*Psychological Medicine* (2016), **46**, 897–907. © Cambridge University Press 2016
doi:10.1017/S0033291715002895

REVIEW ARTICLE

# Meta-connectomics: human brain network and connectivity meta-analyses

**N. A. Crossley[1,2,3]*, P. T. Fox[4,5] and E. T. Bullmore[6,7,8]**

[1] *Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK*
[2] *Institute for Biological and Medical Engineering, Schools of Medicine, Biological Sciences and Engineering, P. Catholic University of Chile, Chile*
[3] *Department of Psychiatry, School of Medicine, P. Catholic University of Chile, Chile*
[4] *Research Imaging Institute and Department of Radiology, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA*
[5] *South Texas Veterans Health Care System, Research Service, San Antonio, TX, USA*
[6] *Behavioural & Clinical Neuroscience Institute, Department of Psychiatry, University of Cambridge, Cambridge, UK*
[7] *Cambridgeshire & Peterborough NHS Foundation Trust, Cambridge, UK*
[8] *GlaxoSmithKline, ImmunoPsychiatry, Alternative Discovery & Development, Cambridge, UK*

Abnormal brain connectivity or network dysfunction has been suggested as a paradigm to understand several psychiatric disorders. We here review the use of novel meta-analytic approaches in neuroscience that go beyond a summary description of existing results by applying network analysis methods to previously published studies and/or publicly accessible databases. We define this strategy of combining connectivity with other brain characteristics as 'meta-connectomics'. For example, we show how network analysis of task-based neuroimaging studies has been used to infer functional co-activation from primary data on regional activations. This approach has been able to relate cognition to functional network topology, demonstrating that the brain is composed of cognitively specialized functional subnetworks or modules, linked by a rich club of cognitively generalized regions that mediate many inter-modular connections. Another major application of meta-connectomics has been efforts to link meta-analytic maps of disorder-related abnormalities or MRI 'lesions' to the complex topology of the normative connectome. This work has highlighted the general importance of network hubs as hotspots for concentration of cortical grey-matter deficits in schizophrenia, Alzheimer's disease and other disorders. Finally, we show how by incorporating cellular and transcriptional data on individual nodes with network models of the connectome, studies have begun to elucidate the microscopic mechanisms underpinning the macroscopic organization of whole-brain networks. We argue that meta-connectomics is an exciting field, providing robust and integrative insights into brain organization that will likely play an important future role in consolidating network models of psychiatric disorders.

*Received 17 November 2015; Accepted 27 November 2015; First published online 26 January 2016*

**Key words:** Connectome, cytoarchitectonics, gene expression, graph theory, neuroimaging.

## Introduction

In the last decade, the number of neuroimaging studies has increased markedly in psychiatric journals, promising to improve the understanding and treatment of mental health disorders by shedding light on how the brain is (dis)organized in health and disease. A widely used approach has been to consider brain function, and dysfunction, at the level of interactions or connections between brain regions collectively constituting a network. Within this framework, several mental health disorders have been associated with abnormalities of brain connectivity or networks (Kelly *et al.* 2011; Gong & He, 2015), with dysconnectivity theories of schizophrenia being a prominent example (Friston & Frith, 1995; Bullmore *et al.* 1997; Stephan *et al.* 2009).

However, there are many challenges in imaging studies of human brain connectivity, and it is perhaps unsurprising that the area has its share of controversies and inconsistent findings (Spence *et al.* 2000; Vul *et al.* 2009). Some of the challenges are technically specialized, such as the effects of small transient head movements on the estimation of functional connectivity from resting state functional magnetic resonance imaging (fMRI; Power *et al.* 2012), and will require specialist methodological efforts to resolve (Patel *et al.* 2014). But some of the challenges are more general. For example, most network studies of psychiatric disorders have been based on small-medium sample sizes, that are often inadequately powered or with limited replicability (Kapur *et al.* 2012). Published studies usually use structural MRI or resting-state fMRI, which

* Address for correspondence: Dr N. A. Crossley, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK.
(Email: nicolas.crossley@kcl.ac.uk)

https://doi.org/10.1017/S0033291715002895 Published online by Cambridge University Press

limits cognitive or psychological interpretation of network properties. Another challenge is related to the macroscopic view of the brain provided by MRI, which will not be sufficient to understand the complex neurobiological mechanisms underpinning brain function and dysfunction (Bargmann & Marder, 2013). Thus, there is a pressing need to link the macroscopic scale examined by neuroimaging data with more microscopically detailed knowledge about the cellular and molecular profiles of distinct brain regions in health and disease.

We here review results from some recent articles that have taken a novel approach to the analysis of neuroimaging connectivity data, which might provide a way forward to deal with some of these strategic issues in neuroimaging science. These studies have used publicly available datasets or published articles, working with meta-data in a similar way to traditional meta-analyses, but going beyond the goal of increasing the power of small studies. Instead, they have focused on incorporating new information into connectivity studies, e.g. integrating network models of the brain with data on cognitive task performance, clinical diagnosis, or cortical cytoarchitecture. We describe this novel approach as 'meta-connectomics', a term we define broadly as the use of different methods of network analysis in the context of previously published primary studies and/or publicly accessible databases, in an effort to understand more about brain network organization in health and disease. Specifically we will explore how recent studies have related brain network topology to normal cognitive function, to disorder-related abnormalities of local brain structure and function, and to cellular and transcriptional data on individual network nodes. For more general texts on connectomics and brain network analysis see Sporns (2011) and Fornito *et al.* (2016).

Although our focus will be on human neuroimaging, we should note that some of the earliest examples of meta-connectomics involved collation of primary tract-tracing studies of anatomical connectivity in mammalian cortex with a view to providing a whole-brain perspective. The use of injectable tracers, which are actively transported within neurons, has a long tradition in neuroscience to map the brain connectivity of a specific region. The primary tract-tracing literature comprised multiple individual studies describing the anatomical connections of a specific brain region. Several initiatives collated these meta-data, providing foundational results about the hierarchical organization of the visual system in the macaque (Felleman & Van Essen, 1991), and the complex 'small-world' topology of whole-brain networks in the macaque (Stephan *et al.* 2001) and the cat (Scannell *et al.* 1995).

## Linking brain connectivity to cognition using co-activation meta-analysis

Meta-analysis has been widely used in neuroimaging research, initially to combine studies reporting volumes of specific anatomical regions (Wright *et al.* 2000). From an early stage in neuroimaging history, the use of a common stereotactic coordinate system was advocated in order to make results comparable across studies (Fox, 1995). This allowed the development of novel meta-analytic methods which summarized studies reporting voxel-level results (Eickhoff *et al.* 2009; Radua *et al.* 2012). However, connectivity studies have not been widely meta-analysed due to the large variability in the methods used in the primary literature, which have precluded an adequate comparison between studies.

Although meta-analytic methods have not been able to resolve questions of statistical power in connectivity studies by combining multiple primary studies, meta-data has been used in alternative ways to address connectivity, particularly by analysis of functional co-activation. In order to understand co-activation studies, we need to look back at what we understand by functional brain connectivity. Functional connectivity has been defined as the 'temporal correlation between remote neurophysiological events' (Friston, 1994). A typical functional connectivity study would thus measure the correlation or coherence between a pair of regional fMRI or electroencephalogram (EEG) time series recorded with the participant 'at rest' or during task performance (Fig. 1*a*). Co-activation meta-analytic studies also infer functional connectivity between two areas by looking at their correlated activity. However, instead of focusing on correlated activity between time-points (the series of fMRI volumes typically acquired every 2 s), the co-activation method looks at correlated activity between primary studies in the published literature (Fig. 1*b*). Unlike more traditional meta-analytic approaches, which mainly summarize the primary data in terms of the same variables as originally reported, co-activation meta-analyses use the relationship between activations measured locally in the primary data to infer connectivity between local regions in the brain functional co-activation network. In other words, whereas meta-analyses traditionally aim to answer with greater precision the same question that was already addressed by the primary studies, co-activation meta-analyses seek to answer a question that was not posed originally in any of the primary studies. Recent reviews have discussed more extensively the methodological issues in meta-connectivity analysis (Laird *et al.* 2013; Fox *et al.* 2014).

Resting-state fMRI is currently the preferred method for functional connectivity analyses because it is safe

https://doi.org/10.1017/S0033291715002895 Published online by Cambridge University Press

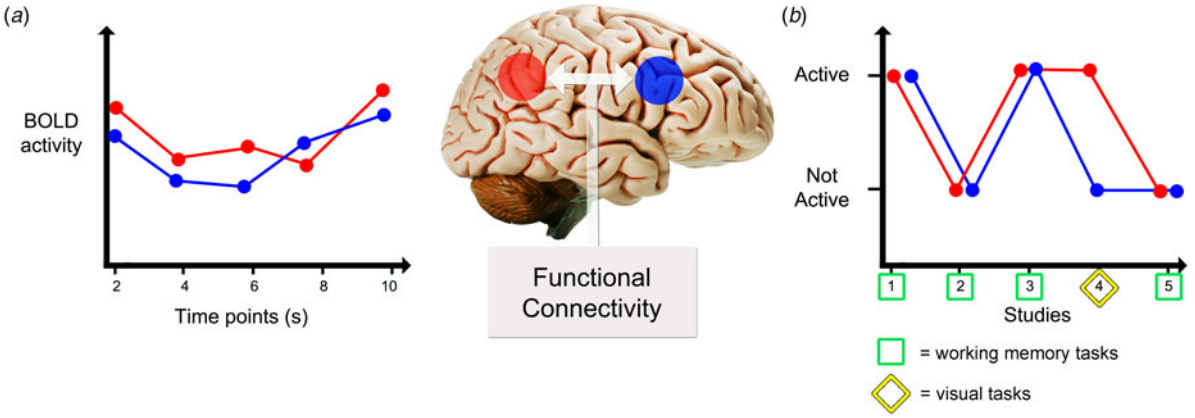



**Fig. 1.** Functional connectivity and co-activation studies. (*a*) Functional connectivity is usually inferred from the correlation between two brain regions' activities as registered in a resting-state functional magnetic resonance imaging (fMRI) scanning session. (*b*) Co-activation approaches infer functional connectivity from the frequency with which the two regions are reported to be active simultaneously during any task. As such, it is similar to traditional resting-state fMRI studies, in that it looks at the similarity in the activity between two regions. It differs in the time-frame used, where resting state looks at different volumes in one session, and co-activation looks at similarities across different published studies. The advantage of a co-activation approach is that one can infer the cognitive characteristics that elicit a functional connection between regions. In the figure shown, both regions were consistently co-activated during working memory tasks (squares), but not during visual tasks (diamond).

and relatively quick to acquire sufficient data (Birn *et al.* 2013). Resting-state experiments avoid the potential confounder of differential task performance in clinical populations (Greicius, 2008), and provide a whole-brain representation. However, resting-state functional connectivity is a design that by definition excludes controlled behaviour, so it is difficult to relate the network topology derived from resting-state data to cognitive functions. Co-activation networks have emerged to fill this knowledge gap. We can map the anatomical locations of activations (and de-activations) in the primary literature to a cortical parcellation template that corresponds to the nodes of a functional network. If two nodal regions, say left and right insula, are frequently co-activated across the primary literature, we can draw an edge or line between these nodes in a graphical representation of the functional co-activation network. Conversely, pairs of nodes that are not frequently co-activated will not be connected by an edge. Moreover, since the edges represent co-activation under cognitively specified experimental conditions, it is possible to identify edges and other topological features that are more-or-less specifically related to domains of cognitive function.

A seminal example of a meta-analytic study linking cognitive function to networks, pre-dating the recent growth of connectomic studies, identified a set of regions that were consistently deactivated across multiple cognitive tasks (Shulman *et al.* 1997) and were later described as the default mode network (Shulman *et al.* 1997; Raichle & Snyder, 2007). Following a similar line, subsequent methodological work focusing on co-activation patterns has been able to use task-based studies to build whole-brain functional connectivity networks with clear cognitive labels. For example, co-activation analyses have explored the connectivity patterns of brain structures including the anterior cingulate (Koski & Paus, 2000), amygdala (Robinson *et al.* 2010), insula (Uddin *et al.* 2014), dorsolateral prefrontal cortex (Cieslik *et al.* 2013) and dorsomedial prefrontal cortex (Eickhoff *et al.* 2014), supplementary motor area (Eickhoff *et al.* 2011), fusiform gyrus (Caspers *et al.* 2014), caudate (Robinson *et al.* 2012), nucleus accumbens (Cauda *et al.* 2011), pulvinar (Barron *et al.* 2015), and the basal ganglia (Postuma & Dagher, 2006). Specific predictions from co-activation meta-analytic approaches could then be tested in single-session experiments (Robinson *et al.* 2010). Meta-data can thus provide a prior model for the links between network organization and cognition, which can then be tested experimentally by more focused activation paradigms.

As well as describing cognition-related connectivity patterns of specific brain regions, studies have used co-activation approaches to inform more extensive cognitive networks. For example, meta-data have been used to build specific models of default-mode network function (Laird *et al.* 2009); and have provided novel insights about the so-called resting-state networks (RSNs) obtained from independent component analyses (ICA; De Luca *et al.* 2006). ICA typically finds specific activity patterns each of which is expressed by an anatomically distributed set of regions comprising an RSN. Intriguingly, the organization of a

https://doi.org/10.1017/S0033291715002895 Published online by Cambridge University Press

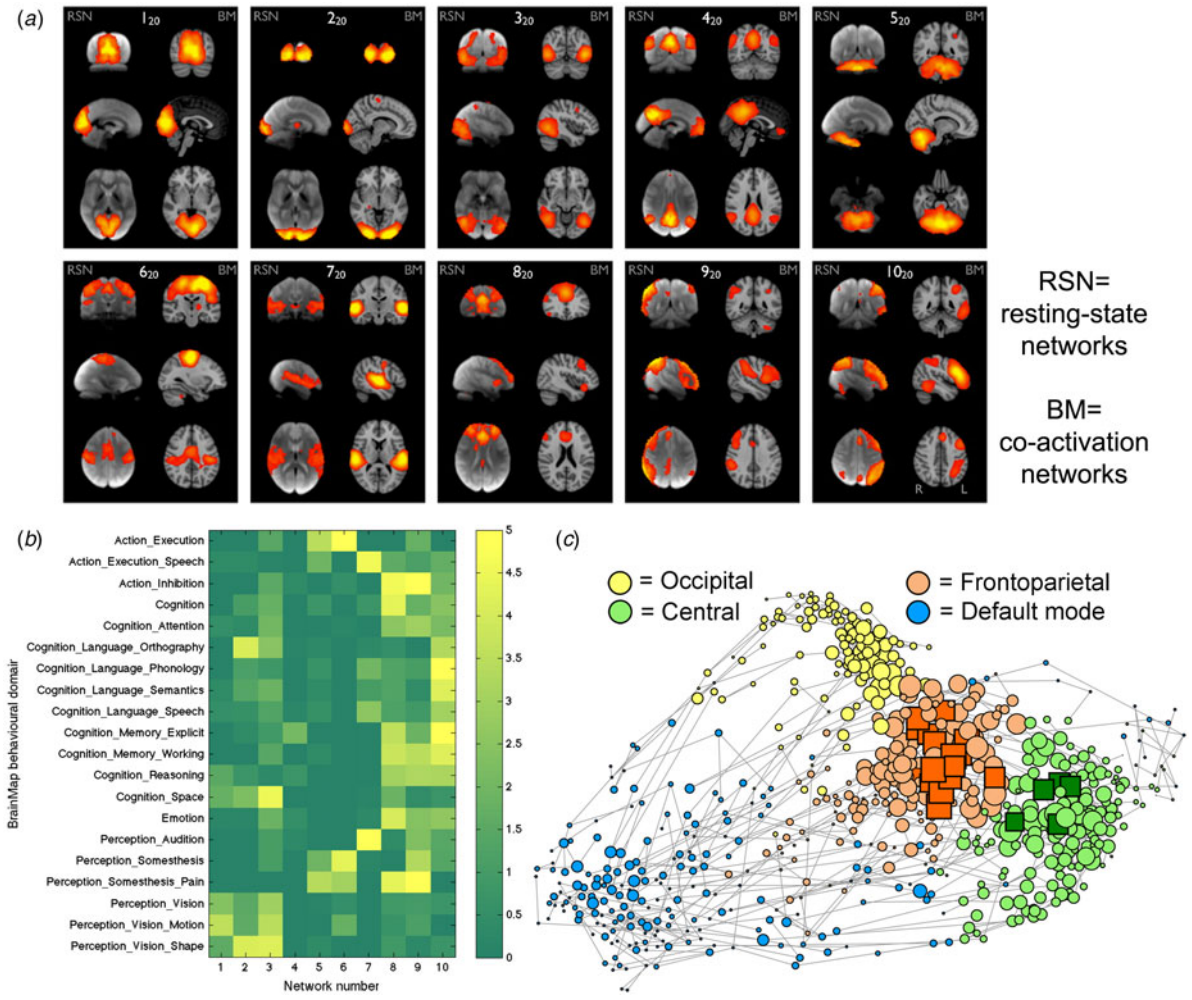



**Fig. 2.** Cognition and the brain's functional network organization. (*a*) Independent component analysis of co-activation data (right side of each individual panel) defines networks corresponding closely to the RSNs obtained from resting-state functional magnetic resonance imaging (left side of individual panels). (*b*) Analyses of the cognitive characteristics of the tasks showing co-activation in the above networks allowed characterization of the cognitive aspects of resting-state networks. Color scale shown is representing arbitrary units, in which each row has been normalized so that its mean value is one. ((*a*) and (*b*) reproduced from (Smith *et al.* 2009), with permission). (*c*) Graph theoretical analysis of functional co-activation data demonstrated a similar organization of cognitively specialized network modules, here depicted in groups with different colours, and in a spatial arrangement such that frequently co-activated nodes are located in close proximity to each other. Connecting these specialized modules is a more domain-general group of central and highly connected regions forming a rich club (nodes marked as squares) (reproduced from Crossley *et al.* 2013, with permission).

functional network derived from co-activation analysis closely corresponds to the RSNs derived from analysis of resting-state fMRI time series (Fig. 2*a*; Smith *et al.* 2009). In other words, for every RSN, there is an anatomically homologous network identified by meta-analysis of co-activation, which has allowed cognitive labels to be attached to specific RSNs (Fig. 2*b*; Smith *et al.* 2009; Laird *et al.* 2011).

The RSNs of ICA are conceptually related to the topological modules of graph theory. A module defines a subset of nodes that are densely connected to each other but sparsely connected to nodes in any other module of the network (Bullmore & Sporns, 2009). It has been shown that modules correspond to RSNs defined by ICA (Crossley *et al.* 2013). These highly segregated building blocks of the functional brain network are also linked together by a group of highly connected hub regions, forming a so-called rich club (van den Heuvel & Sporns, 2011). Co-activation analysis demonstrated that this group of highly connected regions was less cognitively specialized than the more peripheral modules (Crossley *et al.* 2013). Echoing Fodor (Fodor, 1983), the brain functional network thus seems to be organized into cognitively specialized modules, which are linked by a domain-general club of highly connected hub regions (Fig. 2*c*).

https://doi.org/10.1017/S0033291715002895 Published online by Cambridge University Press

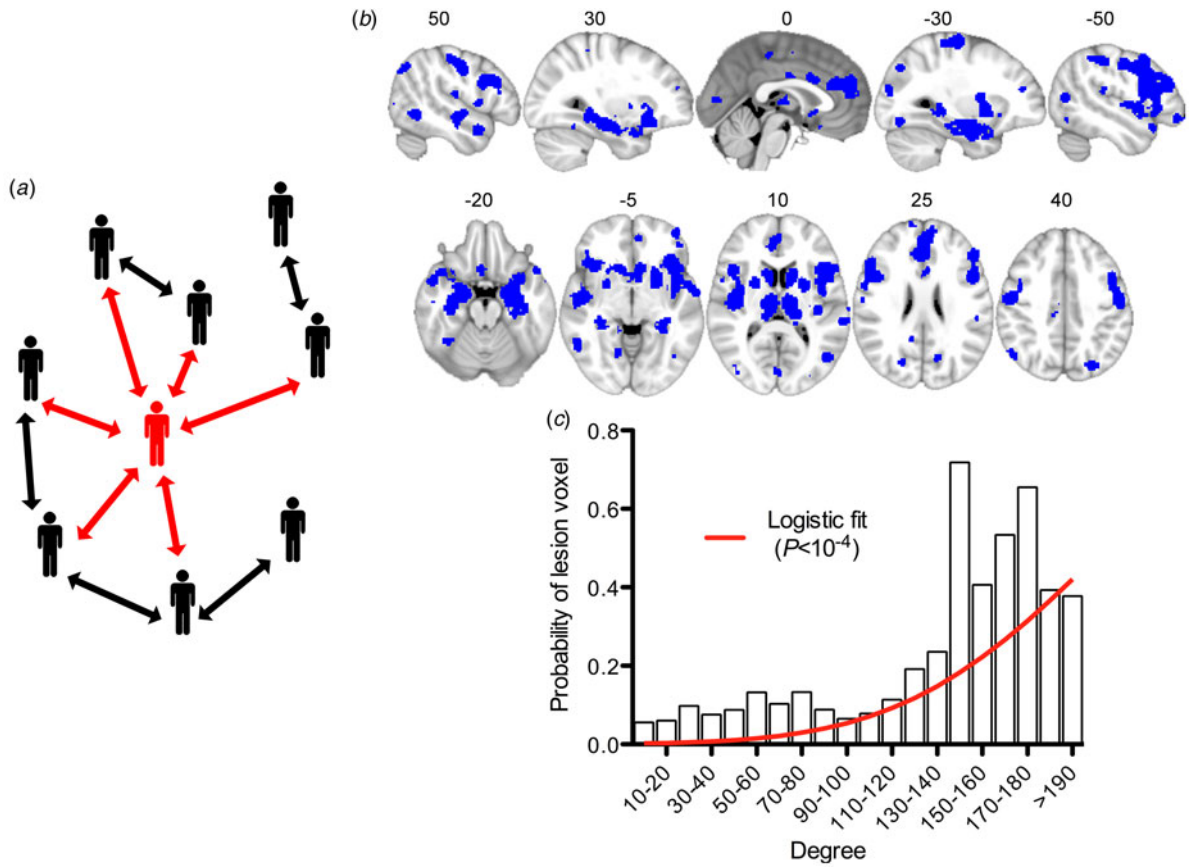



**Fig. 3.** The network position of a node determines its role. (*a*) Social network analyses quantify the intuition that a central node or person (highlighted in red) with many connections would have more immediate access to many resources in the network, whether this is borrowing money or accessing information. However, if the most central agent loses contact with the rest of the network this can lead to disintegration of the network as a whole and the isolation of more peripheral agents. (*b*) Meta-analytic pooling of structural MRI studies from 26 different brain disorders demonstrated the existence of certain regions where abnormalities were consistently reported. (*c*) The probability of a brain region being "lesioned", on average over all disorders, significantly increased as a logistic function of the degree of the corresponding regional node in the normative connectome. [Panels (*b*) and (*c*) from Crossley *et al.* 2014, with permission.]

## Defining the role of a brain region by its interactions

One important idea from network science that has recently translated to neuroscience is that the role of a local node can be quantitatively defined in terms of its topological profile of connections to other nodes in the system (Bullmore & Sporns, 2009). Using graph theory, complex systems are simply rendered as a collection of nodes linked by edges; and the same graphical representation can be used to represent almost anything, from people and their friendship links, to brain regions and their axonal connectivity. From this theoretical framework, network science has provided a simple insight: the web of connections provides or constrains the functional opportunities available to a specific node (Wasserman & Faust, 1994). For example, friendship ties in a social network might facilitate exchange of resources between subjects. People who have more friends (or are more 'central' in network terms) will be more likely to borrow money from other people than those (more peripheral) people with fewer friends. Similarly, they will be more likely to learn some new information that enters the social system (Fig. 3*a*). The translation of this idea into brain sciences was relatively straightforward: one could study how the network position in the brain conditions or constrains the appearance of certain neural processes, such as pathological abnormalities of brain structure or function.

Several studies have now shown that the network location of pathological lesions is not trivial. For example, diffusion tensor imaging (DTI) studies in schizophrenia have shown that although abnormalities are widespread in the brain, they are concentrated in the connections of the high degree hub regions in schizophrenia (van den Heuvel *et al.* 2013). The topological role of lesions might have prognostic value, as has been shown for localized brain injuries, where lesions of nodes spanning different modules cause

https://doi.org/10.1017/S0033291715002895 Published online by Cambridge University Press

larger network reconfiguration and more severe cognitive impairments (Gratton *et al.* 2012; Warren *et al.* 2014). The position in the network might also suggest a specific pathophysiological process, as has been proposed for Alzheimer's disease, where the close agreement between disease progression and the connections of the brain network fits well with a trans-synaptic pathogenic mechanism (Raj *et al.* 2012; Zhou *et al.* 2012).

Meta-analysis has contributed a more general view on brain disorders and how they are related to underlying network organization. The hypothesis that meta-analysis has addressed is whether the brain's network structure modulates to some extent how different diseases affect the brain. This implies that there should be some areas of the brain that, due to the topological position they have in the network, are rendered more vulnerable, more symptomatic, or both; and therefore should be more frequently implicated in brain disorders. Although this hypothesis could be tested using a single scanner and many patients with different diagnoses, the use of meta-data provides advantages in terms of the scale and scope of the disorders included. We recently used meta-data from 392 studies including 9874 patients and 11 502 healthy controls to show that there is an extensive anatomical overlap between structural abnormalities or MRI 'lesions' found in 26 brain disorders (Crossley *et al.* 2014) (Fig. 3*b*), with a similar result reported in another study of a subgroup of psychiatric disorders (Goodkind *et al.* 2015). Furthermore, we showed that these structural abnormalities were concentrated in highly connected brain regions, as theoretically predicted by the brain's network structure and its response to computationally simulated lesions (Fig. 3*a*, *c*). Importantly, different subsets of hubs seem to be affected in different disorders, e.g. frontal lobe hubs were most impacted by schizophrenia and temporal lobe hubs were most impacted by Alzheimer's disease. The specific pathophysiology of a disorder presumably determines which specific hubs or modules are affected (Seeley *et al.* 2009), with disorders traditionally classified as neurological displaying a greater similarity in their structural changes than psychiatric disorders (Crossley *et al.* 2015*b*).

Other studies have explored brain functional data using this kind of network mapping approach. For example, task-related deactivations are local phenomena that frequently accompany task-related activations. By mapping deactivations across 110 contrasts from 67 studies in healthy subjects, we showed that the dyadic pair of an activation in one region accompanied in the same task by deactivation of another region frequently spanned modules and linked rich club to more peripheral nodes (Crossley *et al.* 2013). This suggests that deactivations define the boundaries between modules, and between the core and the periphery, in the community structure of human brain functional networks.

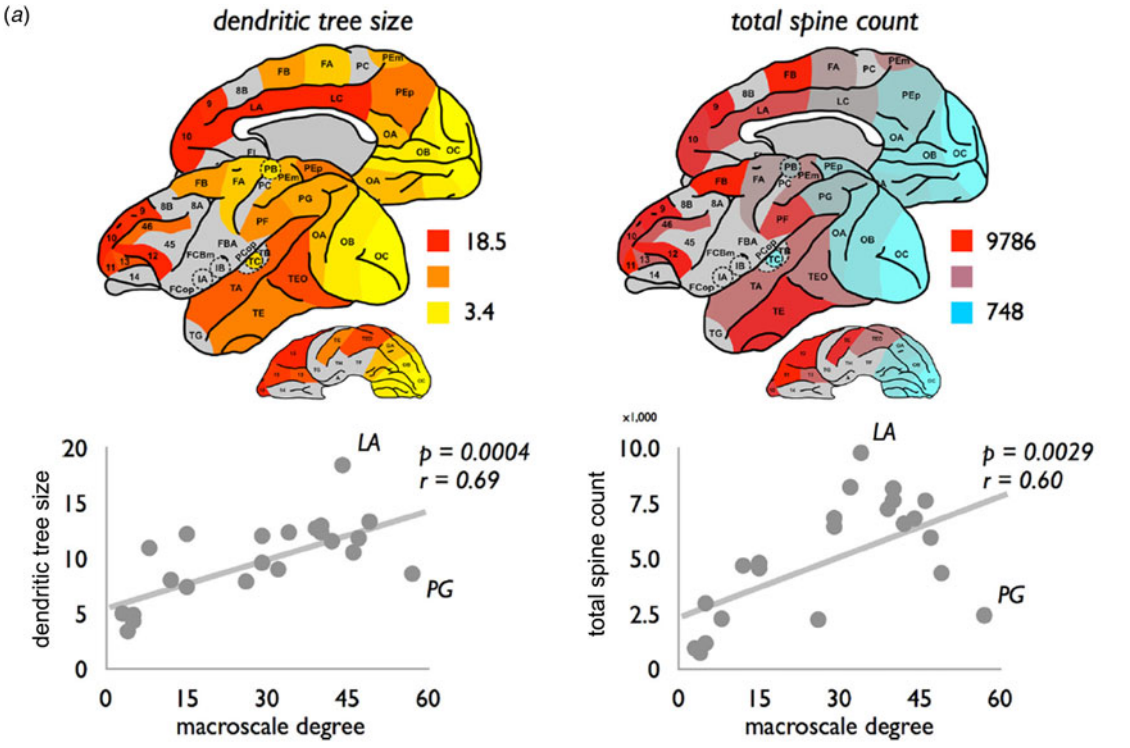
We applied a similar approach to study abnormal functional activations. We studied regions that were consistently under-activated (or over-activated) by task performance in patients with schizophrenia compared to controls across 723 different contrasts from 314 primary studies. We found that over-activations were located close to under-activations in topological space, but not in physical space, and both under- and over-activations were concentrated in high degree hub nodes of the normative connectome. This was in line with the compensatory theory of brain functioning, whereby activation of high-degree and cognitively flexible hub regions would be expected to compensate for topologically neighbouring hubs that were pathologically damaged and thus failed to activate normally during task performance (Crossley *et al.* 2015*a*).

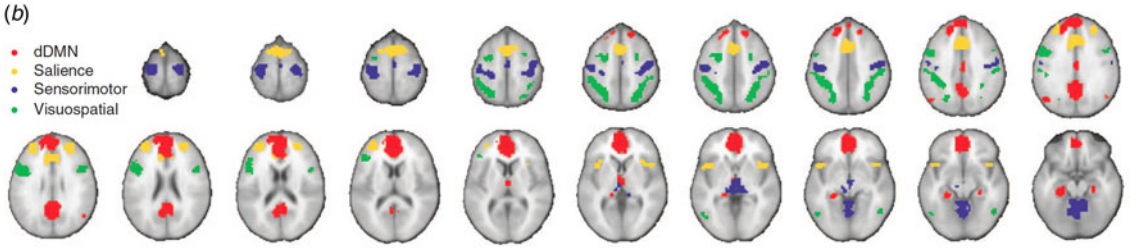
### Microscopic substrates of large-scale networks

Meta-connectomics has also been used to explore the microscopic architecture of specific points in the network. Studying the microscopic characteristics of brain regions and their relationship to the macroscopic organization of the brain has a long tradition in neuroscience (Zilles & Amunts, 2010). More recently, studies have directly linked measures of cytoarchitectonics or gene expression to the topological roles of the corresponding node in the connectome.

An example of such an analysis was based on viral tract tracing data in the macaque (Scholtens *et al.* 2014). This study used several sources of published data to relate the macroscopic network properties of the macaque brain to histologically defined variations of its brain regions. They showed that regions of the network with high degree (high macroscopic connectivity) had greater dendritic branching of pyramidal neurons in cortical layer III, as well as more dendritic spines: two possible indicators of a greater number of synapses (high microscopic connectivity) in network hubs (Fig. 4*a*). The same group has recently used a similar approach to relate macroscopic characteristics of the human brain (as defined by an analysis of the structural network of the Human Connectome Project data; Van Essen *et al.* 2013), with the microscopic architecture of different regions defined by the work by Von Economo & Koskinas from 1925 (van den Heuvel *et al.* 2015). It was shown that the size of cortical neurons in layer III (and not in other layers) was positively correlated with the macroscopic connectivity of the region, with hub regions having larger layer III neurons. This association was independent from the number of neurons or the width of the layer. In line with

https://doi.org/10.1017/S0033291715002895 Published online by Cambridge University Press




(c)

| | | |
|---|---|---|
| All splits (most stable) | ADAM23 ANKRD6 ATP6V1C2 BAIAP3 C3orf55 CARTPT CCDC39 CD70 CDK1 CNTN6 CRYBA2 CTXN3 CXXC11 DMRT3 EPN3 FEZF1 FZD7 GAL **GLRA3** GNA14 GNGT2 GRP HSD11B1 KANK4 **KCNA1 KCNA3 KCNA5 KCNC1 KCTD15** KRT1 KRT31 LAIR2 LINC00238 LMOD3 LRRC38 LYPLA2 MGP MYH7 MYLK3 NEB **NECAB2** NEFH NEUROD6 NGFR NOL4 NOV NRP1 ONECUT2 PCP4 PIRT PNMT PRR15 PRSS35 PTGS1 RBP4 RBPMS2 RHOBTB2 RSPH9 SCARA5 **SCN1B SCN4B** SEMA7A SHD SHISA9 SIX3-AS1 SLC16A6 SLC22A10 SLN SV2C SYT10 ***SYT2*** TDO2 TGFBI TINCR TLX2 TNNT2 TRIM29 TSHZ3 | AMDHD1 ASGR2 CD163L1 COL5A2 CYP2C18 FAM163A ***GABRA5*** GALP GPR26 GPR88 GPX3 HPCAL1 IL13RA2 ISCU NEXN NKAIN4 NPBWR2 ONECUT3 OR51E2 PLCH1 **PVALB** ***SNAP25*** SPHKAP TMEM52 TSPAN8 ZCCHC18 | 5/6 splits |
| | ALOX12 CALB1 **CCBE1** CD6 CDR2L CPLX1 ENPP6 GMPR GOLT1A GPR20 HOXD1 HPCA IL33 IQCJ KLK1 KLK8 LGR6 LINC00617 MS4A8 MYBPC1 NUPR1L PYDC1 RTP1 SEMA3C SH3RF2 SLC16A5 SLC20A2 SLC39A12 SOST WISP1 WISP2 WNT4 | 4/6 splits |

**Fig. 4.** Relating cellular and molecular characteristics to macroscopic brain network organization. (*a*) Complexity of the neurons in layer III of the macaque, measured by the size of the dendritic tree and spine count, was correlated with the degree centrality of corresponding regional nodes of the macroscopic connectome (reproduced from Scholtens *et al.* 2014, with permission). (*b*) Human brain regions that are functionally connected to form resting state networks in fMRI data also have a high similarity in their transcription profiles. Organized correlated activity across the four networks described in (*b*) follows closely the transcription of the subset of genes shown in (*c*). Genes highlighted in bold code ion channels, and those in italic code neurotransmitters. All genes are grouped according to reliability of the data referred to as 'splits' in the original manuscript (see Richiardi *et al.* 2015 for details; reproduced with permission).

https://doi.org/10.1017/S0033291715002895 Published online by Cambridge University Press

their previous findings in the macaque, the authors argued that the size of layer III neurons is correlated with dendritic branching and synaptic density. As such, both of these studies point towards a more complex cytoarchitectonic structure in highly central regional nodes of the connectome, which would allow for a higher capacity to integrate information. This insight could provide a link between network theories suggesting dysfunctional hubs in schizophrenia (Crossley *et al.* 2015*a*) and neuropathological findings showing smaller cortical neuronal size in patients with schizophrenia (Harrison, 1999), particularly in layer III (Rajkowska *et al.* 1998).

Alongside cytoarchitectonic correlates of macroscopic level of connectivity (degree or strength), it is also possible to explore the relationship between cytoarchitecture and modular organization (van den Heuvel *et al.* 2015). As previously described, modules are groups of highly interconnected regions that are also sparsely connected to nodes in other modules. Furthermore, modules are likely specialised in specific cognitive procedures. Van den Heuvel *et al.* (2015) showed that regions within the same module had more similar cytoarchitectonic profiles than those from different modules. One could argue that regions involved in a specific cognitive task may share a similar, functionally specific cytoarchitectonic architecture.

Likewise the IMAGEN consortium explored the molecular mechanisms that underpin human fMRI network organization (Richiardi *et al.* 2015), particularly focusing on RSNs. They combined neuroimaging data with data from the Allen Brain Atlas database, which includes detailed transcription profiles of multiple brain regions in the healthy brain (Hawrylycz *et al.* 2012). Briefly, samples from different brain regions of six healthy donors were obtained, and microarray data on multiple gene transcription products were analysed. Using this database, Richiardi *et al.* (2015) found that the transcription profiles of regions within well-known RSNs, namely the default-mode, salience, visual and sensorimotor networks, were more similar than expected by chance (Fig. 4*b*). The similarity was particularly driven by a subset of 136 genes enriched for ion channels (displayed in Fig. 4*b*). Furthermore, it was shown in independently acquired genetic and imaging data in adolescents, that polymorphisms in this set of genes were also related to network activity.

## Future perspectives of meta-connectomics in psychiatry

Traditional meta-analyses have had a big impact in neuroimaging studies and other fields by pooling publicly available data to increase their statistical power. We here discussed how the field of meta-connectomics has taken the use of publicly available data one step beyond, by combining available information with network models of the brain. This 'meta-analytic pivot', with a new focus on integration of multi-modal data rather than simply maximising statistical power, is providing robust and novel insights into the brain, with some of the findings having direct relevance to our understanding of psychiatric disorders. As we have illustrated here, meta-connectomics has been used to clarify the cognitive functions associated with specific aspects of network topology, to link the anatomical locations of pathological lesions to their topological roles, and to relate nodal topology to the cellular and genomic profiles of brain regions.

However, we also have to be aware of the limitations of meta-connectomic approaches, and try to control for them. By definition, meta-connectomics works with published data or available datasets. As such, the most important limitation is related to the constraints and quality of the primary data. For example, meta-analysis can suffer from publication bias (Egger *et al.* 2001), where only significant results (or datasets) become available. It is therefore important for the growth and rigor of meta-connectomics that there have been some significant and ongoing efforts to make large primary databases available for this purpose (Mennes *et al.* 2013; Van Horn & Gazzaniga, 2013). Imaging databases such as the BrainMap database (Fox & Lancaster, 2002; Laird *et al.* 2005), which has been collating primary neuroimaging studies since 1987, continue to grow; new resources such as the Allen Brain Atlas are being developed and freely provide novel and high-quality sources of information on brain connectivity, cytoarchitectonics and gene expression.

As a way of exploiting large existing datasets to achieve a more integrated understanding of the human connectome and its mechanistic substrates, meta-connectomics is likely to prove of increasing value in clarifying the brain network abnormalities associated with a wide range of psychiatric and neurodegenerative disorders.

## Acknowledgements

PTF is supported by a National Institute of Health (NIH) award (R01MH074457).

## Declaration of Interest

ETB is employed half-time by the University of Cambridge and half-time by GlaxoSmithKline (GSK); he holds stock in GSK.

https://doi.org/10.1017/S0033291715002895 Published online by Cambridge University Press

## References


**Bargmann CI, Marder E** (2013). From the connectome to brain function. *Nature Methods* **10**, 483–490.

**Barron DS, Eickhoff SB, Clos M, Fox PT** (2015). Human pulvinar functional organization and connectivity. *Human Brain Mapping* **36**, 2417–2431.

**Birn RM, Molloy EK, Patriat R, Parker T, Meier TB, Kirk GR, Nair VA, Meyerand ME, Prabhakaran V** (2013). The effect of scan length on the reliability of resting-state fMRI connectivity estimates. *NeuroImage* **83**, 550–558.

**Bullmore E, Sporns O** (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience* **10**, 186–198.

**Bullmore ET, Frangou S, Murray RM** (1997). The dysplastic net hypothesis: an integration of developmental and dysconnectivity theories of schizophrenia. *Schizophrenia Research* **28**, 143–156.

**Caspers J, Zilles K, Amunts K, Laird AR, Fox PT, Eickhoff SB** (2014). Functional characterization and differential coactivation patterns of two cytoarchitectonic visual areas on the human posterior fusiform gyrus. *Human Brain Mapping* **35**, 2754–2767.

**Cauda F, Cavanna AE, D'Agata F, Sacco K, Duca S, Geminiani GC** (2011). Functional connectivity and coactivation of the nucleus accumbens: a combined functional connectivity and structure-based meta-analysis. *Journal of Cognitive Neuroscience* **23**, 2864–2877.

**Cieslik EC, Zilles K, Caspers S, Roski C, Kellermann TS, Jakobs O, Langner R, Laird AR, Fox PT, Eickhoff SB** (2013). Is there 'one' DLPFC in cognitive action control? Evidence for heterogeneity from co-activation-based parcellation. *Cerebral Cortex* **23**, 2677–2689.

**Crossley N, Mechelli A, Ginestet C, Rubinov M, Bullmore E, McGuire P** (2015*a*). Altered hub functioning and compensatory activations in the connectome: a meta-analysis of functional neuroimaging studies in schizophrenia. *Schizophrenia Bulletin*. Published online: 15 October 2015. doi:10.1093/schbul/sbv146.

**Crossley NA, Mechelli A, Scott J, Carletti F, Fox PT, McGuire P, Bullmore ET** (2014). The hubs of the human connectome are generally implicated in the anatomy of brain disorders. *Brain* **137**, 2382–2395.

**Crossley NA, Mechelli A, Vertes PE, Winton-Brown TT, Patel AX, Ginestet CE, McGuire P, Bullmore ET** (2013). Cognitive relevance of the community structure of the human brain functional coactivation network. *Proceedings of the National Academy of Sciences USA* **110**, 11583–11588.

**Crossley NA, Scott J, Ellison-Wright I, Mechelli A** (2015*b*). Neuroimaging distinction between neurological and psychiatric disorders. *British Journal of Psychiatry* **207**, 429–434.

**De Luca M, Beckmann CF, De Stefano N, Matthews PM, Smith SM** (2006). fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *NeuroImage* **29**, 1359–1367.

**Egger M, Smith GD, Sterne JA** (2001). Uses and abuses of meta-analysis. *Clinical Medicine* **1**, 478–484.

**Eickhoff SB, Bzdok D, Laird AR, Roski C, Caspers S, Zilles K, Fox PT** (2011). Co-activation patterns distinguish cortical modules, their connectivity and functional differentiation. *NeuroImage* **57**, 938–949.

**Eickhoff SB, Laird AR, Fox PT, Bzdok D, Hensel L** (2016). Functional segregation of the human dorsomedial prefrontal cortex. *Cerebral Cortex* **26**, 304–321.

**Eickhoff SB, Laird AR, Grefkes C, Wang LE, Zilles K, Fox PT** (2009). Coordinate-based activation likelihood estimation meta-analysis of neuroimaging data: a random-effects approach based on empirical estimates of spatial uncertainty. *Human Brain Mapping* **30**, 2907–2926.

**Felleman DJ, Van Essen DC** (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex* **1**, 1–47.

**Fodor JA** (1983). *The Modularity of Mind: An Essay on Faculty Psychology*. MIT Press: Cambridge, Mass, London.

**Fornito A, Zalesky A, Bullmore ET** (2016). Fundamentals of Brain Network Analysis. Academic Press, in press.

**Fox PT** (1995). Spatial normalization origins: objectives, applications, and alternatives. *Human Brain Mapping* **3**, 161–164.

**Fox PT, Lancaster JL** (2002). Opinion: mapping context and content: the BrainMap model. *Nature Reviews Neuroscience* **3**, 319–321.

**Fox PT, Lancaster JL, Laird AR, Eickhoff SB** (2014). Meta-analysis in human neuroimaging: computational modeling of large-scale databases. *Annual Review of Neuroscience* **37**, 409–434.

**Friston K** (1994). Functional and effective connectivity in neuroimaging: a synthesis. *Hum Brain Mapping* **2**, 56–78.

**Friston KJ, Frith CD** (1995). Schizophrenia: a disconnection syndrome? *Clinical Neurosciences* **3**, 89–97.

**Gong Q, He Y** (2015). Depression, neuroimaging and connectomics: a selective overview. *Biological Psychiatry* **77**, 223–235.

**Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata LB, Ortega BN, Zaiko YV, Roach EL, Korgaonkar MS, Grieve SM, Galatzer-Levy I, Fox PT, Etkin A** (2015). Identification of a common neurobiological substrate for mental illness. *JAMA Psychiatry* **72**, 305–315.

**Gratton C, Nomura EM, Perez F, D'Esposito M** (2012). Focal brain lesions to critical locations cause widespread disruption of the modular organization of the brain. *Journal of Cognitive Neuroscience* **24**, 1275–1285.

**Greicius M** (2008). Resting-state functional connectivity in neuropsychiatric disorders. *Current Opinion in Neurology* **21**, 424–430.

**Harrison PJ** (1999). The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain* **122**, 593–624.

**Hawrylycz MJ, Lein ES, Guillozet-Bongaarts AL, Shen EH, Ng L, Miller JA, van de Lagemaat LN, Smith KA, Ebbert A, Riley ZL, Abajian C, Beckmann CF, Bernard A, Bertagnolli D, Boe AF, Cartagena PM, Chakravarty MM, Chapin M, Chong J, Dalley RA, Daly BD, Dang C, Datta S, Dee N, Dolbeare TA, Faber V, Feng D, Fowler DR, Goldy J, Gregor BW, Haradon Z, Haynor DR, Hohmann JG, Horvath S, Howard RE, Jeromin A, Jochim JM, Kinnunen M, Lau C, Lazarz ET, Lee C, Lemon TA, Li L, Li Y, Morris JA, Overly CC, Parker PD, Parry SE, Reding M, Royall JJ, Schulkin J, Sequeira PA, Slaughterbeck CR,**


https://doi.org/10.1017/S0033291715002895 Published online by Cambridge University Press

**Smith SC, Sodt AJ, Sunkin SM, Swanson BE, Vawter MP, Williams D, Wohnoutka P, Zielke HR, Geschwind DH, Hof PR, Smith SM, Koch C, Grant SG, Jones AR** (2012). An anatomically comprehensive atlas of the adult human brain transcriptome. *Nature* **489**, 391–399.

**Kapur S, Phillips AG, Insel TR** (2012). Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Molecular Psychiatry* **17**, 1174–1179.

**Kelly C, Zuo XN, Gotimer K, Cox CL, Lynch L, Brock D, Imperati D, Garavan H, Rotrosen J, Castellanos FX, Milham MP** (2011). Reduced interhemispheric resting state functional connectivity in cocaine addiction. *Biological Psychiatry* **69**, 684–692.

**Koski L, Paus T** (2000). Functional connectivity of the anterior cingulate cortex within the human frontal lobe: a brain-mapping meta-analysis. *Experimental Brain Research* **133**, 55–65.

**Laird AR, Eickhoff SB, Li K, Robin DA, Glahn DC, Fox PT** (2009). Investigating the functional heterogeneity of the default mode network using coordinate-based meta-analytic modeling. *Journal of Neuroscience* **29**, 14496–14505.

**Laird AR, Eickhoff SB, Rottschy C, Bzdok D, Ray KL, Fox PT** (2013). Networks of task co-activations. *NeuroImage* **80**, 505–514.

**Laird AR, Fox PM, Eickhoff SB, Turner JA, Ray KL, McKay DR, Glahn DC, Beckmann CF, Smith SM, Fox PT** (2011). Behavioral interpretations of intrinsic connectivity networks. *Journal of Cognitive Neuroscience* **23**, 4022–4037.

**Laird AR, Lancaster JL, Fox PT** (2005). BrainMap: the social evolution of a human brain mapping database. *Neuroinformatics* **3**, 65–78.

**Mennes M, Biswal BB, Castellanos FX, Milham MP** (2013). Making data sharing work: the FCP/INDI experience. *NeuroImage* **82**, 683–691.

**Patel AX, Kundu P, Rubinov M, Jones PS, Vertes PE, Ersche KD, Suckling J, Bullmore ET** (2014). A wavelet method for modeling and despiking motion artifacts from resting-state fMRI time series. *NeuroImage* **95**, 287–304.

**Postuma RB, Dagher A** (2006). Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. *Cerebral Cortex* **16**, 1508–1521.

**Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE** (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage* **59**, 2142–2154.

**Radua J, Mataix-Cols D, Phillips ML, El-Hage W, Kronhaus DM, Cardoner N, Surguladze S** (2012). A new meta-analytic method for neuroimaging studies that combines reported peak coordinates and statistical parametric maps. *European Psychiatry* **27**, 605–611.

**Raichle ME, Snyder AZ** (2007). A default mode of brain function: a brief history of an evolving idea. *NeuroImage* **37**, 1083–1090; discussion 1097–9.

**Raj A, Kuceyeski A, Weiner M** (2012). A network diffusion model of disease progression in dementia. *Neuron* **73**, 1204–1215.

**Rajkowska G, Selemon LD, Goldman-Rakic PS** (1998). Neuronal and glial somal size in the prefrontal cortex: a postmortem morphometric study of schizophrenia and Huntington disease. *Archives of General Psychiatry* **55**, 215–224.

**Richiardi J, Altmann A, Milazzo AC, Chang C, Chakravarty MM, Banaschewski T, Barker GJ, Bokde AL, Bromberg U, Buchel C, Conrod P, Fauth-Buhler M, Flor H, Frouin V, Gallinat J, Garavan H, Gowland P, Heinz A, Lemaitre H, Mann KF, Martinot JL, Nees F, Paus T, Pausova Z, Rietschel M, Robbins TW, Smolka MN, Spanagel R, Strohle A, Schumann G, Hawrylycz M, Poline JB, Greicius MD** (2015). Brain networks. Correlated gene expression supports synchronous activity in brain networks. *Science* **348**, 1241–1244.

**Robinson JL, Laird AR, Glahn DC, Blangero J, Sanghera MK, Pessoa L, Fox PM, Uecker A, Friehs G, Young KA, Griffin JL, Lovallo WR, Fox PT** (2012). The functional connectivity of the human caudate: an application of meta-analytic connectivity modeling with behavioral filtering. *NeuroImage* **60**, 117–129.

**Robinson JL, Laird AR, Glahn DC, Lovallo WR, Fox PT** (2010). Metaanalytic connectivity modeling: delineating the functional connectivity of the human amygdala. *Human Brain Mapping* **31**, 173–184.

**Scannell JW, Blakemore C, Young MP** (1995). Analysis of connectivity in the cat cerebral cortex. *Journal of Neuroscience* **15**, 1463–1483.

**Scholtens LH, Schmidt R, de Reus MA, van den Heuvel MP** (2014). Linking macroscale graph analytical organization to microscale neuroarchitectonics in the macaque connectome. *Journal of Neuroscience* **34**, 12192–12205.

**Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD** (2009). Neurodegenerative diseases target large-scale human brain networks. *Neuron* **62**, 42–52.

**Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, Petersen SE** (1997). Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. *Journal of Cognitive Neuroscience* **9**, 648–663.

**Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, Filippini N, Watkins KE, Toro R, Laird AR, Beckmann CF** (2009). Correspondence of the brain's functional architecture during activation and rest. *Proceedings of the National Academy of Sciences USA* **106**, 13040–13045.

**Spence SA, Liddle PF, Stefan MD, Hellewell JS, Sharma T, Friston KJ, Hirsch SR, Frith CD, Murray RM, Deakin JF, Grasby PM** (2000). Functional anatomy of verbal fluency in people with schizophrenia and those at genetic risk. Focal dysfunction and distributed disconnectivity reappraised. *British Journal of Psychiatry* **176**, 52–60.

**Sporns O** (2011). Networks of the Brain. MIT Press.

**Stephan KE, Friston KJ, Frith CD** (2009). Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. *Schizophrenia Bulletin* **35**, 509–527.

**Stephan KE, Kamper L, Bozkurt A, Burns GA, Young MP, Kotter R** (2001). Advanced database methodology for the collation of connectivity data on the macaque brain (CoCoMac). *Philosophical Transactions of the Royal Society of London, Series B: Biological Sciences* **356**, 1159–1186.

https://doi.org/10.1017/S0033291715002895 Published online by Cambridge University Press

**Uddin LQ, Kinnison J, Pessoa L, Anderson ML** (2014). Beyond the tripartite cognition-emotion-interoception model of the human insular cortex. *Journal of Cognitive Neuroscience* **26**, 16–27.

**van den Heuvel MP, Scholtens LH, Feldman Barrett L, Hilgetag CC, de Reus MA** (2015). Bridging cytoarchitectonics and connectomics in human cerebral cortex. *Journal of Neuroscience* **35**, 13943–13948.

**van den Heuvel MP, Sporns O** (2011). Rich-club organization of the human connectome. *Journal of Neuroscience* **31**, 15775–15786.

**van den Heuvel MP, Sporns O, Collin G, Scheewe T, Mandl RC, Cahn W, Goni J, Hulshoff Pol HE, Kahn RS** (2013). Abnormal rich club organization and functional brain dynamics in schizophrenia. *JAMA Psychiatry* **70**, 783–792.

**Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K** (2013). The WU-Minn human connectome project: an overview. *NeuroImage* **80**, 62–79.

**Van Horn JD, Gazzaniga MS** (2013). Why share data? Lessons learned from the fMRIDC. *NeuroImage* **82**, 677–682.

**Vul E, Harris C, Winkielamn P, Pashler H** (2009). Puzzlingly high correlations in fMRI studies of emotion, personality, and social cognition. *Perspectives on Psychological Science* **4**, 274–290.

**Warren DE, Power JD, Bruss J, Denburg NL, Waldron EJ, Sun H, Petersen SE, Tranel D** (2014). Network measures predict neuropsychological outcome after brain injury. *Proceedings of the National Academy of Sciences USA* **111**, 14247–14252.

**Wasserman S, Faust K** (1994). *Social Network Analysis: Methods and Applications*. Cambridge University Press: USA.

**Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM, Bullmore ET** (2000). Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry*. **157**, 16–25.

**Zhou J, Gennatas ED, Kramer JH, Miller BL, Seeley WW** (2012). Predicting regional neurodegeneration from the healthy brain functional connectome. *Neuron* **73**, 1216–1227.

**Zilles K, Amunts K** (2010). Centenary of Brodmann's map – conception and fate. *Nature Reviews. Neuroscience* **11**, 139–145.

https://doi.org/10.1017/S0033291715002895 Published online by Cambridge University Press