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Human brain mapping: A systematic comparison of parcellation methods for the human cerebral cortex

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ABSTRACT

The macro-connectome elucidates the pathways through which brain regions are structurally connected or functionally coupled to perform a specific cognitive task. It embodies the notion of representing and understanding all connections within the brain as a network, while the subdivision of the brain into interacting functional units is inherent in its architecture. As a result, the definition of network nodes is one of the most critical steps in connectivity network analysis. Although brain atlases obtained from cytoarchitecture or anatomy have long been used for this task, connectivity-driven methods have arisen only recently, aiming to delineate more homogeneous and functionally coherent regions. This study provides a systematic comparison between anatomical, connectivity-driven and random parcellation methods proposed in the thriving field of brain parcellation. Using resting-state functional MRI data from the Human Connectome Project and a plethora of quantitative evaluation techniques investigated in the literature, we evaluate 10 subject-level and 24 groupwise parcellation methods at different resolutions. We assess the accuracy of parcellations from four different aspects: (1) reproducibility across different acquisitions and groups, (2) fidelity to the underlying connectivity data, (3) agreement with fMRI task activation, myelin maps, and cytoarchitectural areas, and (4) network analysis. This extensive evaluation of different parcellations generated at the subject and group level highlights the strengths and shortcomings of the various methods and aims to provide a guideline for the choice of parcellation technique and resolution according to the task at hand. The results obtained in this study suggest that there is no optimal method able to address all the challenges faced in this endeavour simultaneously.

1. Introduction

Understanding the brain's behaviour and function has been a prominent and ongoing research subject for over a century (Sporns, 2011). Neuronal interconnections constitute the primary means of information transmission within the brain and are, therefore, strongly related to the way the brain functions (Smith et al., 2013). These connections constitute a complex network that can be estimated at the macro scale via modern imaging techniques such as Magnetic Resonance Imaging (MRI) (Craddock et al., 2013). While structural connectivity networks are typically inferred from diffusion MRI (dMRI), functional networks can be mapped using resting-state functional MRI (rs-fMRI) (Honey et al., 2009; Eickhoff et al., 2015). The former allows estimation of the physical connections, while the latter elucidates putative functional connections between spatially remote brain regions. Analysing brain connectivity from a network theoretical point of view has shown significant potential for identifying organisational principles in the brain and their connections to cognitive procedures and brain disorders (Supekar et al., 2008; Bassett et al., 2008; Smith et al., 2009). This allows to study the brain and its function from a new perspective that accounts for the complexity of its architecture. One of the critical steps in the construction of brain connectivity networks is the definition of the network nodes (Sporns, 2011; Eickhoff et al., 2015). Adopting a vertex- or voxel-based representation yields networks that are very noisy and of extremely high dimensionality, making subsequent network analysis steps often intractable (Thirion et al., 2014). An alternative approach to node definition is to subdivide the brain into a set of distinct regions - i.e. parcellate the brain-, where each parcel corresponds to a node of the connectivity network.

Traditionally, parcellations derived from anatomical landmarks (e.g. AAL) or cytoarchitectonic information (e.g. Brodmann areas) have been used to define regions of interest (ROIs) for network analysis (Sporns, 2011). Whereas such parcellations are of great importance in order to derive neuro-biologically meaningful brain atlases, they might

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fail to fully reflect the intrinsic organisation of the brain and capture the functional variability inherent in individual brains, due to brain maturation or injury. Furthermore, they are typically generated on a single or small set of individuals, which can make them biased and unable to accurately represent population variability. This can lead to ill-defined nodes in the constructed network. For example, it has been shown that the anterior cingulate cortex (ACC) exhibits a great amount of heterogeneity in structural (Beckmann et al., 2009) and functional connectivity (Margulies et al., 2007), despite the fact that it is typically represented as a single ROI in a standard anatomical brain atlas (Tzourio-Mazoyer et al., 2002).

Alternatively, random parcellations can be used to define the network nodes. However, this kind of approach could fail to represent the underlying connectivity faithfully and lead to loss of information (Smith et al., 2011). More recent parcellation approaches attempt to overcome these problems by using connectivity information (e.g. rs-fMRI or dMRI data) to drive parcellations (Eickhoff et al., 2015). Since connectivity-based parcellations are directly obtained from the underlying data, such methods can potentially provide highly homogeneous and functionally coherent parcels and separate regions with different patterns of connectivity more accurately. With this idea in mind, several connectivity-driven parcellation methods have been proposed, usually in association with clustering techniques (Thirion et al., 2014). These methods are based on hierarchical clustering (Mumford et al., 2010; Bellec et al., 2010; Arslan and Rueckert, 2015; Moreno-Dominguez et al., 2014), *k*-means (and its fuzzy counterpart) (Tomassini et al., 2007; Mezer et al., 2009; Golland et al., 2008), Gaussian mixture models (Yeo et al., 2011; Lashkari et al., 2010), spectral graph theory (van den Heuvel et al., 2008; Craddock et al., 2012; Arslan et al., 2015; Parisot et al., 2016a; Shen et al., 2013; Arslan et al., 2016), Markov random fields (MRF) (Ryali et al., 2013; Honnorat et al., 2015; Parisot et al., 2016b), edge detection (Cohen et al., 2008; Laumann et al., 2015; Gordon et al., 2016), region growing (Blumensath et al., 2013; Bellec et al., 2006), independent component analysis (ICA) (Beckmann and Smith, 2004; Smith et al., 2009), Bayesian modelling (Baldassano et al., 2015), meta-analytic connectivity techniques (Eickhoff et al., 2011; Power et al., 2011), dictionary learning (Varoquaux et al., 2011), and many more as extensively reviewed in (Eickhoff et al., 2015; Thirion et al., 2014; de Reus and van den Heuvel, 2013). Although these methods have been thoroughly validated against alternative approaches, a different experimental setup with varying assumptions was used in each case. In addition, the absence of ground truth makes the evaluation of different parcellation methods even more challenging as there is no universally-accepted parcellation that can be used as reference.

In this paper, we propose a systematic comparison of existing parcellation methods using publicly available resources and evaluation measures that are widely used in the literature through a structured experimental pipeline. We focus on resting-state fMRI (rs-fMRI), as the majority of connectivity-driven parcellation methods we are investigating have been developed and tested using this modality. We aim to provide some insight into the reliability of parcellations in terms of reflecting the underlying mechanisms of cognitive function, as well as, revealing their potential impact on network analysis. Thirion et al. (2014) did a similar study at a lower scale, focusing on the analysis of three clustering techniques for fMRI-based brain parcellation, but it only approaches the problem from a clustering point of view. Our study, however, provides a large-scale systematic comparison of the state-of-the-art parcellation methods that encompasses many different aspects in a unified experimental setting.

The main contributions of our study are the following: (1) We evaluate 10 subject-level and 24 groupwise methods using publicly available datasets provided by the Human Connectome Project (Van Essen et al., 2013b). (2) Our experiments consist of quantitative assessments of parcellations at both subject and group levels and for different resolutions. (3) We evaluate parcellations not only from a data clustering point of view but also with regards to network analysis and multi-modal consistency. Our evaluation includes reproducibility (e.g. Dice coefficient and adjusted Rand index), cluster validity analysis (e.g. Silhouette coefficient and parcel homogeneity) and multi-modal comparisons with task fMRI activation, myelin and cytoarchitectural maps. In addition, we compute network statistics with respect to the underlying parcellation and devise simple network-based tasks (such as gender classification) to evaluate the potential impact of parcellations on network analysis at different scales. It should be noted that our aim is not to directly compare single subject parcellations to group-level ones as groupwise parcellations are subject to methodological biases (e.g. registration) which can affect their performance.

The remainder of this paper is organised as follows: Section 2 summarises the procedures pursued during the generation and evaluation of parcellations. Experimental results are presented in Section 3. In Section 4, we discuss the reliability and applicability of parcellations for network analysis and summarise the impact of this study with some insight into the future of brain parcellation.

2. Materials and methods

A summary of the processing pipelines is given in Fig. 1. A brief description of subject- and group-level methods is provided in Tables 1 and 2–3, respectively. We provide further algorithmic/implementation details for each method in Supplementary Material 1.

2.1. Data

This study is carried out using data from the publicly available Human Connectome Project (HCP) database (Van Essen et al., 2013b), S900 release. All connectivity-driven parcellations are derived from the rs-fMRI acquisitions of 100 unrelated subjects (54 female, 46 male adults, aged 22-35). This dataset is publicly available as the “Unrelated 100” in the HCP database and is referred to as “Dataset 1” in the remainder of this paper. For evaluation purposes, we gather a different set of 100 unrelated subjects from the HCP database (Dataset 2) comprising randomly selected 50 male and 50 female adults of age 22-35. The evaluation is performed on Dataset 2 so as to reduce the possible bias towards parcellations computed from Dataset 1 with respect to the provided ones. All subjects had their scans successfully completed for all imaging modalities covered by the HCP.

We use rs-fMRI as our primary data modality for the generation and evaluation of parcellations. This is because most methods selected for this study were developed for rs-fMRI driven parcellation, and rs-fMRI allows test-retest measurements across acquisitions, subjects, and groups. The rs-fMRI scans for each subject were conducted in two sessions, consisting of a total of four runs of approximately 15 minutes each. The sessions were held on different days and during the scans the subjects were presented a fixation cross-hair, projected against a dark background, which prevented them from falling asleep. All subjects

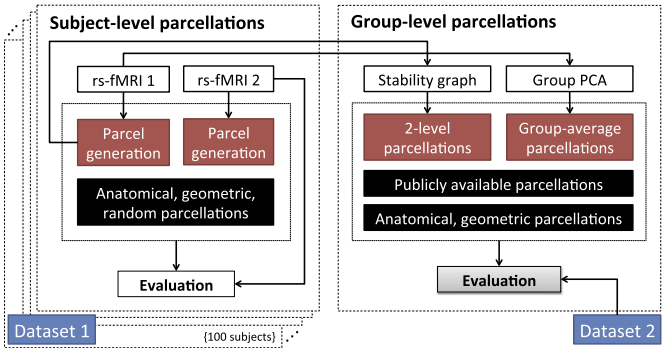

Fig. 1. Visual outline of parcellation generation steps for the subject- and group-level parcellations.