Medical Image Analysis 000 (2015) 1–15

Contents lists available at ScienceDirect

Medical Image Analysis

journal homepage: www.elsevier.com/locate/media

On characterizing population commonalities and subject variations in brain networks☆

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ARTICLE INFO

Article history:
Received 10 November 2014
Revised 25 June 2015
Accepted 21 October 2015
Available online xxx

Keywords:
Connectivity analysis
Non-negative matrix factorization
Multi-layer graph clustering
Population difference
Autism spectrum disorder

ABSTRACT

Brain networks based on resting state connectivity as well as inter-regional anatomical pathways obtained using diffusion imaging have provided insight into pathology and development. Such work has underscored the need for methods that can extract sub-networks that can accurately capture the connectivity patterns of the underlying population while simultaneously describing the variation of sub-networks at the subject level. We have designed a multi-layer graph clustering method that extracts clusters of nodes, called 'network hubs', which display higher levels of connectivity within the cluster than to the rest of the brain. The method determines an atlas of network hubs that describes the population, as well as weights that characterize subject-wise variation in terms of within- and between-hub connectivity. This lowers the dimensionality of brain networks, thereby providing a representation amenable to statistical analyses. The applicability of the proposed technique is demonstrated by extracting an atlas of network hubs for a population of typically developing controls (TDCs) as well as children with autism spectrum disorder (ASD), and using the structural and functional networks of a population to determine the subject-level variation of these hubs and their inter-connectivity. These hubs are then used to compare ASD and TDCs. Our method is generalizable to any population whose connectivity (structural or functional) can be captured via non-negative network graphs.

1. Introduction

Computational techniques applied to neuro-imaging data have shown anomalies in brain activity (Ghanbari et al., 2013) and structural connectivity (Ingalhalikar et al., 2014; Matthews et al., 2013) in neuro-developmental disorders such as schizophrenia (Price et al., 2007; Skudlarski et al., 2010) and autism spectrum disorder (Jou et al., 2011; Vissers et al., 2012). Structural connectivity relies on diffusion imaging to characterize anatomical connections between brain regions (Mori and van Zijl, 2002; Friman et al., 2006). It is quantified using probabilistic (Behrens et al., 2003; Behrens et al., 2003; Friman et al., 2006) or streamline (Mori and Barker, 1999; Mori et al., 1999; Mori and van Zijl, 2002) tractography performed on the diffusion imaging data, resulting in non-negative measures indicative of structural connectivity between brain regions. Functional connectivity based on fMRI, MEG or EEG is investigated at rest or during tasks by quantifying the similarity of temporal characteristics or coherence of brain activity between brain regions using methods such as correlation (Martijn and Hilleke, 2010), synchronization likelihood (Barttfeld et al., 2011; Kim et al., 2013; van Dellen et al., 2013), and coherence (Sakkalis, 2011), or phase-amplitude coupling (PAC) (Berman et al., 2015). Such measures tell us whether there is a structural pathway or functional communication between the two regions (or with PAC connectivity in a local region as well as between regions), and the strength of the connection. While task-related functional connectivity captures brain networks associated with information processing (Sporns et al., 2000), resting state functional connectivity facilitates the study of connectivity in the absence of external stimulation, (Mantini et al., 2007; Assaf et al., 2010).

Autism spectrum disorder (ASD) is a developmental disorder characterized by social and communication impairments, as well as repetitive and restricted behaviors (APA, 1994, 2000). Research indicates that many ASD symptoms are associated with abnormal structural and functional brain connectivity (Vissers et al., 2012; Edgar et al., 2015; Ghanbari et al., 2014). Current theories of brain connectivity in ASD primarily report local over-connectivity in the frontal regions and long range under-connectivity (Just et al., 2012; Vissers et al., 2012). For example, MRI structural connectivity studies suggest ASD is characterized by enhanced short-range and decreased long-range

☆ This paper was recommended for publication by Nicholas Ayache.

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http://dx.doi.org/10.1016/j.media.2015.10.009
1361-8415/

connectivity (Courchesne and Pierce, 2005). MRI functional connectivity studies also report abnormalities, with atypical connectivity between brain regions reported in fMRI studies of ASD, in domains such as social interaction (Perkins et al., 2010), face processing (Critchley et al., 2000; Schultz et al., 2000), as well as in other cognitive tasks (Castelli et al. 2002; Just et al., 2004 , 2007). Electroencephalography (EEG) and magnetoencephalography (MEG) have also examined resting-state activity in ASD, showing that brain connectivity in ASD does not fit into the small-world network model observed in controls (Barttfeld et al., 2011), and that in ASD functional connectivity is deficient in long-range fronto-occipital connections and is excessive in short-range frontal connections (Coben et al., 2008; Barttfeld et al., 2011). Local occipital-parietal resting-state connectivity abnormalities have also been recently reported (Berman et al., 2015).

Given that many neurodevelopmental disorders are thought to be disorders of connectivity, the analysis of brain connectivity is of high importance. Recently, connectivity analysis has focused on representing brain connectivity using graphs, where the brain is divided into regions of interest (ROI), each of which is a node in the graph, with the edges weighted with the connection strength between two brain ROIs. Graph representations are, however, of high dimensionality, and thus difficult to analyze and interpret. Graph theory metrics (Bullmore, 2009; Rubinov and Sporns, 2010) have been recently introduced to analyze the complex organization of brain networks by providing features such as small-worldness, modularity, centrality, and participation coefficient (Sporns et al., 2007; Bassett et al., 2011; Ingalhalikar et al., 2014). Although some of these features have shown to be associated with pathology (Barttfeld et al., 2011; Rudie et al., 2012; Griffa et al., 2013), they are difficult to interpret for non-sparse and highly variable connectivity networks.

Commonalities in these networks over a population, and the variation at the individual level, underline the need for a network analysis methodology that can extract sub-networks that are able to characterize the population network structure while reducing dimensionality. Ideally, these sub-networks will describe local brain processes, with sub-network interactions measuring communication between sub-networks, thereby characterizing long- and short-range connectivity patterns. This would provide an interpretable brain network map while also facilitating statistical analyses that describe how this brain network is affected by disease. Although traditional approaches such as principal and independent components analysis (PCA and ICA) (Calhoun et al., 2008) provide dimensionality reduction, such approaches when applied to functional or structural connectivity networks, in the absence of positivity constraints, produce components that often lack physiological interpretability. Such positivity constraints are needed in the case of DTI-based connectivity matrices, as the connection measures quantify the anatomical connectivity between regions; hence its relationship with anatomy is the constraining factor for it to be non-negative. In functional connectivity, too, when the connectivity is quantified by a non-negative measure, like synchronization likelihood, as opposed to correlation, the components or sub-networks obtained from analysis are interpretable in the same space of connectivity quantification if they are non-negative.

Recently, hierarchical mixture model was used estimated functional networks in resting state fMRI (Liu et al., 2014). This model finds networks that account for both within subject coherence and between-subject consistency of the network label maps, however does not constrain the networks with non-negativity that is important for interpretability in applications such as MEG or DTI.

To overcome this issue, non-negative matrix factorization (NMF) and its alternatives have recently gained attention and have been effective in providing an interpretable set of bases characterizing multivariate data. Since its introduction by Lee and Seung (1999), NMF has been successfully employed in applications such as signal processing, pattern recognition, data mining, and medical imaging

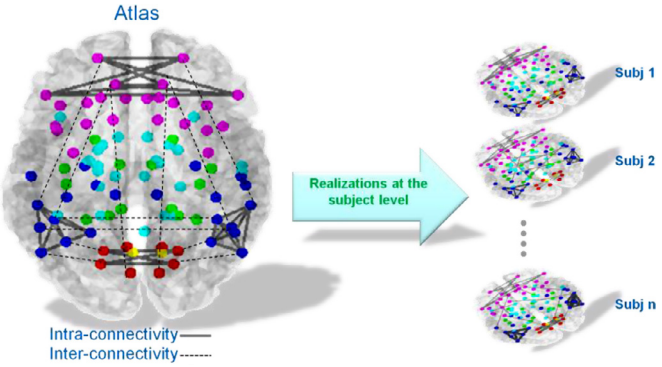

Fig. 1. The brain network is hypothesized to be made up of several hubs that are interconnected (dashed lines), with each hub composed of a set of highly connected nodes (solid lines). The collection of hubs is considered as an atlas of connectivity. On the right, the subject-wise realizations of this network atlas show subject level variation.

(Berry et al., 2007; Yang and Oja, 2010; Batmanghelich et al., 2012; Ghanbari et al., 2013). Despite the advantages in interpretability that NMF offers over other dimensionality reduction techniques (PCA, ICA, etc.), due principally to its part-based representation of data and non-negativity constraints on both the bases and coefficients, it does possess drawbacks. Namely, traditional NMF requires that connectivity matrices be vectorized prior to being used as a feature vector in the analysis pipeline. This vectorization of the connectivity matrix simply treats the relationship (i.e. connectivity) between pairs of nodes as independent and overlooks the inter-dependency between the connections emanating from that node, thereby losing the graph structure that such nodes and their inter-connections form.

In this paper, we present a novel approach that extracts the underlying functional/structural sub-networks that describe the hubs of the brain connectivity network while capturing variation in the population. Our framework does not treat the connectivity between pairs of nodes as being strictly independent, but instead is based on the premise that there are a few underlying sub-networks that describe the population, with variations in these networks representative of variations in the subjects. We have therefore designed a method that extracts sets of nodes – called hubs – that communicate strongly within each set, with the collection of hubs characterizing the population. As the intra- and inter-connectivity of these hubs plays an important role in describing brain connectivity, the presented method determines the dominant network hubs that characterize commonality across subjects within a population, with connectivity between these hubs capturing the individualized variation (e.g., due to inherent heterogeneity or induced by pathology). This collection of network hubs is referred to as a network atlas. Fig. 1-left illustrates a hub atlas composed of four network hubs that are strongly connected within each hub (shown by thick connections) and with inter-connectivity between hubs shown by dashed lines.

The manifestation of the network atlas at the subject level can be highly variable (as illustrated in Fig. 1-right). Hence, the primary aim of this work is to identify the network hubs of the population, which define its atlas of connectivity. These hubs will determine the commonalities across the population networks, as illustrated in Fig. 2(a). As shown in Fig. 2(b), given the connectivity network of a subject and the atlas of hubs, our proposed method will: (a) quantify the contribution of each hub to that subject's network (illustrated by the size of each hub on the right side of Fig. 2(b)), and (b) quantify the overall interaction (inter-connectivity) between pairs of hubs (illustrated by the thickness of connections between hubs on the right side of Fig. 2(b)). These subject-level measures will then be used for statistical analysis and group comparisons.

The approach we take to extract network hubs is based on multi-layer graph clustering. The advent of graph-based clustering

Please cite this article as: Y. Ghanbari et al., On characterizing population commonalities and subject variations in brain networks, Medical Image Analysis (2015), http://dx.doi.org/10.1016/j.media.2015.10.009