Medical Image Analysis 20 (2015) 52–60

Contents lists available at ScienceDirect

Medical Image Analysis

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

Manifold learning on brain functional networks in aging

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ARTICLE INFO

Article history:
Received 11 October 2013
Received in revised form 5 August 2014
Accepted 21 October 2014
Available online 30 October 2014

Keywords:
Resting state fMRI
Symmetric positive definite matrix
Log-Euclidean Riemannian manifold
Locally linear embedding
Ridge regression

ABSTRACT

We propose a new analysis framework to utilize the full information of brain functional networks for computing the mean of a set of brain functional networks and embedding brain functional networks into a low-dimensional space in which traditional regression and classification analyses can be easily employed. For this, we first represent the brain functional network by a symmetric positive matrix computed using sparse inverse covariance estimation. We then impose a Log-Euclidean Riemannian manifold structure on brain functional networks whose norm gives a convenient and practical way to define a mean. Finally, based on the fact that the computation of linear operations can be done in the tangent space of this Riemannian manifold, we adopt Locally Linear Embedding (LLE) to the Log-Euclidean Riemannian manifold space in order to embed the brain functional networks into a low-dimensional space. We show that the integration of the Log-Euclidean manifold with LLE provides more efficient and succinct representation of the functional network and facilitates regression analysis, such as ridge regression, on the brain functional network to more accurately predict age when compared to that of the Euclidean space of functional networks with LLE. Interestingly, using the Log-Euclidean analysis framework, we demonstrate the integration and segregation of cortical–subcortical networks as well as among the salience, executive, and emotional networks across lifespan.

1. Introduction

The brain at rest is not idle but shows continuous, spontaneous fluctuations in activity among spatially distributed but functionally connected regions. Resting state functional magnetic resonance imaging (rs-fMRI) has been recognized as a useful technique to investigate complex patterns of brain functional organization at rest. It has been increasingly used in studies of normal aging and neurodegenerative diseases (Venkataraman et al., 2013; Deligianni et al., 2011; Bluhm et al., 2008; Wang et al., 2010; Tomasi and Volkow, 2012) as it is unbiased to confounds associated with task-based fMRI, such as task difficulty and performance.

A large body of rs-fMRI aging studies have employed graph theory to characterize "small-world" properties of the brain across lifespan, meaning that many networks have both local clustering of connections and a short path length between any two brain regions (Achard and Bullmore, 2007; Bullmore and Sporns, 2012; Meunier et al., 2009). However, a decrease of both global and local network efficiency was shown in older adults in comparison to young adults (Achard and Bullmore, 2007). Using graph theory, Newman's modularity metric can be defined to measure the strength of division of the brain functional network into modules. Previous studies (e.g., (Meunier et al., 2009)) revealed that normal brain aging was associated with changes in modularity of sparse functional networks. In particular, both young and older brain networks demonstrated significantly non-random modularity but the older brain showed a reduced number of intermodular connections to frontal modular regions and an increased number of connector nodes in posterior and central modules (Meunier et al., 2009). In addition to the aforementioned metrics that characterize the topology of the brain functional network, researchers also investigated age-related effects on the connectivity of individual structures and showed the age decline of major functional connectivity hubs in the 'default-mode' network (DMN) (Damoiseaux et al., 2008a; Bluhm et al., 2008; Wang et al., 2010; Tomasi and Volkow, 2012). A reduction of the connectivity between the anterior cingulate cortex and bilateral insular in salience network in older adults

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http://dx.doi.org/10.1016/j.media.2014.10.006
1361-8415/

suggested an age-related deficits in decision-making and sensory integration (Onoda et al., 2012; Seeley et al., 2007). Decreased functional connectivity in the left premotor area and right cingulate motor cortex was found in older adults in comparison to young adults (Wu et al., 2007).

Recently, support vector machine (SVM) has been employed on rs-fMRI for the prediction of individual brain maturity, in which a subset of elements in the functional connectivity matrix derived from rs-fMRI were used as features (Dosenbach et al., 2010). Wang et al. (2012) assumed that variations of the functional networks are driven by variations in a small subset of unknown parameters. A supervised locality preserving projection (LPP) algorithm (He et al., 2005) was employed to learn a low-dimensional representation of brain development from many individuals at different ages and support vector regression (SVR) models were designed in this low-dimensional space for making continuously valued predictions about the functional development levels of individual brains. However, arithmetic operations on the matrices of brain functional networks, such as non-convex Euclidean operations, could result in undesirable properties of the matrices as discussed below.

Brain function network modeling has thus far largely based on (partial) correlation analysis of rs-fMRI time series data among brain regions, suggesting that the brain functional network can be fully characterized by a symmetric positive semi-definite matrix. Ideally, if the brain parcellated regions, served as network nodes, are functionally distinct from each other, then the functional network can be represented by a symmetric positive definite (SPD) matrix. When considering a SPD matrix as an element in a finite-dimensional Euclidean space, arithmetic operations, such as mean, does not satisfy certain desirable properties. For example, the linear average of SPD matrices is not the inverse of the linear average of the inverses of the SPD matrices. There have been great efforts on carrying out computations with SPD matrices in a curved space, called a manifold, in medical image analysis (Fillard et al., 2007; Arsigny et al., 2006; Pennec et al., 2006). In the manifold setting, a SPD matrix can be represented as an element in a vector space in which the mean and variance of SPD matrices can be easily computed with certain desirable properties. For instance, Arsigny et al. (2007) proposed a Riemannian framework on SPD matrices, which leads to the computation of the mean of SPD matrices while preserving the aforementioned desirable properties. It has been widely used to study the mean and variation of diffusion tensor imaging of the brain (Fillard et al., 2007). This manifold setting of SPD has been recently employed to investigate brain functional-connectivity difference in post-stroke patients (Varoquaux et al., 2010), which demonstrates an increase in statistical power in detecting functional disconnections in the patients when compared to the Euclidean setting of SPD. Manifold learning analysis was also widely used for studying anatomical shapes (e.g. (Aljabar et al., 2011)).

Here, we adopt the Riemannian framework of SPD matrices introduced by Arsigny et al. (2007) and propose a new analysis framework to utilize the full information of brain functional networks for computing the mean of a set of brain functional networks and embedding brain functional networks into a low-dimensional space in which regression and classification analyses can be easily employed. For this, we first represent the brain functional network by a SPD matrix computed using sparse inverse covariance estimation (Huang et al., 2010). Huang et al. (2010) employed the sparse inverse covariance estimation approach to compute functional connectivity matrices at different sparsity levels and detected differences of functional connectivity among mild cognitive impairment patients, Alzheimer's patients and normal controls. We then impose a Log-Euclidean Riemannian manifold structure on brain functional networks whose norm gives a convenient and practical way to define a mean. The metric in the Log-Euclidean Riemannian manifold leads to easy and efficient computation of the mean of SPD matrices. This is different from the work in Varoquaux et al. (2010), where affine-invariant metric in the Riemannian manifold of SPD matrices is used and involves intensive computation of matrix inverses, square roots, logarithms, and exponentials. Varoquaux et al. (2010) proposed a matrix variate probabilistic model suitable for inter-subject comparison of functional connectivity matrices on the affine-invariant manifold of SPD matrices, leading to a new algorithm for principled comparison of connectivity coefficients between pairs of regions. Finally, based on the fact that the computation of linear operations can be done in the tangent space of this Riemannian manifold, we adopt Locally Linear Embedding (LLE) (Roweis and Saul, 2000) to the Log-Euclidean Riemannian manifold space for embedding the brain functional networks into a low-dimensional space. Using this framework, we show the evolution of the brain functional network across lifespan and the comparison between the Log-Euclidean and Euclidean spaces of brain functional networks in terms of the prediction accuracy of biological age.

2. Methods

2.1. Subjects

This study was approved by the National University of Singapore Institutional Review Board. All participants provided written informed consent prior to the participation. Two-hundreds and fourteen healthy Singaporean Chinese volunteers aged 21–80 years old were recruited (males: 93; females: 121) for this study. The participants were recruited via advertisements and screened for eligibility through a phone interview prior to an onsite visit. Volunteers with the following conditions were excluded: (1) major illnesses/surgery (heart, brain, kidney, lung surgery); (2) neurological or psychiatric disorders; (3) learning disability or attention deficit; (4) head injury with loss of consciousness; (5) non-removable metal objects on/in the body such as cardiac pacemaker; (8) diabetes or obesity; (9) a Mini-Mental State Examination (MMSE) score of less than 24 (Ng et al., 2007). This study only included 178 right-handed subjects (age: 22–79 years; males: 71; females: 107) who completed structural and function MRI. The distribution of age among these subjects is shown in Fig. 1.

2.2. MRI acquisition and analysis

MRI was performed on a 3T Siemens Magnetom Trio Tim scanner using a 32-channel head coil at Clinical Imaging Research Centre of the National University of Singapore. The image protocols

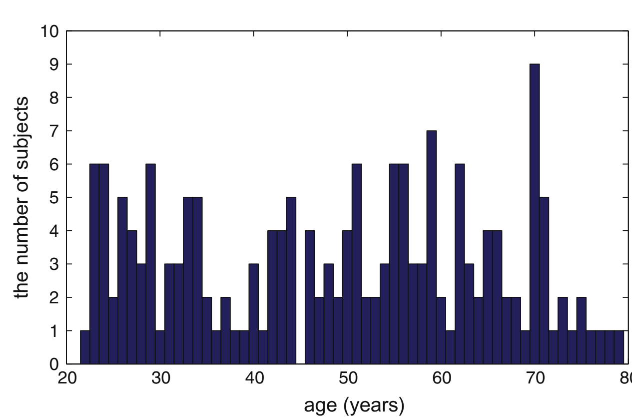

Fig. 1. Age distribution among 178 subjects.