c,d,e,f)
extra-striate
visual
(b,c,d,e,f)
insular-temporal/ACC
(b,c,d,f)
left
parietal-frontal
(b,c*,d,f)
right
parietal-frontal
(b,c*,d,f)
default mode network
(b,d,f)
frontal
(d,f)

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

- 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.
- A direct association between functional and structural connectivity has been suggested by combining resting-state fMRI with structural **diffusion tensor imaging measurements (DTI)**.
- 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.
- Functional and structural organization of the brain network are likely to be linked, but may not be a one-to-one relationship.

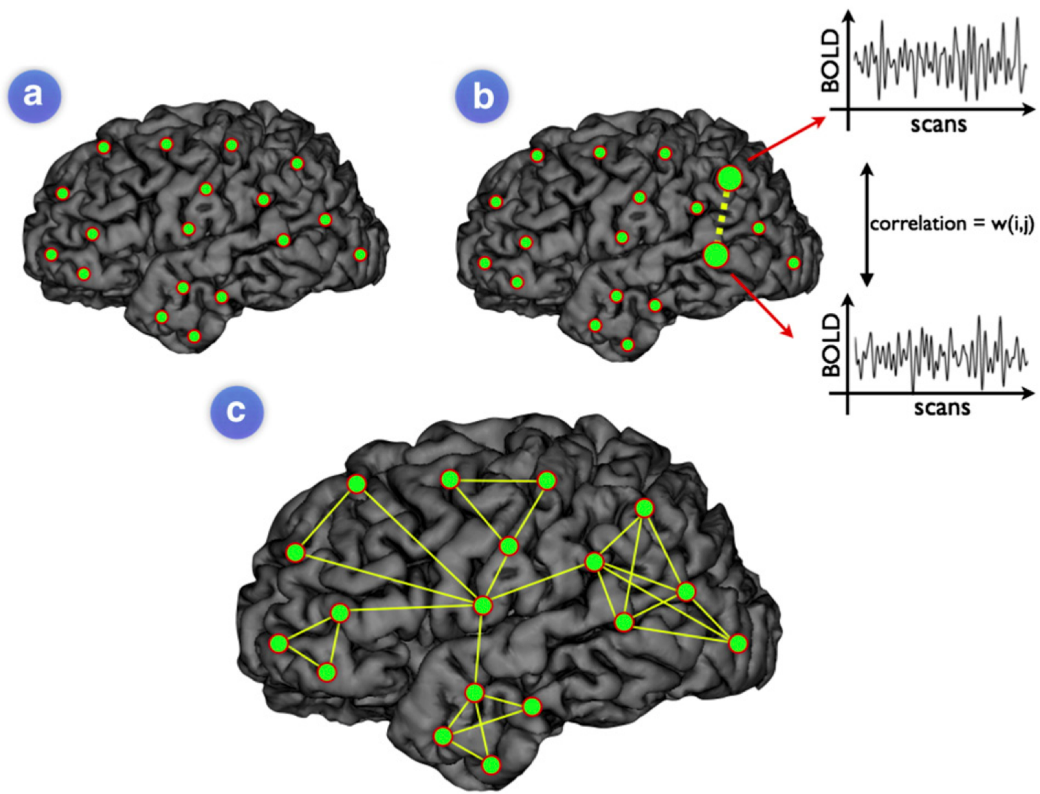
Examining the organization of the brain network

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

Graph analysis

- 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. (Figure 3)
- Based on a predefined cortical template (e.g. Brodmann template) or fMRI voxels, or a hybrid approach somewhere in between.
- Level of functional connectivity between two regions is computed as the level of correlation between the time-series.
- Determining the existence of a functional connection by using a predefined cut-off threshold or by using a weighted approach.

Figure 3



Graph analysis

- Graph properties: clustering-coefficient, characteristic path length, node degree and degree distribution, centrality and modularity. (Figure 4)
- 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.
- The **degree** of a node describes the number of connections of a node and provides information about the existence of highly connected **hub** nodes in the brain network.

Graph analysis

- Important additional information of the formation of hubs in networks comes from **centrality** measures.
- If a node has a high level of centrality , it facilitates a large number of shortest routes in the network, indicating that it has a key role in the overall communication efficiency of a network.
- The level of **modularity** of a graph describes to which extent groups of nodes in the graph are connected to the members of their own group

Figure 4

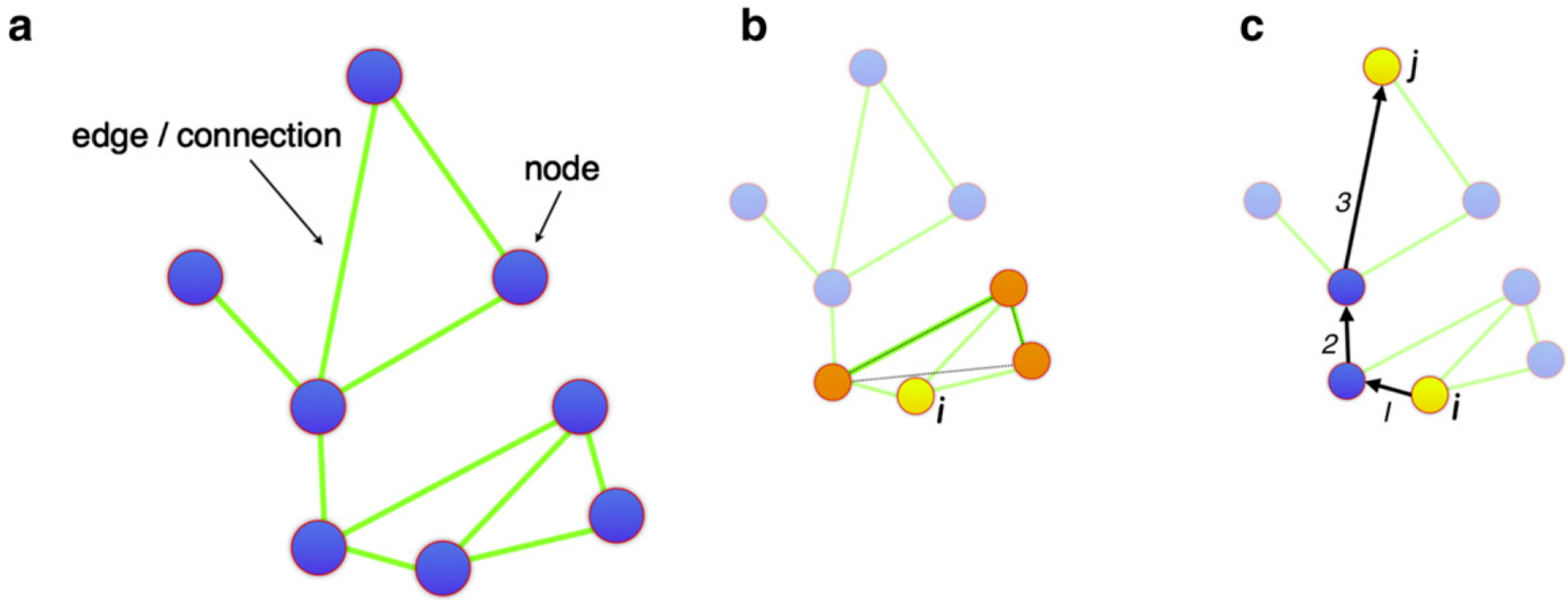
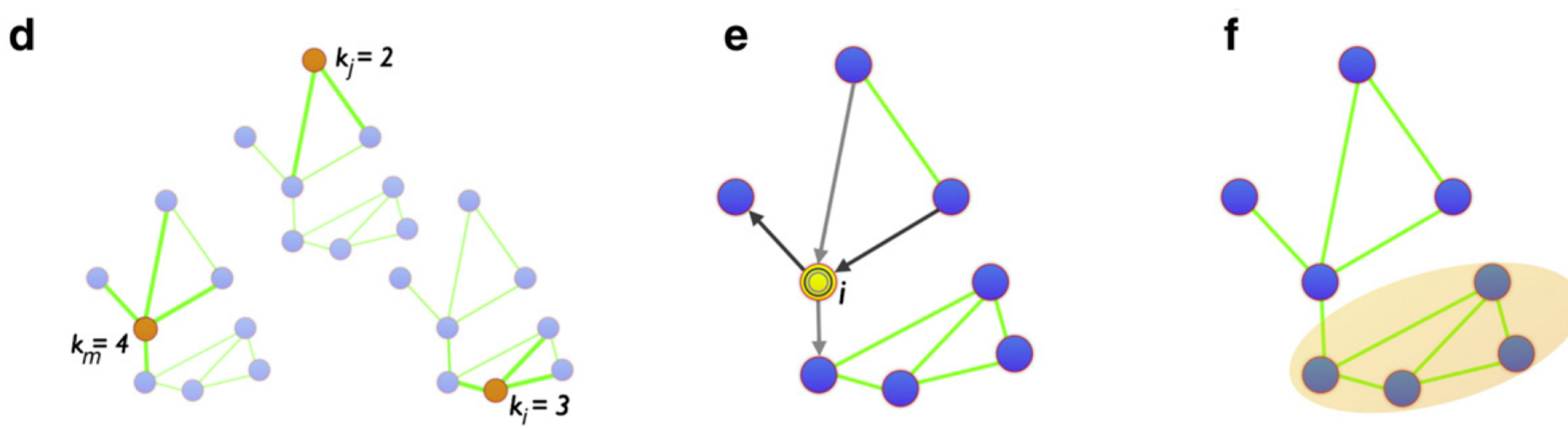


Figure 4



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

- Studies show that the brain network is organized according to an efficient **small-world** organization. (Figure 5)
- **Small-world networks** are known for (1) their high level of local connectedness, but still (2) with a very short average travel distance (i.e. low path length) between the nodes of the network.
- 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**.

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

- **Scale-free networks** and **exponentially truncated power-law** networks are known for their high level of resilience against random attack.
- However, a scale-free organization is vulnerable to specialized attacks on the connected hub nodes.
- Recent MEG results have suggested that specialized attack on brain hub nodes may result in reduced network efficiency as observed in Alzheimer's patients.

Figure 5

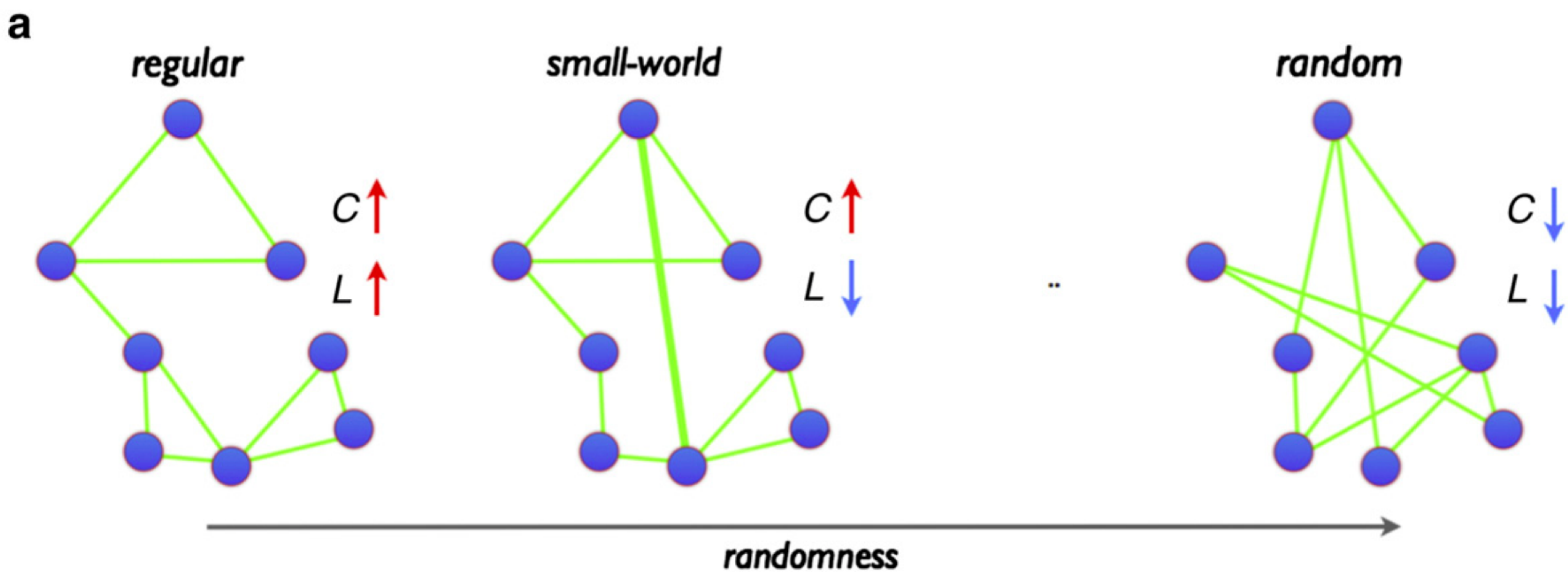
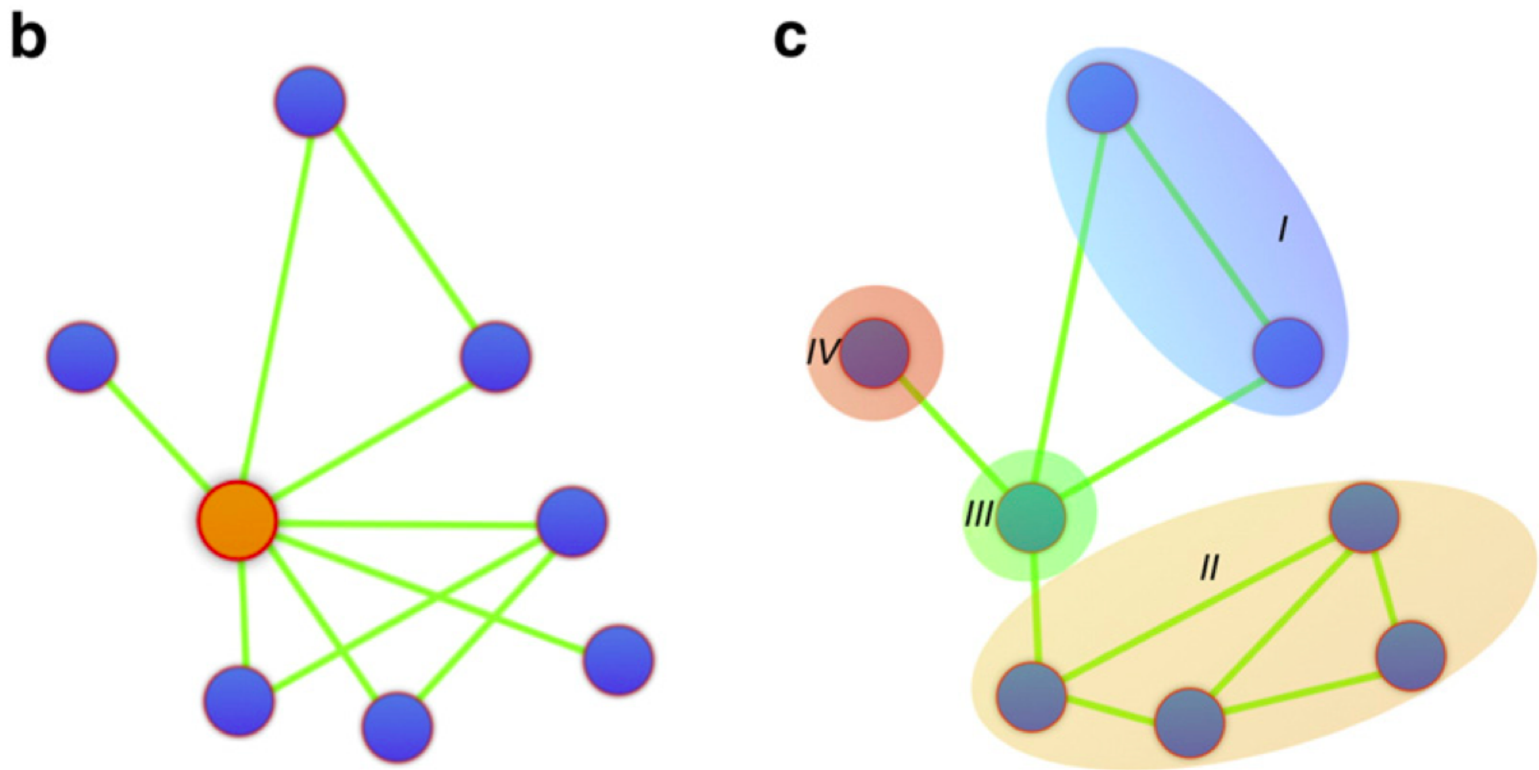


Figure 5



Linking functional connectivity to cognition

- Activity and connectivity of the default mode network has been suggested to be involved in the integration of cognitive and emotional processing and monitoring the world around us.
- 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.
- 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.
- 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.

Functional connectivity and neurological and psychiatric brain disorders

- Neurodegenerative diseases are targeting interconnected cortical networks, rather than single regions.
- Alzheimer's disease has been linked to decreased default mode functional connectivity.
- Widespread functional disconnectivity between brain regions has been suggested to underlie schizophrenia.
- The white matter cingulum tract is known to interconnect the MFC and PCC regions of the default mode network.

Conclusion

- Functional communication within the human brain is organized according to an efficient topology that combines efficient local information processing with efficient global information integration.
- Functional connections of resting-state networks tend to be strongly related to structural white matter connections.