ESTIMATION OF HIGH-DIMENSIONAL BRAIN CONNECTIVITY NETWORKS USING FUNCTIONAL MAGNETIC RESONANCE IMAGING DATA

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DEDICATION

This thesis is dedicated to my parents, who always give their constant and unconditional love and support to me in everything I do.

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ABSTRACT

Recent studies in neuroimaging show increasing interest in mapping the brain connectivity. It can be potentially useful as biomarkers in identifying neuropsychiatric diseases as well as tool for psychological studies. This study considers the problem of modeling high-dimensional brain connectivity using statistical approach and estimate the connectivity between functional magnetic resonance imaging (fMRI) time series data measured from brain regions. The high-dimension of fMRI data (N) corresponding to the number of brain regions, is typically much larger than sample size or the number of time points taken (T). In this setting, the conventional connectivity estimators such as sample covariance and least-square (LS) estimator are no longer consistent and reliable. In addition, the traditional analysis assumes the brain network to be time-invariant but recent neuroimaging studies show brain connectivity is changing over the experimental time course. This study developed a novel shrinkage approach to characterize directed brain connectivity in high-dimension. The shrinkage method is involved in incorporating shrinkage-based estimators (Ledoit-Wolf (LW) and Rao-Blackwell LW (RBLW)) in the covariance matrix and LS-based linear regression fitting of vector autoregressive (VAR) model, to reduce the mean squared error of estimates in both high-dimensional functional and effective connectivity. This allows better conditioned and invertible estimated matrix which is important to generate a reliable estimator. Then, the shrinkage-based VAR estimator has been extended to estimate time-evolving effective brain connectivity. The shrinkage-based methods are evaluated via simulations and applied to fMRI resting-state data. Simulation results show reduced mean squared error of estimated connectivity matrix in LW and RBLW-based estimators as compared to conventional sample covariance and LS estimators in both static and dynamic connectivity analysis. These estimators show robustness towards the increasing dimension. Result on real resting-state fMRI data showed that the proposed methods are able to identify functionally-related resting-state brain connectivity networks and evolution of connectivity states across time. It provides additional insights into human whole-brain connectivity during at rest as compared to previous finding particularly in the directionality of connectivity in high-dimensional brain networks.

ABSTRAK

Kajian pengimejan neuro terkini menunjukkan peningkatan minat dalam pemetaan perhubungan rangkaian otak, ia berpotensi digunakan untuk mengenal pasti penyakit psikiatrik neurologi serta sebagai alat dalam kajian psikologi. Kaedah statistik digunakan dalam kajian ini untuk memodelkan dan menganggarkan perhubungan otak daripada data-data berdimensi tinggi yang diukur melalui pengimejan resonans magnet kefungsian (fMRI). Dimensi data fMRI (N) sepadan dengan bilangan kawasan otak, biasanya lebih besar dari ukuran sampel atau bilangan titik waktu diambil (T). Dalam tetapan ini, penganggar konvensional seperti sampel kovarians dan kuasa dua terkecil (LS) tidak konsisten dan tepat dalam anggaran. Selain itu, analisis tradisional menganggar data fMRI sebagai data yang statik tetapi kajian neuroimaging baru-baru ini menunjukkan perhubungan otak berubah sepanjang waktu eksperimen. Kaedah penyusutan dicadangkan untuk memodelkan perhubungan otak berarah yang berdimensi tinggi. Ia menggabungkan penaksir berasaskan penyusutan Ledoit-Wolf (LW) dan Rao-Blackwell LW (RBLW) dalam matriks sampel kovarians dan regresi berkadar langsung LS bawah model vektor autoregresif (VAR), untuk mengurangkan kesilapan persegi dalam anggaran sambungan fungsi dan efektif yang berdimensi tinggi. Ini memastikan anggaran matriks dalam keadaan yang baik dan boleh diubahsuai. Penganggar penyusutan ini kemudianya dilanjutkan untuk menganggarkan perhubungan otak efektif bagi tujuan merakam sifat dinamik isyarat otak. Kaedah penyusutan yang dicadangkan telah dinilai melalui simulasi dan diaplikasikan pada data fMRI yang berkeadaan rehat. Hasil simulasi menunjukkan pengurangan pada kesilapan persegi di matriks perhubungan yang dianggarkan oleh penganggar LW dan RBLW berbanding dengan penganggar sampel kovarians dan LS dalam analisis perhubungan statik dan dinamik. Penganggar-penggangar ini juga dapat memastikan ketepatan terhadap dimensi yang semakin meningkat. Aplikasi pada data fMRI yang berkeadaan rehat menunjukkan kaedah penyusutan dapat mengenal pasti perhubungan otak berehat yang berlainan fungsi dan perubahannya sepanjang masa. Ia memberikan gambaran berguna tentang perhubungan otak manusia semasa rehat berbanding dengan hasil kajian sebelumnya, terutamanya dalam perhubungan rangkaian otak yang berdimensi tinggi ini.

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LIST OF ABBREVIATIONS

1D	-	1-dimension
2D	-	2-dimensions
3D	-	3-dimensions
AAL	-	Automated anatomical labeling
ADHD	-	Attention deficit hyperactivity disorder
AFNI	-	Analysis of Functional NeuroImages
AM	-	Autobiographical memory
BOLD	-	Blood oxygen level-dependent
BV	-	Brain Voyager
CC	-	Cross-correlation
CSF	-	Cerebrospinal fluid
CT	-	Computerized tomograhy
DAE	-	Deep auto-encoder
DCC	-	Dyanmic conditional correlation
DCM	-	Dynamic causal modeling
DICOM	-	Digital imaging and communications in medicine
DMN	-	Default mode network
DOF	-	Degree of freedom
DTI	-	Diffusion tensor imaging
DWI	-	Diffusion-weighted imaging
ECoG	-	Electrocorticography
EEG	-	Electroencephalogram
EPI	-	Echo-planar imaging
EWMA	-	Exponential weighted moving average
fMRI	-	Functional magnetic resonance imaging
fNIRS	-	Functional near-infrared spectroscopy

FOV	-	Field of view
FPCN	-	Fronto-parietal cognitive control network
FSL	-	FMRIB Software Library
FWHM	-	Full width half maximum
GCM	-	Granger causality modeling
GLM	-	General linear model
GUI	-	Graphical user interface
HC	-	Hippocampus
HMM	-	Hidden Markov model
HRF	-	Hemodynamic response function
ICA	-	Independent component analysis
IPC	-	Inferior parietal cortex
IPL	-	Inferior parietal lobule
ITC	-	Inferior temporal cortex
LS	-	Least-square
LTI	-	Linear time-invariant
LW	-	Ledoit-Wolf
LW-VAR	-	Ledoit-Wolf shrinkage vector autoregressive
MAR	-	Multivariate autoregressives
MCI	-	Mild cognitive impairment
MDD	-	Major depressive disorder
ME	-	Motor execution
MEG	-	Magnetoencephalography
MELODIC	-	Multivariate Exploratory Linear Optimized Decomposi-
	-	tion into Independent Components
MI	-	Motor imagery
MNI	-	Montreal Neuroimaging Institute
MPFC	-	Medial prefrontal cortex
MRA	-	Magnetic resonance angiography

MRI	-	Magnetic resonance imaging
MSE	-	Mean squared error
MSFA	-	Multi-scale factor analysis
MVAR	-	Multivariate vector autoregressive
NIfTI	-	Neuroimaging Informatics Technology Initiative
NITRC	-	NeuroImaging Tools & Resource Collaboratory
OAS	-	Oracle approximating shrinkage
OCM	-	Oculomotor
PCC	-	Posterior cingulate cortex
PEB	-	Parametric empirical Bayes
PET	-	Positron emission transmission
PMd	-	Left dorsal premotor cortex
PWI	-	Perfusion-weighted imaging
RBLW	-	Rao-Blackwell Ledoit-Wolf
RF	-	Radiofrequency
RFT	-	Random field theory
ROI	-	Regions of interest
RSMFC	-	Random subspace method for functional connectivity
RSN	-	Resting-state network
rtfMRI-nf	-	Real-time fMRI neurofeedback
SCAD	-	Smoothly clipped absolute deviation
SEM	-	Structural equation modeling
SINGLE	-	Smooth incremental graphical lasso estimation
SIRV	-	Spherically invariant random vectors
SMA	-	Supplementary motor area
SN	-	Simulated networks
spDCM	-	Spectral dynamic causal modeling
SPL	-	Superior parietal lobule
SPM	-	Statistical parametric mapping

SVAR	-	Switching vector autoregressive
SWC	-	Sliding-window correlations
TE	-	Echo time
TI	-	Total interdependence
TR	-	Repetition time
TV-AR	-	Time-varying autoregressive
TV-VAR	-	Time-varying vector autoregressive
VAR	-	Vector autoregressive
WHO	-	World Health Organization

LIST OF SYMBOLS

$\hat{\mathbf{A}}_{LS}$	-	Estimated matrix by LS estimator
$\hat{\mathbf{A}}_{LW}$	-	Estimated matrix by LW shrinkage estimator
$\mathbf{A}_{\ell}$	-	VAR coefficients with lag ℓ
$\mathbf{A}_{\ell t}$	-	Coefficient matrix at lag ℓ during time t
$\mathbf{A}_{p}$	-	Estimated VAR coefficients on p order
$\hat{\mathbf{A}}_{t}^{LW}$	-	Estimated LW estimator of time-varying AR parameters
a_{ij}	-	Cross-correlation between i and j
α_{AB}	-	Coefficient of directed connections from A to B
α_{AC}	-	Coefficient of directed connections from A to C
α_{CB}	-	Coefficient of directed connections from C to B
B_0	-	External magnetic field strength
B_j	-	Bilinear parameter for j^{th} input
$\boldsymbol{\beta}$	-	Matrix composed of all lags
$\hat{\boldsymbol{\beta}}_{LS}$	-	Matrix composed of LS coefficients with all lags
$\hat{\boldsymbol{\beta}}_{LW}$	-	Matrix composed of LW coefficients with all lags
$\mathbf{C}_j$	-	A set of K clusters
$cov(y_{it}, y_{jt})$	-	Cross-covariance between the signal y_{it} and signal y_{jt}
$\mathbf{E}$	-	Noise components of each timepoint
Σ	-	Population covariance matrix
$\hat{\Sigma}_{LW}$	-	Estimated matrix from LW shrinkage estimator
$\hat{\Sigma}_{RBLW}$	-	Estimated matrix from RBLW shrinkage estimator
Σ_{η}	-	Noise covariance structure
$\boldsymbol{\varepsilon}_t$	-	Noise coefficient on time t
σ	-	Variance
σ^2	-	Standard deviation

$\hat{\mathbf{F}}$	-	Shrinkage target
ϕ_y	-	Connectivity strength value of y signal
k_x	-	k-axes in x-direction
k_y	-	k-axes in y-direction
k_z	-	k-axes in z-direction
K	-	Number of K-means clusters
K	-	Number of connectivity state
ℓ_{LS}	-	Changes of estimation error by LS
ℓ_{LW}	-	Changes of estimation error by LW
ℓ_{RBLW}	-	Changes of estimation error by RBLW
N	-	Number of dimension
$N(0, \sum)$	-	Gaussian distribution with zero mean and covariance $\sum$
n_r	-	Number of voxel for each ROI
$\hat{\rho}_{LW}$	-	LW shrinkage coefficient
$\hat{\rho}_{RBLW}$	-	RBLW shrinkage coefficient
$\hat{\mathbf{S}}$	-	Sample covariance matrix
$\hat{S}_t^{KM}$	-	Estimated state sequence at time point t
T	-	Sample size
T	-	Tesla
$T1$	-	Longitudinal relaxation time
$T2$	-	Spin-spin relaxation time
$U[-0.25 \quad 0.25]$	-	Uniform distribution between value -0.25 and 0.25
$U[-0.5 \quad 0.5]$	-	Uniform distribution between value -0.5 and 0.5
$u(t)$	-	Input function of stimulus
$\boldsymbol{\mu}$	-	Mean
$\boldsymbol{\mu}_j$	-	Median cluster of $\mathbf{C}_j$
$\hat{\boldsymbol{\mu}}_t$	-	Sample mean
$WN(0, \mathbf{R})$	-	Gaussian white noise (mean zero, covariance matrix $\mathbf{R}$)
ω	-	Precession frequency

$\mathbf{X}$	-	Matrix of previous observations
$\mathbf{Y}$	-	fMRI time series data matrix
y_t	-	Multivariate time series
$y(t)$	-	Hemodynamic response or time series signal
y_{kt}	-	k-dimensional time series measured on time t
γ	-	Gyromagnetic ratio

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CHAPTER 1

INTRODUCTION

1.1 Introduction

Conventional neuroimaging studies focused on structural analysis especially in white matter, grey matter and central nervous system. It has been a shift of research interest from human brain surface morphometry to functional and effective connectivity mapping of the brain, i.e. interactions between different brain regions as a network, thanks to the recent advances in neuroimaging technology available nowadays on medical devices such as magnetic resonance imaging (MRI), functional MRI (fMRI), diffusion tensor imaging (DTI), electroencephalogram (EEG), magnetoencephalography (MEG) etc [1]. The advances in neuroimaging technology and techniques developed have sparked new insights into the relationship between different brain regions during the performance of some tasks or respond to stimulus or even during a resting state.

Computational neuroscience is a multi-disciplinary study combining cognitive neuropsychology, biomedical engineering, statistics, physics, etc. One aim is to construct a brain activation map and also brain connectivity map for neuroimaging data [2]. The identified brain maps can reveal valuable information on the functional integration and segregation between different brain regions (hearing, motor, vision, sensory, smell etc.) of the human brain networks for the study of cognitive psychology and various neuropsychiatric disorder. Identifying the disruptions in the brain maps of patients with brain disorders relative to healthy subject is potentially useful for establishing bio-markers towards the development of reliable and robust diagnostic tools in clinical and pre-clinical settings.

Statistical models such as covariance matrix have been used to quantify functional brain connectivity. However, there are still challenges in developing more efficient techniques for modelling the complex and high-dimensional structure of the brain connectivity network.

This thesis developed a novel shrinkage-based approach that is capable of analyzing large-sized brain connectivity networks from high-dimensional fMRI data. The covariance matrix and least square estimator are widely applied in various studies especially in time series analysis, such as biomedical signals, financial time series and etc. However, these conventional estimators are no longer accurate when the dimension of the signals are larger than the sample size. This thesis addresses some of the important problems in functional and effective brain connectivity estimation. In this work, the research consider the problem of high-dimensional brain connectivity estimation for both the functional and effective brain connectivity and time-varying brain connectivity states by using fMRI data.

1.2 Problem Background

A report from the World Health Organization (WHO) addressed that neurological disorder ranging from epilepsy to dementia, from brain stroke to headache, has affected almost up to 1 billion people worldwide. Another report, *Neurological disorders: Public health challenges*, has reported the number of people who suffered from epilepsy worldwide has reached 50 million while 24 millions people have suffered from Alzheimer's and other dementia problem. As for the fatal rate, an estimate of 6.8 million people die every year due to neurological diseases [3]. Thus early detection of these diseases is crucial in reducing fatality, increase recovery rate as well as prevent recurrence of the same disease. Biomedical signal processing is useful for advance medical and clinical diagnostic for early detection and diagnostic. Brain signal is a type of biomedical signals that can measure neurological activity in the brain, collected in different modalities, e.g., electroencephalogram (EEG), computerized tomography (CT), positron emission transmission (PET), and fMRI.

Magnetic Resonance Imaging (MRI) is one of the clinically recognized non-invasive diagnostic methods which is accepted extensively among experts in the medical field. This technique allows construction of brain images in both structural and functional way to study anatomical structure and physiology function of a particular organ and system. MRI scanners use strong magnetic fields, electric field gradients, and radio waves in generating images of joints, cartilage, muscle structure, tendons, ligaments and brain structure. The method is non-invasive and so far there is no evidence shows subjects are at risk for being exposed to radiation. Several available techniques from MRI machine are spin echo, gradient echo, inversion recovery, diffusion-weighted imaging (DWI), perfusion weighted imaging (PWI), functional MRI (fMRI), magnetic resonance angiography (MRA) and venography.

Since its introduction in 1991, functional MRI (fMRI) has been widely used in neuroscience research [4]. The principle of fMRI is based on blood oxygen level-dependent (BOLD) contrast to produce a 3-dimensions (3D) image of the subject. The acquired data contain information on both structural and functional data of the scanned body part. When applied in brain scanning, fMRI images can be used to map brain activation and brain connectivity.

Brain connectivity analysis is a multi-dimensional analysis where the researchers are interested in identifying any interconnections or inter-dependencies between different brain regions [5]. There are two types of brain connectivity commonly studied, i.e. functional connectivity and effective connectivity. Functional connectivity is the temporal correlation between spatially remote neurophysiological events, expressed as the deviation from statistical independence across these events in distributed neuronal groups and areas. Effective connectivity describes a network of directional influence of one neural element over another [5]. Research on brain connectivity could provide potential insights to the brain function and the identified brain connectivity pattern can be used as biomarkers of neuropsychiatric diseases such as Alzheimer's, dementia and epilepsy [6] related to brain network of healthy subjects. Brain connectivity analysis is carried out on time series data extracted from fMRI images.

Conventional statistical inference focuses on lower-dimensional data when the length of the time-series (T) is much larger than the number of brain sites studied (N), however, this is exactly the reverse of the situation in neuroimaging data. The number of functional magnetic imaging (fMRI) time series associated with the brain regions can be an order of ten thousand but observed in only hundreds of scans. It poses some statistical challenges, where relatively short time-series (due to limited time scans) are measured over thousands of voxels [7, 8]. The traditional covariance matrices and their inverses are playing big roles in the analysis of cross-sectional dependencies between multivariate data or time series. However, they are only consistent and invertible in low-dimensional condition although easy to construct and unbiased. Inferring and estimating the true covariance matrix from the high-dimensional neuroimaging data is a critical statistical problem. Sample covariance matrix, a commonly used estimator of the population covariance matrix, is no longer reliable when the dimension is very high compared to the sample size. Modern sciences and engineering commonly involve analysis of high-dimensional data. Thus, the problem of estimating high-dimensional covariance matrices and their precision matrices is addressed in this research. In particular, this thesis consider a class of shrinkage-based estimators for identifying high-dimensional functional and effective connectivity from fMRI data.

Multi-dimensional analysis is able to provide the information on how the brain regions are interconnected and inter-dependent to one another. Conventionally, univariate method such as autoregressive modeling [9, 10] has been used to infer temporal dependency in the brain signals. However, the univariate analysis neglects the spatial dependence between different signals measured from distinct locations of the brain [11, 12]. Instead of using univariate models, multivariate models are more favorable due to the process of univariate autoregressive only includes correlation in time precedence of a signal and the correlation between regions is not taken into account [13, 14]. The inter-regional connectivity is unable to be determined directly from univariate models. Therefore, generalization of univariate model to multivariate model is needed to characterize brain connectivity networks [15]. By incorporating multivariate model in the analysis, the inter-regional correlation could give additional information to discriminate between different brain conditions by measuring the synchronization between coupling regions and the coherency among them [16].

Recent studies on brain connectivity analysis have reported on non-stationarity of brain connectivity network which stands on the statement of functional connectivity patterns changing over time, in both task-related fMRI data [17, 18, 19] and resting-state data [20, 21]. The time evolution of effective connectivity has been reported in task-related data [22, 23, 24]. These studies motivate the study of time-varying connectivity patterns in human brain over time. To address the problem of estimating non-stationary brain connectivity, this research adopt the approach of time-varying multivariate autoregressive model.

Windowing analysis is used for current studies of non-stationary signals [25, 26, 27]. Selection of the window frame size is the limitation to the method itself because a small window frame is needed to achieve a good temporal resolution but it will be a destructive move to the frequency content of the signals. Applying large window frames will cause bad temporal resolution. This effect is known as spectral leakage problem [12]. To solve this, a time-varying autoregressive (TV-AR) model is proposed. Non-stationarity of brain signals was further demonstrated in recent studies [17, 18, 19] on brain connectivity analysis. These studies motivate researchers to analyze and quantify the temporal dynamics in connectivity pattern over time. The most commonly used approach to model dynamic causality network is multivariate autoregressive (MVAR) model [28, 29]. To date, MVAR is the most reliable modeling method for dynamic system under the assumption of the stationary inter-regional integration with manually determined time frame [30]. This is rather difficult to segregate the brain-conditions in resting-state data, but would not be a problem in the known simulation framework. Thus, the implementation of complex multivariate autoregressive model with the non-stationary assumption is critical in solving this problem.

1.3 Statement of Problems

In this thesis, the problems of estimating high dimensional connectivity of large size brain network from fMRI data are considered and summarized into four main issues as follows:

(a) fMRI time series data measured from distant brain regions are typically of large-dimensional due to the huge number of nodes in a brain network and hence a huge number of connectivity parameters to be estimated.

(b) The common approach to quantifying functional connectivity is by estimating the covariance matrix (cross-covariances between fMRI signal for every pair of brain regions). However, it poses a critical challenge when estimating a high-dimensional covariance matrix to characterize a large brain connectivity network. The dimension of the neuroimaging signals N (referring to the number of brain regions) is usually comparable and higher than the sample size T (i.e., the length of neuroimaging signal). To estimate a full-brain network from fMRI data, the dimension N (referring to the number of voxels) can be in the order of 10,000 or above but then the number of scans T is often only around few hundreds. In this high-dimensional setting, particularly when $N \geq T$, the traditional covariance estimator, sample covariance matrix is no longer reliable, consistent and invertible. This will lead to low statistical power in detecting true brain network connections. Due to this limitation, most connectivity studies focus on the analysis of only a few specialized regions of interest (ROI) instead of whole brain connectivity.

(c) Similarly, for estimating the effective connectivity of large brain networks (a generalized of functional connectivity to quantify the directionality of connections between brain regions), the least squares estimator of a high-dimensional VAR model is no longer consistent, when the signal dimension is high, which renders the estimated directed brain connectivity not reliable.

(d) Existing studies have proposed various high-dimensional estimation methods for estimating large-scale brain connectivity network, which however focused mostly on static or stationary connectivity where interactions between brain regions are assumed to be constant across the time course of experiments. Thus there is a need to develop methods to model the time-varying connectivity patterns of large-scale dynamic brain network that are changing over time.

1.4 Objectives of the Research

The main objectives of this research are as below:

(a) To propose a class of shrinkage-based estimators for estimating high dimensional brain connectivity for fMRI data which improve the performance over conventional connectivity estimator (e.g. sample covariance matrix and least squares (LS) estimators) in terms of lower estimation error.

(b) To employ Ledoit-Wolf (LW) and Rao-Blackwell LW (RBLW) shrinkage approach for estimating large-scale functional brain connectivity, which allows better-conditioned and invertible estimator of a high-dimensional covariance matrix.

(c) To introduce a novel high-dimensional VAR estimator based on the shrinkage approach for estimating large scale effective brain connectivity by incorporating shrinkage-based estimators for the Gramian matrix in the LS-based linear regression fitting of VAR.

(d) To generalize the proposed shrinkage-VAR estimator to non-stationary case based on the sliding window approach and K-means clustering in order to handle the time evolution in effective connectivity of large brain networks.

1.5 Scope of Work

The research scopes focused on two main directions which are the estimation of connectivity matrix for brain networks and visualization of the brain connecting map in the resting state human brain. The simulation and real data process application will be carried out on MATLAB and FSL software as a platform. The scope of this study are as follows:

(a) The fMRI dataset used is 25 healthy subjects in resting state with eyes open during the recording session. This dataset is publicly available at the NITRC website (http://www.nitrc.org/projects/trt).

(b) The connectivity analysis is conducted based on 96 regions of interest (ROI) automated anatomical labeling (AAL) atlas. The number of connectivity parameter, N to be estimated is $96 \times 96 = 9216$ parameters, it is high compared to the total number of scans, T is 197.

(c) The statistical analysis of brain connectivity is applied to fMRI time series data, extracted from image data by using a standard preprocessing pipeline through FSL software.

(d) This research focuses on the statistical approach to analyzing high-dimensional brain connectivity, in particular the shrinkage-based approach.

(e) Under the statistical approach, shrinkage-based covariance matrix estimator is applied to functional brain connectivity while shrinkage-based least square estimator of VAR model is applied to effective brain connectivity.

(f) This study also investigates on dynamic brain connectivity analysis with the application of time-varying VAR (TV-VAR) model and shrinkage-based estimator to high-dimensional, dynamic effective brain connectivity.

1.6 Contributions of the Study

This study proposes a class of estimators for analyzing huge brain connectivity which is potentially useful for a better understanding of brain functions in healthy subjects and abnormality in neuropsychiatric disorders. Specifically, the research contributions are given as follows:

(a) A class of shrinkage-based estimators has been proposed for the analysis of large-scale brain network, involving inference of the functional connectivity (statistical dependencies between large numbers of brain regions) or effective connectivity (causal interactions between brain regions), from high-dimensional neurological signals such as fMRI with small sample size.

(b) Two variants of shrinkage-based high-dimensional covariance estimators that is Ledoit-Wolf (LW) and Rao-Blackwell LW (RBLW) (a generalization of LW as method) have been employed to identify large-scale functional connectivity more efficiently.

(c) A novel shrinkage-based estimator has been introduced for estimating high-dimensional VAR models with applications to estimating large-scale effective brain connectivity from fMRI data. It has also been demonstrated by simulation that the proposed estimators to give a more accurate estimator and minimized the mean squared error (MSE) relatively to ground truth as compared to typical LS linear regression fitting under the high-dimensional setting.

(d) A high-dimensional time-varying VAR shrinkage approach has been developed based on sliding window, which is able to efficiently capture the time evolution of the effective connectivity of large-scale brain networks. K-means clustering is then applied to identify distinct dynamic brain connectivity states in resting-state fMRI data.

(e) The developed methods above are generally applicable to a wide range of neuroimaging signals such as EEG, PET, and MRI.

1.7 Thesis Organization

In this thesis, chapter 1 presents the direction of the research namely problem statement, objective, research scopes and significant of the research. Chapter 2 covers the literature review for this research on the basic understanding of brain connectivity, fMRI time series data, and statistical models that are related to current brain connectivity research. Limitations of the current statistical model and research gaps are also discussed in this chapter. In chapter 3, this thesis describes the proposed methods for both functional and effective connectivity. Steps on preprocessing and statistical processing on fMRI data are also covered in this chapter, particularly in static functional and effective connectivity, and also dynamic effective connectivity. Chapter 4 shows the evaluation results obtained from simulation and application on real fMRI data with discussion, including preprocessing and statistical analysis as well as visualization on BrainNet Viewer. This thesis ends with a conclusion and future work in chapter 5.

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