Brain networks atlases

Abstract

The human brain consists of multiple areas and networks with distinct functions. To better understand the functional organization of human brain, methods including independent component analysis and graph theory have been used to delineate functional networks and parcellate the brain. An important discovery was the so-called "default mode network" referring to the usually inactive regions in task fMRI data, which was soon observed by decomposing resting-state fMRI (rs-fMRI) data. Beyond this, several popular and widely-used functional atlases have also identified important task-positive networks such as the dorsal attention network and the frontal-parietal control network. From these pre-defined brain atlases, rs-fMRI features could be extracted for a range of applications, such as to study functional organization across development and aging and predicting behavior from functional connectivity in healthy populations. In clinical applications, these brain atlases have been used to facilitate the prediction of disease symptoms and treatment outcomes, as well as to investigate dysfunctions in patients. Nevertheless, several challenges remain in building and applying brain atlases, in particular with regards to interindividual variability, a topic that will likely remain under investigation in the future.

Introduction

One challenge in studying the human brain comes from its multiscale organization and its complexity as a system. One of the most important source of our knowledge on brain organization stems from ex-vivo histological examinations, such as cytoarchitecture mapping (Amunts et al., 2013). By investigating changes in microstructural features across the brain, different brain territories and areas were delineated. However, this "local" approach to study brain organization is particularly time and resources consuming, and more importantly it does not take into account functional aspects of brain organization emerging from interaction between regions. The advent of neuroimaging scanners has offered the possibility to study brain organization in-vivo, by looking at interaction between brain regions and this, for relatively large samples. Accordingly, the last decade has seen a burst of parcellation studies to delineate brain organization based on connectivity features, in particular based on functional connectivity (Eickhoff, Yeo, & Genon, 2018). Since rs-fMRI could be relatively readily performed, resting-state functional connectivity (RSFC), also sometimes called "intrinsic connectivity", became relatively popular for brain parcellation. By applying matrix factorization approaches to rs-fMRI data, many brain networks and brain regions (representing different scales of brain organization) could be delineated. In the next section, we describe the main matrix factorization techniques that have been used to derive brain atlases. We then present the major milestones of scientific developments in

the field. Following this overview on the last decade, we discuss the main limitations, challenges and opportunities in brain network partitions. Finally, in the last part of this chapter, we review the main applications of function brain atlases, with a particular scope on applications for machine learning approaches, as these approaches represent an important avenue of development in the neuroimaging field for the future.

Methods to delineate brain networks

The first evidence that features brain macroscale organization can be observed at rest with observations of a "default mode network" (DMN) led to the development of different approaches for delineating brain networks or functional systems from rs-fMRI. As a highly interdisciplinary research area, delineation of functional brain networks borrows methods from image segmentation, machine learning and information theory. In this section, we briefly introduce several widely used methods for building functional atlases, including independent component analysis (ICA), K-means, and graph theory. We also discuss the advantages and limitations of these methods, as well as the challenges in this field.

Independent Component Analysis

The application of ICA on fMRI analysis can be traced back to almost 25 years ago (Mckeown et al., 1998). Technically, ICA intends to detect several statistically independent components in a given 2-dimensional matrix. In the application to fMRI data, which can be represented as a (*number of time points*) × (*number of voxels*) matrix per participant, ICA usually decomposes it into two matrices. The first matrix contains the spatial map of each independent component. The second matrix, named *mixing matrix*, corresponds to the temporal dynamics of each component. In resting-state scenarios, the spatial maps can then be further interpreted as different functional brain networks and artifacts (Smith et al., 2009).

Although the mathematical representations of ICA might look similar to principal component analysis (PCA) and general linear model (GLM), readers should be aware of the fundamental difference between these models (Calhoun, Liu, & Adali, 2009). PCA aims to detect the underlying orthogonal directions which capture the most data variance. However, ICA identifies the independent directions in data, meaning that the probabilistic distribution along one direction does not affect the others. It should be noted that statistical independence does not guarantee orthogonality, and vice versa. Although GLM also estimates the original data matrix by a product of two matrices, the regressor matrix is usually pre-designed by researchers, e.g. task-design matrix in analyses of task-based fMRI data. In contrast, the mixing matrix in ICA is estimated by optimizing the spatial independence among components. Furthermore, GLM is usually not used for delineating brain networks in rs-fMRI data.

The advantages of ICA are obvious. It is fully data-driven, and does not require a training procedure. One can easily apply it to any appropriate new dataset. The techniques of ICA are relatively mature in the field of fMRI studies. For instance, the software package FSL (FMRIB Software Library) offers a function called MELODIC to perform ICA on fMRI volumes (Beckmann & Smith, 2004) (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC). Compared to most of other brain network clustering or parcellation methods, ICA can provide "soft" delineation by allowing a voxel to be assigned to multiple brain networks (Eickhoff, Thirion, Varoquaux, & Bzdok, 2015).

However, a persistent debate in the application of ICA to fMRI data concerns the choice of spatial or temporal independency (Calhoun, Adali, Pearlson, & Pekar, 2001b), since ICA can be used in both ways to identify either spatially or temporally independent components (Biswal & Ulmer, 1999). An important consequence of choosing temporal ICA is to generate spatially overlapping and dependent components, since temporal ICA has no assumption on spatial independence. This characteristic of temporal ICA is also useful to detect physiological noise (Boubela et al., 2013), especially global artifacts in rs-fMRI (Glasser et al., 2018) [but see debates from (Power, 2019)], which could be hardly achieved by spatial ICA (Beall & Lowe, 2010). However, it should be noted that temporal ICA is more computational demanding when applied to fMRI data because usually the number of voxels is much larger than the length of timeseries. Cares need to be taken when choosing between spatial and temporal ICA, this choice should depend on the assumption of the specific study designs and on the data.

K-means

Intuitively, the K-means method aims to classify all data points into K clusters so that the interclass distance is maximized and the within-class distance is minimized. Within-class distance captures the average distance between each cluster center and every single data point in this cluster, then averaged across all clusters, whereas interclass distance captures the mean distance between each cluster center and the center of cluster centers. Different distance measures can be used, for instance, the distance between any two data points can be measured by the Mahalanobis distance (a special case is Euclidean distance), the Manhattan distance or the Chebyshev distance.

When K-means algorithm is used for identifying functional brain networks, timeseries of each brain voxel are treated as T-dimensional data points, where T indicates the number of time points (Golland, Golland, Bentin, & Malach, 2008; Goutte, Toft, Rostrup, Nielsen, & Hansen, 1999). Voxels classified into the same cluster are then considered as sharing similar temporal fluctuations and hence are interpreted as a single functional network. Note that, besides time courses, the features of each brain voxel which are used to measure distances can also be patterns in frequency domain (Mezer, Yovel, Pasternak, Gorfine, & Assaf, 2009), or functional connectivity of the current voxel to other brain regions (Zhang & Li, 2012), depending on the purpose of different studies.

However, K-means algorithm is circumscribed by a few limitations. First, the number of clusters needs to be set ad-hoc enforcing the researcher to make explicit assumptions on the true data structure. Second, the choice of distance metric may have an important impact on clustering results (Goutte et al., 1999). Last but not the least, K-means is an iterative algorithm. Cluster centers need to be initialized to start the iteration. Unfortunately, repeating the same algorithm with different initialization often generates diverging clustering results. Some of these limitations can be addressed by hierarchical clustering method, introduced in the next subsection.

Hierarchical Clustering

Hierarchical clustering is a family of iterative methods to build a hierarchy of clusters. The dominating algorithm starts from individual data points, and in each iteration, merges a pair of clusters (from the previous iteration) between which the distance is minimal among all pairs of clusters into a new cluster. The whole procedure is frequently represented by a *dendrogram* (Figure 1B). The height in a dendrogram indicates the distance to what extent the connected clusters can be separated. To put it differently, we can decide the number of clusters to be classified by selecting a cutting-off distance in the dendrogram. For example, by thresholding the distance at 4, we can obtain 3 clusters of these total 7 data points: {D, E}c, {A, B, C}, and {F, G}. This procedure therefore bypasses two problems of K-means: initialization of cluster centers and pre-specification of cluster numbers.

An important reason to use hierarchical clustering for neuroimaging data analysis pertains to our belief on hierarchical structural and functional organization of the brain (Arslan & Rueckert, 2015; Park & Friston, 2013). More specifically, the whole-brain functional brain architectures, mostly derived from rs-fMRI data, can be examined at a hierarchy of resolutions, ranging from hundreds to even a thousand locally integrated areas/parcels (Gordon et al., 2016; Schaefer et al., 2018) to around 5-20 spatially distributed networks (Power et al., 2011; Yeo et al., 2011). It is also worth mentioning that hierarchical clustering can not only be used independently (Cordes, Haughton, Carew, Arfanakis, & Maravilla, 2002; Moreno-Dominguez, Anwander, & Knösche, 2014), but can also be integrated with multiple methods including ICA, K-means and graph theoretical methods for brain parcellation. For example, hierarchical clustering was used to estimate brain modules and systems by classifying independent components derived from individual fMRI (G. Doucet et al., 2011). Alternatively, hierarchical clustering has also been applied to K-means defined “supervoxels” to build individual parcellations, which were further passed to a spectral clustering algorithm for more reliable group-level parcellation (Arslan & Rueckert, 2015). However, a drawback of hierarchical clustering is its high computational complexity, especially for large-scale datasets. For readers’ interests, a detailed technical review on the computational complexity of multiple hierarchical clustering algorithms has been provided by Murtagh and colleagues (Murtagh & Contreras, 2017).

Graph Theory & Spectral Clustering

Like other types of networks (e.g. social networks), brain networks can also be investigated using theories and methods adapted from network science, which are mainly rooted in graph theory (Bullmore & Sporns, 2009; Sporns, 2018). In the field of network science, or graph theory, data of interest are treated as a *graph* consisting of *nodes* connected by *edges* (Figure 1C). Multiple network properties regarding how nodes are connected can then be studied such as nodal degree, cluster coefficient, shortest path length, local/global efficiency, modularity, centrality and small-worldness.

When graph theory is applied to fMRI data, brain regions are treated as nodes in a graph and the edges usually correspond to binarized functional connectivity indicating whether two regions are connected or not (Bassett & Bullmore, 2006). To delineate functional brain networks, multiple graph theoretical methods can be used, such as modularity maximization and Infomap algorithm (Sporns & Betzel, 2016). Intuitively speaking, modularity maximization aims to maximize a modularity quality function, which characterizes on average, how much the observed connections between any two nodes within the same delineated module exceed the number of random connections in null models. That is to say, a module is a collection of nodes which have strong connections to each other, but are loosely connected to nodes in other modules. In contrast, Infomap algorithm decomposes a network into modules depending on the frequency of visits for each node when a random walker travels through the network (Rosvall & Bergstrom, 2008). The direction of node transition in each step relies on connection strength between each pair of nodes. Besides identifying functional networks, graph theory has also been used to study brain network alterations in disease (Hallquist & Hillary, 2018) and development (Power, Fair, Schlaggar, & Petersen, 2010).

A substantial amount of work used spectral clustering, which has a close relationship with graph theory, for functional mapping (Craddock, James, Holtzheimer III, Hu, & Mayberg, 2012; Shen, Tokoglu, Papademetris, & Constable, 2013; van den Heuvel, Mandl, & Pol, 2008). It partitions a graph based on the eigenvalues (i.e. spectrum) and eigenvectors of characteristic matrices of the graph such as *Laplacian matrix*. A popular spectral clustering technique is *normalized cuts*, which was first developed for natural image segmentation (J. Shi & Malik, 2000). This algorithm basically aims to cut a graph by breaking down the least number of edges. An advantage of spectral clustering is its ability to capture clusters with complicated shape and discontinuity (Eickhoff et al., 2015) with the potential disadvantage that the decomposed clusters tend to be equally sized (Craddock et al., 2012).

Additional methods and challenges in the field

Besides the methods introduced in previous subsections, functional atlases have also been derived using less popular approaches, such as region growing (Bellec et al., 2006; Blumensath et al., 2013) and edge detection methods (Cohen et al., 2008; Gordon et al., 2016; Nelson et al., 2010; Wig et al., 2014). Region growing methods start from seed locations (e.g. each cortical voxel), and iteratively merges the

most homogenous (i.e. similar fluctuations in fMRI timeseries) neighbors until a pre-defined threshold is reached. Edge detection methods draw area boundaries based on the local gradient of functional connectivity. Both types of method generate spatially disjoint brain areas which can be further grouped into networks using other methods.

From the machine learning perspective, the models mentioned above (K-means etc.) are more or less *discriminative models*, which build cluster boundaries to discriminate observed data points. In contrast, *generative models* can generate new data instances by estimating the joint probabilistic distribution between the input (e.g. fMRI timeseries or functional connectivity) and the output (e.g. cluster label) variables. For example, a series of work modelled functional brain organizations as a mixture of multiple probabilistic distributions, i.e. using *mixture models* (Kong et al., 2019; Lashkari, Vul, Kanwisher, & Golland, 2010; Yeo et al., 2011). More specifically, functional connectivity profiles of each cortical region were assumed to follow a mixture of von Mises-Fisher distributions, where each distribution had a specific mean functional connectivity profile, corresponding to each cluster, which were estimated by maximum likelihood estimation. In addition, *Latent Dirichlet Allocation* (LDA) has been used to estimate cortical networks which were allowed to be spatially overlapped (Yeo, Krienen, Chee, & Buckner, 2014). Hence, a single cortical region can be involved in multiple networks. LDA, first developed to solve text mining problem (Blei, Ng, & Jordan, 2003), is a three-layer model including document, topic, and word. Relationships between each two layers is characterized by a probabilistic distribution so that a document can contain multiple topics, which can be further composed of multiple words. In brain parcellation applications, these three layers corresponded to the entire cortex, networks, and cortical regions.

A common issue shared across almost all these methods pertains to choosing the "right" number of clusters/components. Crucial information could be neglected if only a very few clusters are selected. In contrast, higher-order models might be overfitted to noise. One approach to select the optimal model orders is to adopt methods from information theory, such as *Akaike's information criterion* and *Bayesian information criterion* (Calhoun, Adali, Pearlson, & Pekar, 2001a; Y. O. Li, Adali, & Calhoun, 2007; Thirion, Varoquaux, Dohmatob, & Poline, 2014). These criteria calculate the trade-off between model complexity (number of clusters/components here) and goodness-of-fit of the model, taking both overfitting and underfitting into account. Alternatively, reproducibility/stability or reliability measures can also be used to select the number of clusters/components (Yeo et al., 2011). *Intra-class correlation coefficients*, a common metric for reliability, has been used to estimate the number of ICA components (Zuo et al., 2010). Reproducibility can be assessed by measures including adjusted Rand index, adjusted mutual information, and Dice overlap coefficient either on resampled data obtained by bootstrap (or cross-validation) or across independent datasets (Bellec, Rosa-Neto, Lyttelton, Benali, & Evans, 2010; Craddock et al., 2012; Thirion et al., 2014). In the absence of "ground-truth parcellation", stability and reproducibility of delineated brain networks across different data collection and preprocessing pipelines

and clustering techniques are important proxies for underlying neurobiological validity (Eickhoff et al., 2018).

For methods such as ICA and K-means, a common problem is the difficulty to generalize individual-level components/clusters (i.e. components derived at the subject-level) to group-level components/clusters (Calhoun et al., 2009). Nonetheless, several methods have been proposed to overcome this difficulty by concatenating (or averaging) images from multiple participants before applying ICA, or averaging the ICA results across participants, etc. (Calhoun, Adali, McGinty, et al., 2001; Calhoun, Adali, et al., 2001a; Guo & Pagnoni, 2008; Schmithorst & Holland, 2004). When K-means was first applied to each individual participant's data, a group analysis can be conducted by maximizing the number of voxels/regions consistently assigned to the same clusters across individuals (Golland et al., 2008). This can also be achieved by the bootstrap procedure proposed by Bellec et al. (Bellec et al., 2010), in which two regions were assigned to the same group-level cluster if the probability that they belonged to the same cluster at individual level were maximized. Alternatively, K-means can also be applied directly to group-level features, e.g. a t-test map of functional connectivity across all participants (Zhang & Li, 2012).

Although references to the methods we mentioned in this section where mostly based on rs-fMRI, these methods can be used to delineate brain networks and areas from any kind of connectivity or similarity of neuroimaging features. For example, ICA and graph theoretical modeling can be also used on co-activation data provided by meta-analytic approaches (coactivation-based parcellations) (P. T. Fox, Lancaster, Laird, & Eickhoff, 2014). Furthermore, as mentioned above, ICA was first applied to task-based fMRI data for delineating task-evoked vs. task-inactive areas, then to rs-fMRI. Similarly, the multi-level bootstrap analysis based on hierarchical clustering and K-means, first developed on rs-fMRI data that we mentioned above (Bellec et al., 2010), can also be applied to derive stable clusters in task-based fMRI (Orban et al., 2015).

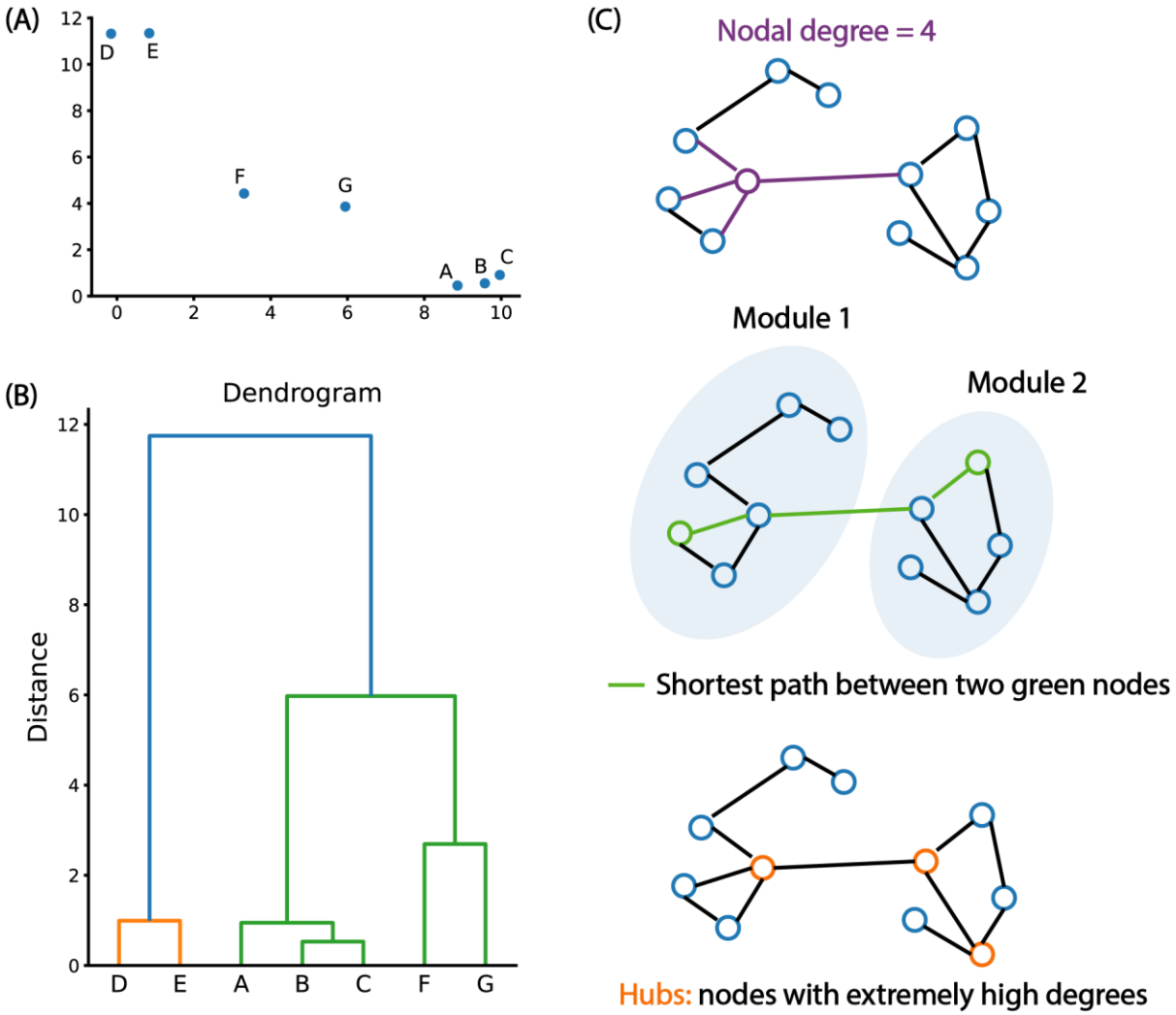

Figure 1. (A&B) Illustration of hierarchical clustering. A dendrogram in (B) can be created based on the distance among seven data points shown in the two-dimensional space in (A). (C) Some terminologies used in graph theory.

From evidence of individual networks to brain network atlases

Searching for canonical networks in resting-state signal

A Task Negative Network and a Task Positive Network

Capitalizing on the approaches described above, several networks or functional systems have been progressively disentangled. Following up of the evidence of a default mode network, a Task Negative Network and a Task Positive Network (see Figure 2) were proposed as anti-correlated networks by Fox et al. (2005). This was done by examining correlation in resting-state signals between six predefined seed regions. Three of these regions were hypothesized as "task-positive regions" since they usually show activity increases during attention-demanding cognitive tasks: the intraparietal sulcus (IPS), the frontal eye field (FEF) and the middle temporal region (MT+). In contrast, the medial prefrontal cortex

(MPF), the posterior cingulate cortex/precuneus (PCC) and the lateral parietal cortex (LP) were considered as "task-negative" regions as routinely exhibiting activity decrease during attention-demanding tasks. Despite the anti-correlated nature of these networks were subsequently vividly debated (Anderson et al., 2011; M. D. Fox, Zhang, Snyder, & Raichle, 2009; Saad et al., 2012), this seminal study pathed the way towards the identification of the main functional systems that support human cognition from fMRI signal at rest. It indeed demonstrated that the macroscale organization of the brain is preserved in spontaneous low-frequency BOLD signal fluctuations across the brain. Accordingly, several following studies aimed to further delineate canonical networks by capitalizing on RSFC.

A ventral attentional network, a dorsal attentional network and a fronto-parietal control network

Soon after, Fox et al. (2006) further demonstrated that two different attention systems (see Figure 2), a ventral one and a dorsal one, could be observed in rs-fMRI data of healthy participants. These two systems were previously conceptualized based on a collection of behavioral, neuroimaging, lesion, and electrophysiological studies. The derived model hence proposed that different attentional operations during sensory orienting are carried out by two separate frontoparietal systems, a bilateral dorsal attention system involved in top-down orienting of attention and a right-lateralized ventral attention system involved in reorienting attention in response to salient sensory stimuli. Fox. et al. (2006) further demonstrated that these systems could be observed in spontaneous fluctuations of the signal at rest. Their study also revealed regions in the prefrontal cortex correlated with both systems suggesting a potential mechanism for mediating the functional interaction between systems. Along the same line, Vincent et al. (2008) showed evidence for a fronto-parietal control system in intrinsic functional connectivity, this network being spatially interposed between the dorsal attention system and the hippocampal-cortical memory system. Hence, slightly different, but closely related, conceptualizations of brain control and attentional networks organization emerged from the study of intrinsic connectivity across samples of healthy participants.

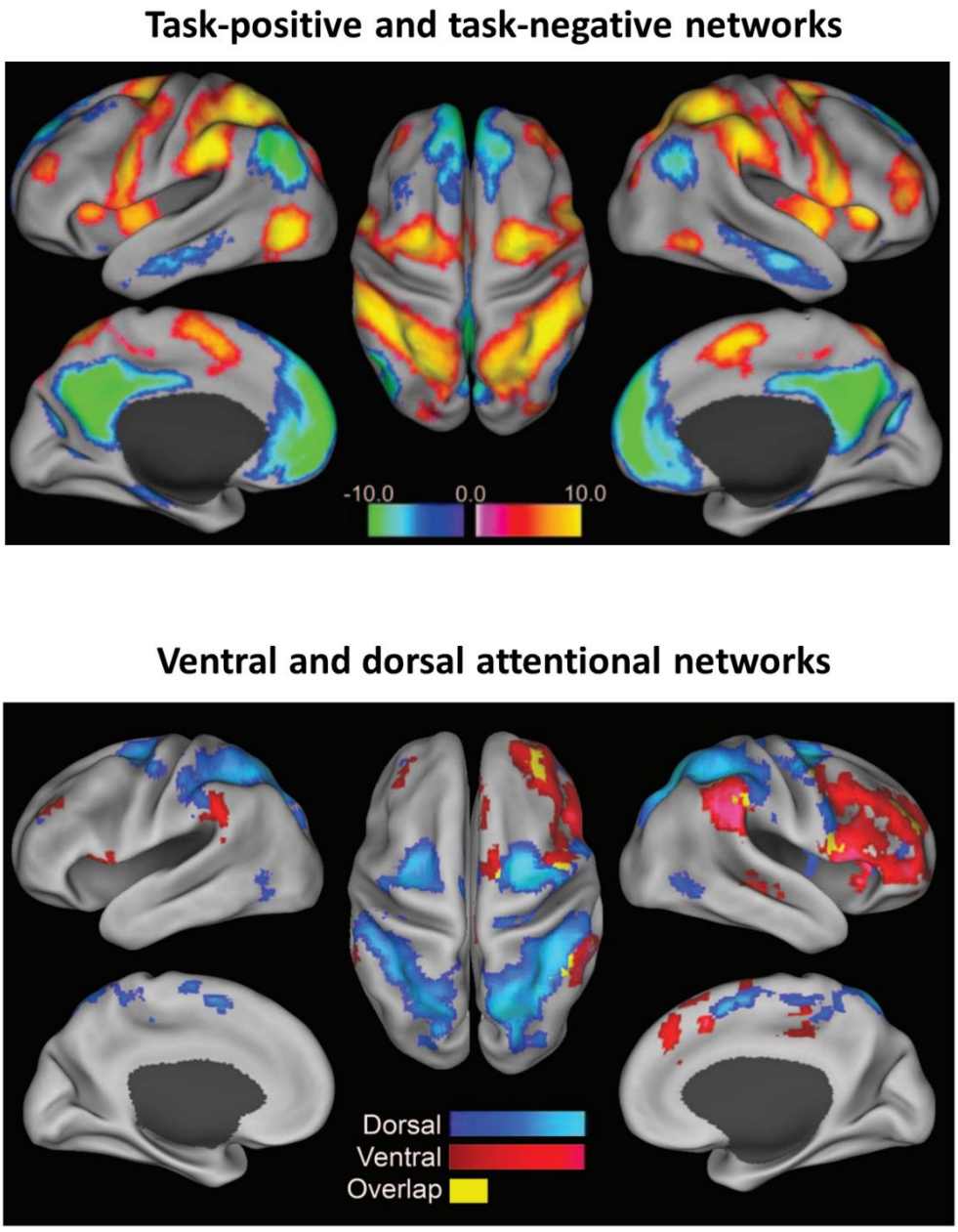

Figure 2. The task-positive vs task negative networks [upper part, from M. D. Fox et al. (2005)] and the ventral and dorsal attentional networks [lower part, from M. D. Fox et al. (2006)] evidence in rs-fMRI signal.

The default mode subnetworks

In the same vein, the conceptualization of the default mode network could also be further refined by examining graph-theoretic and clustering functional connection properties of the DMN regions in healthy participants. By doing so, Andrews-Hanna et al., (2010) suggested two DMN subnetworks. In line with previous studies [e.g. (Buckner et al., 2009)], they showed that the PCC and aMPFC (anterior medial prefrontal cortex) are crucial hubs showing high betweenness centrality, while the other DMN

regions could be dissociated into two distinct subsystems. A ‘‘dorsal medial prefrontal cortex (dMPFC) subsystem” is formed by the dMPFC, temporoparietal junction (TPJ), the lateral temporal cortex (LTC), and the temporal pole (TempP) and a ‘‘medial temporal lobe (MTL) subsystem is formed by the ventral MPFC (vMPFC), the posterior inferior parietal lobule (pIPL), the retrosplenial cortex (Rsp), the parahippocampal cortex (PHC), and the hippocampal formation (HF+). The relevance of these two subnetworks for human cognition was then further demonstrated with task-fMRI experiments.

Data-driven decomposition of RSFC into networks

Parcellation into canonical networks

By being able to confirm and further characterize core brain networks evidenced from a range of methods other than fMRI, as well as by task-fMRI, rs-fMRI established its validity for the study of brain organization. Following a first wave of relatively hypothesis-driven studies described above, several brain network atlases have been developed by partitioning the cortex into a certain number of networks (G. Doucet et al., 2011; Gordon et al., 2016; Laumann et al., 2015). One of the most popular and widely-utilized atlas in that framework has been developed by Yeo et al. (2011). The authors identified 7 main networks (see Figure 3) including relatively local networks, that are the visual and somatomotor networks, as well as relatively distributed, generally association, networks. Among these latter, one is the limbic network, while the paralimbic networks include the DMN, the dorsal attention, the ventral attention and the fronto-parietal networks in agreement with prior reports.

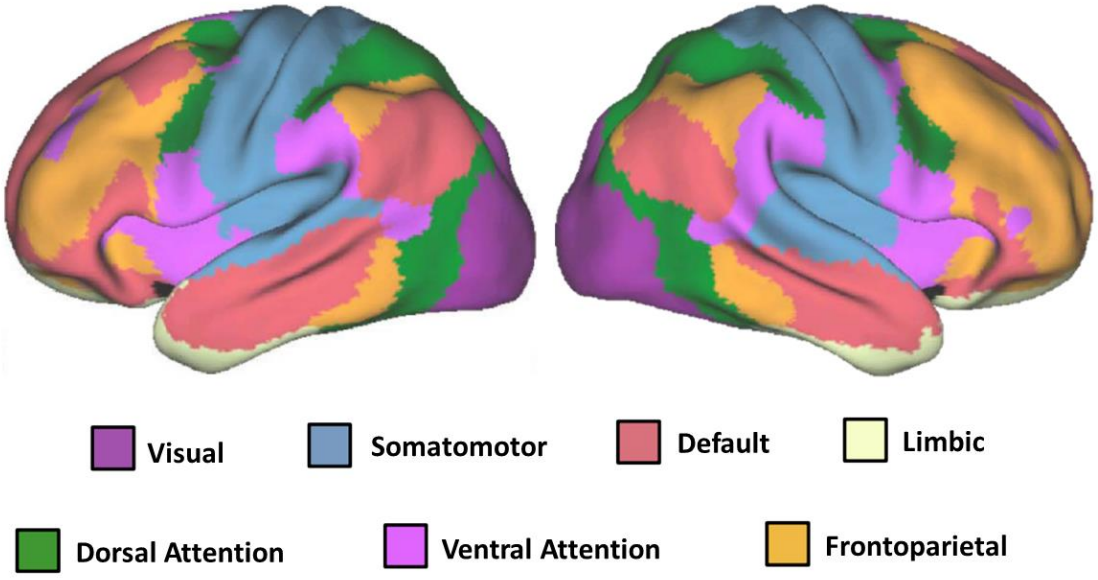

Figure 3. The seven canonical networks from Yeo et al. (2011).

In a similar view, Power et al. (2011) investigated graphs and subgraphs corresponding to functional networks in the distributed patterns of high RSFC between brain regions. They hence showed that the ‘‘Task Positive System’’ previously reported actually consists of multiple subgraphs, including the dorsal attention network, the fronto-parietal task control network, and the cingulo-opercular task control network. Hence, while using different approaches and samples, these two mile-stone studies show highly convergent findings thus highlighting the existence of robust functional networks in RSFC patterns with bilaterally distributed visual, sensorimotor, default mode, and attention networks.

The neurobiological insight

These parcellations of the RSFC patterns had a significant impact of the field by providing a set of canonical networks with a data-driven approach. These parcellations were not only robust by showing replicability across resampling or different datasets, but they also show neurobiological validity. While this latter quality of brain parcellation remains difficult to investigate [for a review see (Eickhoff et al., 2018)], a common criterion of evaluation relies on comparison with features of brain organization evidenced by post-mortem histological work and/or invasive in-vivo techniques. Hence, the neurobiological validity of Yeo et al. and Power et al. network atlases was supported by their correspondence with well-established primary sensory-motor systems. Another validity criterion for brain parcellation based on RSFC is the convergence with the patterns of brain organization shown in task fMRI, in particular when using co-activation meta-analytic approaches on a large set of task fMRI studies (see next section for more information). Several networks delineated in RSFC by Yeo et al. and Power et al. hence demonstrated an important convergence with robust co-activation patterns revealed by decomposition approaches (Smith et al., 2009; Yeo, Krienen, et al., 2015). Thus, these parcellations have proven to be not only reliable from a technical standpoint, but also valid from a neurobiological standpoint.

Refining brain networks

Capitalizing on these robust atlases, follow-up investigations have provided further insight into the principles of brain organization. In addition to the 7-network partition, Yeo et al. (2011) also found a robust partition of RSFC patterns into 17 networks hence further fractionating the 7 networks into smaller networks. Many of these smaller networks were local networks, representing broad brain regions or functional modules, such as the ventral somatomotor region. Together with other studies [e.g. (Craddock et al., 2012; Shen et al., 2013)], Yeo et al.’s study brought evidence that decomposition approaches applied to RSFC ultimately (i.e. at a high level of partition) can be used to disentangle individual functional brain regions. Accordingly, RSFC has been used intensively in the last fifteen years to parcellate the brain and/or to parcellate some specific regions [for a review see (Eickhoff et al., 2018)].

One important point of discussion that arise from those studies is that, although functional organization of the brain (as for example reflected in RSFC) to a great extend correspond to anatomical features and organization, divergence between structural and functional organizations has been frequently reported and discussed, for example in the human hippocampus (Eickhoff et al., 2018; Genon, Bernhardt, La Joie, Amunts, & Eickhoff, 2021). Furthermore, follow-up investigations of the network features confirmed the main canonical networks function as relatively isolated modules. However, in contrast, to the somatomotor and early visual cortices which appeared relatively segregated, several association regions, such as the precuneus and the medial prefrontal cortex appeared to participate in multiple networks, hence supporting large-scale integration (Yeo et al., 2014; Yeo, Krienen, et al., 2015). Thus, decomposition approaches applied to RSFC importantly complement the insight provided by histological approaches in understanding brain organization.

Despite the limitations of unconstrained signal to study human neurocognitive systems have been often debated [e.g. (Spreng, 2012; Williamson, 2007)], since, for example, brain regions that do not show signal correlation at rest may be coupled during task, RFSC has been frequently used to refine or complement the features of specific neurocognitive systems. For instance, the node and edge properties within a task-based language network of 32 brain regions have been characterized by using RSFC (Labache et al., 2019). A core network (SENT_CORE) including 18 brain regions was hence identified, within which the pars triangularis of the inferior frontal gyrus and the superior temporal sulcus were identified as hubs based on their degree centrality, betweenness, and participation values. This insight provided by RFSC thus allowed the authors to hypothesize that these two hubs correspond to epicentres of sentence processing. In the same vein, RSFC was used to provide an extended spatial definition of the multi-demand networks, which was further subdivided into subnetworks by using hierarchical clustering (Camilleri et al., 2018). Hence, in addition to be used to define canonical networks based on whole brain decomposition, RSFC was also used to refine and complement our understanding of specific networks representing important neurocognitive systems.

Limitations, challenges and opportunities in brain network partitions

By enjoying good reliability and important neurobiological insight, popular RSFC-based atlases have provided a referential framework for functional network analyses in a variety of studies, both in healthy and clinical populations (see next section). It should be noted, however that these popular atlases have been derived from surface-based data and consequently, many subcortical regions are not included in these atlases. Examples thereof are the basal ganglia and the hippocampus complex, which are particularly relevant for understanding human cognitive functioning and dysfunction [e.g. (Liu et al., 2020; Strange, Witter, Lein, & Moser, 2014)]. Accordingly, more recently, several studies have used high-quality data to parcellate subcortical structures partly or fully based on RSFC [e.g. (Plachti et al.,

2019; Ye Tian, Margulies, Breakspear, & Zalesky, 2020)] and/or to integrate subcortical structures in cortical network partitions [e.g. (Ji et al., 2019)].

Another important point of attention in the extensive use of canonical network atlases for neuroscientific studies in healthy and clinical populations is the degree of generalizability across the population of these "group average atlases". To address this question, the robust identification of RSFC-based networks across multiple rs-fMRI sessions in an individual has been compared to a group average partition (Laumann et al., 2015). This comparison revealed that most functional systems were grossly topologically similar in the individual and the group, hence supporting the use of group average atlases. However, some differences were also observed between the individual and the group partitions. For example, though the group consensus map includes a region in the lateral occipital-temporal cortex (between the default mode and visual systems) without clear network assignment; in the individual, this same region showed unambiguous system affiliation (Laumann et al., 2015). These observations are consistent with reports of interindividual variability in RSFC [e.g. (Mueller et al., 2013)] and raised the possibility to better understand interindividual variability in behavioral phenotype from individualized parcellation (Kong et al., 2019; Zilles & Amunts, 2013).

Evidence of interindividual variability in brain network partition, and thus in brain functional architecture, also raised the question of the need for population-specific atlases. For instance, the need for sex-specific functional networks has been suggested (Salehi, Karbasi, Shen, Scheinost, & Constable, 2018). Along the same line, brain network partitions in older adults population may differ from those of younger adults thus calling for age group-specific atlases (G. E. Doucet et al., 2021). Whether or not between-group variability is important enough to justify the use of population-specific atlas remain as a relatively open question. That question will be particularly relevant when considering different ethnicity and/or different geographical populations, such as European, African and Asian populations for which population-specific structural brain templates already exist [e.g. (Lee et al., 2016; Rao et al., 2017; Sivaswamy, Thottupattu, Mehta, Sheelakumari, & Kesavadas, 2019; Tang et al., 2010)]. Thus, future studies should evaluate the relevance and practical utility of population specific functional brain atlases.

Applications of brain networks atlases

By providing a robust definition of large-scale networks and brain areas, functional atlases have been applied in a wide range of studies. Soon after their developments, the main functional atlases have been used in clinical studies to identify specific dysfunction in patients (Baker et al., 2014), as well as to study brain organization in childhood (Marek et al., 2019) and functional connectivity changes in aging (Betzel et al., 2014). They have also been broadly used in cognitive neuroscience to better understand the function of brain networks and regions [for a review see (Genon, Reid, Langner, Amunts, &

Eickhoff, 2018)] and interindividual variability in behavior [e.g. (Hearne, Mattingley, & Cocchi, 2016)]. Along the same line, they have been employed to better understand genetic loading on brain organization (Teeuw et al., 2019) and to study the influence of specific environmental condition on brain functioning, such as to demonstrate the effects of sleep deprivation (Yeo, Tandi, & Chee, 2015). In that context, it should be noted that one vital advantage brought by the use of these atlases in a wide range of studies is to offer a common framework to compare findings across studies and, more importantly, to integrate them across different fields of study.

One alternative approach to using brain network atlases for investigating RSFC, for example, in clinical population, consists in deriving the networks from the data at hand. This is frequently done by using ICA (see second section of this chapter) [e.g. (L. Shi et al., 2018)]. However, such an approach comes with the risk of double-dipping (Kriegeskorte, Simmons, Bellgowan, & Baker, 2009). Furthermore, deriving networks from the dataset at hand requires some extra work to identify relevant networks that may not straightforwardly correspond to canonical networks [see (Uddin, Yeo, & Spreng, 2019) for a related discussion] and to discard potentially spurious components. Finally, the networks thereby defined often do not enjoy the stability and generalizability assessments offered by popular atlases.

Canonical networks for machine learning approaches

Deriving the networks form the same dataset on which the research questions is applied became more problematic when studies started capitalizing on machine learning approaches with strict cross-validation. In a cross-validation setting, the dataset is divided into a training and test (holdout) subsample (or set). The model (e.g. predicting intelligence score from RSFC using a linear model) is developed on the training data and tested in the holdout subsample (so by examining the accuracy of intelligence score prediction in the unseen sample). This process of randomly splitting the data into training and test sets is usually repeated for a limited number of times. Generalizability of the model is then evaluated by summarizing (e.g. averaging) out-of-sample accuracies on the holdout sets. In such a framework, the training and test samples should absolutely not share any information. Accordingly, the networks that will serve as features for the predictive model should not be computed as premature featurization, before the cross-validation. In other words, the networks cannot be defined on the original dataset that will serve for testing the model. In that context, functional brain atlases represent a precious resource offering stable and valid networks to be used in machine learning models.

In a didactic view, two types of machine learning approaches can be distinguished: predictive approaches and multivariate associative approaches [or “doubly-multivariate approach” (Smith & Nichols, 2018)]. Brain network atlases have been used for the two types of approaches. In the framework of predictive approaches, brain network atlases can be used when aiming to classify participants into groups, such as to classify patients, based on brain functional connectivity. Furthermore, several studies have employed these atlases when aiming to predict a behavioral measure

from RSFC. Both applications (classification and behavioral prediction) are further developed below. Additionally, several studies have been interested in relating brain functional connectivity to a range of non-brain variables, in particular behavioral variables using a "doubly-multivariate approach". This latter approach is also presented in the last section below.

Connectivity-based prediction approaches in healthy and clinical populations

The pre-defined brain atlases and network structures, characterizing the functional organization of human brain, offer practical tools to reduce data dimensionality for downstream analyses including the prediction of psychometric measures in healthy population and the prediction of symptoms in patients with mental disorders. A pioneer work for predicting individual behavioral scores (e.g. fluid intelligence) from RSFC in healthy population (Finn et al., 2015) used both the Shen atlas (Shen et al., 2013) and the networks derived by Yeo et al. (2011). A behavioral prediction protocol based on connectomes computed across pre-defined functional areas was later proposed and became particularly popular (Shen et al., 2017). Inspired by these works, a series of studies emerged, focusing on predicting specific cognitive measures such as sustained attention and creativity (Beaty et al., 2018; Jiang et al., 2019; Rosenberg et al., 2015), investigating effects of different preprocessing strategies and algorithms on predictive ability (He et al., 2020; J. Li et al., 2019), exploring the feature importance for predicting different categories of psychometric measures (Chen et al., 2020; Ye Tian & Zalesky, 2021; Wu et al., 2021), or comparing the predictive ability across rest, task and naturalistic fMRI modalities (Finn & Bandettini, 2021; Abigail S. Greene, Gao, Noble, Scheinost, & Constable, 2020; Abigail S. Greene, Gao, Scheinost, & Constable, 2018). Importantly, these studies capitalized on several pre-defined brain atlases derived from rs-fMRI (Power et al., 2011; Schaefer et al., 2018; Shen et al., 2013) or multimodal data including fMRI (Glasser et al., 2016) in order to calculate functional connectivity as brain features.

In addition, these brain atlases have played an important role not only in behavioral prediction in healthy population, but also in predicting disease symptoms in patients. For instance, based on the Power atlas (Power et al., 2011), functional connectivity was able to provide additional prediction power of the longitudinal outcomes of autism spectrum disease (e.g. social autistic traits) beyond age and baseline behavioral scores (Plitt, Barnes, Wallace, Kenworthy, & Martin, 2015). Using functional connectivity computed from the same brain atlas, researchers have also investigated its predictability of therapeutic response in individuals with obsessive-compulsive disorder, which would be potentially insightful for personalized medicine to identify patients who might benefit more from the treatment (Reggente et al., 2018). Furthermore, functional connectivity of dorsomedial prefrontal cortex regions, extracted from the Craddock atlas (Craddock et al., 2012), was able to predict the treatment effect of repetitive transcranial magnetic stimulation for major depressive disorder (Salomons et al., 2014). Overall, functional atlases would be crucial tools to extract functional brain features for predicting symptom

severity and treatment outcomes, which could further help the development of precision medicine in the future.

Connectivity in multivariate associative approaches

Besides predictive models based on machine learning algorithms, relationships between brain and behavioral/psychometric/demographic measures can also be explored by multivariate association models such as canonical correlation analysis (CCA) and partial least square (PLS). Such studies can be addressed by the name of "brain-wide association studies" (BWAS). A mile-stone study in this line of research was performed by applying CCA on functional connectivity among the parcels identified by a group ICA and more than 100 non-imaging subject measures. This approach revealed a positive-negative axis in the non-imaging measures associated with a pattern in functional connectivity that had high CCA component loadings in default mode network (Smith et al., 2015). Across healthy participants and patients with schizophrenia, schizoaffective disorder, bipolar disorder and attention-deficit/hyperactivity disorder, three transdiagnostic components corresponding to general psychopathology, cognitive dysfunction and impulsivity were observed to be associated with whole-brain functional connectivity patterns calculated from the Schaefer atlas (Schaefer et al., 2018), especially and strikingly in the somatosensory-motor networks (Kebets et al., 2019) (see Figure 4). Similarly, associations between psychometric/demographic measures and functional connectivity computed from the Glasser atlas (Glasser et al., 2016) have been investigated in healthy and clinically depressed adolescents and young adults (Mihalik et al., 2019). Furthermore, reproducibility of BWAS has been examined where functional connectivity was extracted based on the Gordon atlas (Gordon et al., 2016; Marek et al., 2020). Thus, brain network atlases represent a crucial resource for representing neuroimaging features used as input in brain-wide association studies.

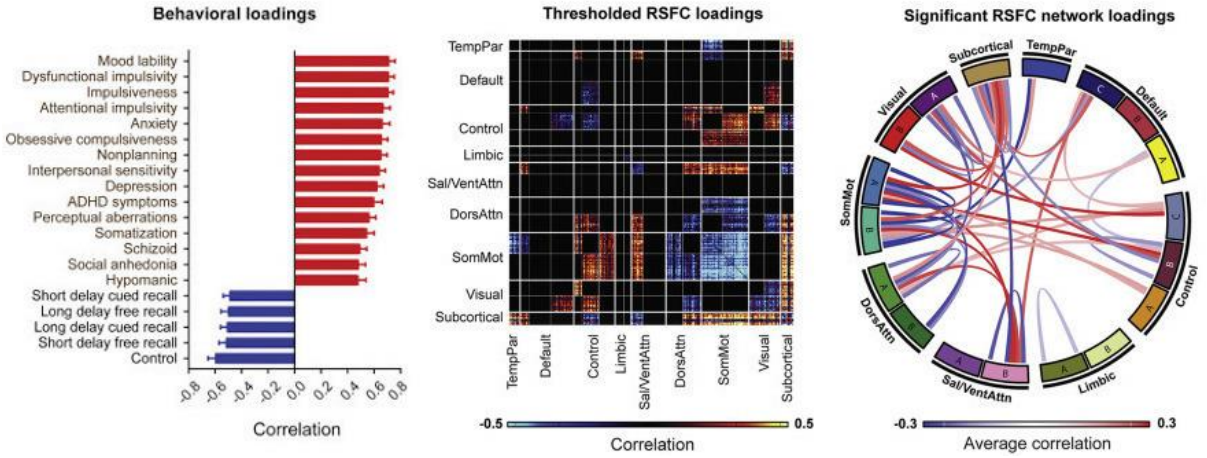

Figure 4. Loadings of the first PLS transdiagnostic component on behavioral measures (left) and on RSFC (middle). The component loadings on RSFC were then averaged within and between networks, shown in a circular plot (right). Adapted from Kebets et al. (2019).

Brain network atlases for feature reduction and alternative approaches

As developed in the previous paragraphs, a range of studies employing machine learning approaches to relate functional connectivity to clinical and behavioral profiles have capitalized on functional atlases derived from rs-fMRI data. Regardless of whether these atlases represent the main canonical networks or local brain regions, they allow to represent RSFC data in a lower dimensional space than the original voxel-wise or vertex-wise data, which is crucially needed for any of the multivariate analyses developed above. In other words, they offer a feature reduction approach independent from the data in which the analysis is performed. Such feature reduction is typically required for neuroimaging data (since for example, computing functional connectivity at the voxel level would result in a pair-wise connectivity matrix of hundreds of thousands of voxels). In addition to be computationally prohibitive, such high dimensional data would be problematic for many machine learning models. For instance, the ratio between the number of features and the number of observations (i.e. participants in a neuroimaging study) has been shown to dramatically influence the reliability of doubly multivariate approaches, such as canonical correlation analysis (Helmer et al., 2021). Thus, functional atlases are vital for machine learning studies in neuroimaging by offering a data representation whose neurobiological qualities have been extensively evaluated and that can thus serve as a reference framework across studies. Meanwhile, they also crucially address the need for independent feature reduction from a technical standpoint.

While the most popular functional atlases are based on RSFC and accordingly many studies have used canonical networks from these atlases, robust functional networks are also provided by meta-analytic approaches of task fMRI and PET studies. As above mentioned, meta-analytic connectivity modelling provides networks of regions that are consistently co-activated together across a range of neuroimaging studies (Langner, Rottschy, Laird, Fox, & Eickhoff, 2014). Additionally, meta-analytic approaches are also applied to neuroimaging experiments to identify a set of regions commonly activated in relation to a specific cognitive concept (Müller et al., 2018). It can hence be assumed that the found set of regions form the network supporting the investigated cognitive process or function (such as autobiographical memory, working memory or motor functions). Accordingly, these networks could be, in turn, used to investigate the relationship between RSFC and behavioral phenotypes [e.g. (Nostro et al., 2018; Pläschke et al., 2017)]. Thus, research capitalizing on meta-analytic networks can interestingly complement those capitalizing on RSFC canonical networks in better understanding the relationship between interindividual variability in RSFC and interindividual variability in behavior.

Conclusions

Several techniques can and have been used to delineate brain networks and parcellate the brain into functional regions based on rs-fMRI data. By well-complementing previous knowledge on brain local organization derived from histological work with features of macroscale organization, these techniques

have significantly contributed to a better understanding of brain organization and function. Regardless of the techniques used, however, a common challenge resides in the choice of the optimal number of components into which the data should be decomposed while considering the multiscale organization of the brain. Accounting for this complexity, several atlases are now available at different levels of subdivisions. Canonical networks provided in popular functional atlases nevertheless still represent a vital resource in neuroimaging research by offering a common reference framework for investigating replicability across studies and better understanding relationship between brain and behavior in healthy and clinical populations. Furthermore, these atlases crucially provide adequate brain features representation for the application of machine learning approaches, which in turn will contribute to the development of brain-based prediction for personalized medicine. In that framework, better understanding and addressing interindividual variability in brain functional organization, and hence in brain atlases, represents an important avenue of research for future studies.

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