論文 / 著書情報
Article / Book Information

題目(和文)	
Title(English)	Group Effective Connectivity Model of Episodic Memory-related Cognitive Functions
著者(和文)	SaetiaSupat
Author(English)	Supat Saetia
出典(和文)	学位:博士(学術), 学位授与機関:東京工業大学, 報告番号:甲第12006号, 授与年月日:2021年3月26日, 学位の種別:課程博士, 審査員:小池 康晴,金子 寛彦,杉野 暢彦,吉村 奈津江,永井 岳大
Citation(English)	Degree:Doctor (Academic), Conferring organization: Tokyo Institute of Technology, Report number:甲第12006号, Conferred date:2021/3/26, Degree Type:Course doctor, Examiner:,,,,
学位種別(和文)	博士論文
Type(English)	Doctoral Thesis

Group Effective Connectivity Model of Episodic Memory-related Cognitive Functions

by

Supat Saetia

Submitted to the Department of Information Processing
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
at the
TOKYO INSTITUTE OF TECHNOLOGY

Author .....
Department of Information Processing

Certified by .....
Yasuharu Koike
Professor
Thesis Supervisor

Certified by .....
Natsue Yoshimura
Professor
Thesis Supervisor

Certified by .....
Hirohiko Kaneko
Professor
Thesis Supervisor

Certified by .....
Nobuhiko Sugino
Professor
Thesis Supervisor

Certified by .....
Takehiro Nagai
Professor
Thesis Supervisor

Group Effective Connectivity Model of Episodic Memory-related Cognitive Functions

by

Supat Saetia

Submitted to the Department of Information Processing
on , in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

Abstract

Understand brain mechanism is a challenging task, especially if the brain function we are interested in is a cognitive or mental task that difficult to physically observe the physiological changes. Current technology such as functional magnetic resonance imaging (fMRI) enable us to be able to observe brain activity non-invasively. The fMRI data analysis shows us the brain activation pattern during the task performed by the subject during the scan. However, knowing which part is activated during the task alone does not give us the full picture about the brain mechanism. The higher cognitive function such as consciousness or self awareness are likely the result of different part of the brain work in tandem with each other. We can investigate the interaction between each brain regions during the time subject was performing the task from fMRI data in form of connectivity model. Functional connectivity model represents correlation between each regions of the brain while effective connectivity model represents the causal relationship a specific brain region has with others. There are several mathematical frameworks developed to extract causal relationship from a system of signals which could be applied to fMRI blood-oxygen-level-dependent (BOLD) signal as well. Tigramite is a causal discovery framework utilized transfer entropy (TE) to determine causal influences one source has to the rest of the system. In this study, we applied the Tigramite to several modes, such as task-based or resting-state, of memory-related fMRI dataset to construct an effective connectivity model of the cognitive function of interest. Episodic memory is an important cognitive function of human brain. It is theorized to be the basis of higher cognitive functions such as consciousness or self awareness, thus it is intriguing to understand the underlying brain mechanism responsible for episodic memory. The low temporal resolution of BOLD signal poses a challenge to the causal discovery framework, which is a temporal sensitive process. This issue may result in false causal link implication. We demonstrates the application of BOLD signal temporal preprocessing using CONN toolbox to improve the quality of the signal. Furthermore, we demonstrate that the effective model is more informative to the functional one. We also purpose the group-level connectivity model framework to derive a group representative model

because the general model that can explain brain mechanism across population is more preferable. Our resulting models regarding episodic memory-related function agree with the prior knowledges from previous researches. This development allows more comprehensive understanding of the brain function.

Thesis Supervisor: Yasuharu Koike
Title: Professor

Thesis Supervisor: Natsue Yoshimura
Title: Professor

Thesis Supervisor: Hirohiko Kaneko
Title: Professor

Thesis Supervisor: Nobuhiko Sugino
Title: Professor

Thesis Supervisor: Takehiro Nagai
Title: Professor

Acknowledgments

Foremost, I would like to express my sincere gratitude to my advisor Prof. Yasuharu Koike for the continuous support of my Ph.D study and research, for his patience, motivation, enthusiasm, and immense knowledge. His guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my Ph.D study.

Furthermore, I also would like to express my sincere gratitude to Prof. Natsue Yoshimura for support me in learning the technical knowledge regarding fMRI technology and data processing, which is the basis of this research.

Besides my advisor, I would like to thank the rest of my thesis committee, Prof. Hirohiko Kaneko, Prof. Nobuhiko Sugino, and Prof. Takehiro Nagai for their encouragement, insightful comments, and hard questions.

My sincere thanks also goes to Dr. Yousuke Ogata for overseeing acquisition of fMRI data essential for the success of this study.

Contents

List of Figures

List of Tables

Chapter 1

Introduction

Brain is an organ of curiosity that control all function of our body, both physically and mentally, thus it is the core of our existence. Beyond controlling our bodily function and movement, the Brain is capable of many cognitive function that we as a human take for granted. It can observe and make sense of the world around us and also acknowledge the existence of ourselves. It is the organ that is an essence of ourselves, yet we know little about brain mechanism or how it works. In this chapter, I will introduce the background knowledge about the brain, its anatomy and some of it basic function. Later in this chapter, I will discuss in detail about the cognitive function of interest of this study, namely the memory. Finally, I will discuss about the current state of technology that can be used to investigate brain function non-invasive.

1.1 Human brain

From the outermost look, the brain consists of two cerebral hemispheres. The term cerebral means something that related to the brain. The outermost layer is called cerebral cortex. Each hemispheres are connected by the corpus callosum [30]. Each hemispheres can be further divided into four lobes: frontal, parietal, temporal and occipital.

The appearance of bumps and grooves of the brain are referred to as *gyri* and

sulci respectively. These folding of the brain increases the brain's surface area, which in turn, enables more cerebral cortex matter to fit inside the limited space of the skull [17].

Under the cerebral cortex is the white matter, which is areas consisted of myelinated axons. It got its name from its appearance due to relatively light color of lipid content of myelin. The role of the axon bundles in this area is to transmit the neuronal signal between the area with dense neuronal cells, traditionally called gray matter [89].

Deep underneath the white matter lies a gray matter formations called subcortical structures. It consisted of diencephalon, pituitary gland, limbic structures and the basal ganglia. This structures are thought to be an information hubs of the nervous system. They process, relay, and modulate information to different areas of the brain [45].

Thalamus, epithalamus, subthalamus, and hypothalamus are the structures found inside the diencephalon. The role of these structure revolves around survival and optimal function of human body.

The limbic structure comprises of the limbic lobe, hippocampal formation, amygdala, and a part of hypothalamus. These structure is an ancient part of human brain. Their functions are related to primitive bodily responses such as hunger, sexual drive, fight or flight emotional response. The hippocampal formation also responsible for memory related function [61].

All of these aforementioned part of the brain are collectively called cerebrum. Under the cerebrum on the back side of the head is cerebellum. Cerebellum can be divided into an anterior lobe, a posterior lobe and the flocculonodilar lobe. This part plays important role in human motor function, also it may be involved in some cognitive function such as emotional control [40].

The lowermost part at the base of the brain is brainstem. It consists of midbrain, pons and medulla. The brainstem involves in the regulation of many essential processes such as breathing, and body balancing [95].

Here I have briefly introduced the overall anatomy of the brain. Traditionally,

the knowledge about the division of brain areas and their respective functions are obtained from post mortem studies of the brain neuronal cell structure and clinical observations of patients with brain injury. Later in this chapter, I will discuss about the technology that enable us to observe brain function of realtime or near-realtime. However before that, I would like to discuss about the main brain function of interest of this study.

1.2 Human memory

In this section, I would like to discuss the basic knowledge about memory-related function of the brain and its importance to the advancement of the humanity as a whole.

Writing is one of the greatest invention of humanity. It enables us to record our experiences or express our idea, and pass it on to other people or to the next generation. Modern day human has several means of storing information both physically and digitally. However, for most of humanity's existence, it has been only a short period of time since the invention of writing. Before our means of recording information was invented, all we had were our brain, a biological information storage which stores our memories.

Human memory can be practically divided into 2 large group, short-term memory and long-term memory [5]. As the name suggest, short-term memory is an immediate memory required to perform immediate task for the moment, usually it persist for period of several seconds only. It capable of holding only small amount of information and not manipulating that information, for example, when we reciting a phone number or an address. The short-term memory is easily forgotten if there is an immediate distraction.

On the other hand, long-term memory is retained indefinitely inside our brain (excluding the case of forgotten memory, which is another memory-related mechanism of the brain). The long-term memory can be further divided into declarative memory and procedural memory.

Procedural or working memory is a memory that does not require explicit conscious recollection (implicit memory). This memory aid in our execution of task involved in both cognitive and motor skill, from riding a bicycle to reading a book. This memory can be committed into our mind using the process called procedural learning, where the task is repeatedly performed over and over again until neural system form and responsible for performing those specific task.

In contrast, declarative memory is a memory that required conscious, intentional recollection (explicit memory). It is a memory of factual informations, past experiences, or concepts. It can be divided further into 2 types based on type of information it retains. Memory of general knowledge such as facts, ideas, or meaning of a concept is call semantic memory. Another one is episodic memory, which is a memory of personal experience (also called autobiographic memory). This episodic memory contains the information about time, place, associated emotion, and contextual knowledge of past experiences [51]. One of the easily discernible characteristic of semantic and episodic memory is information in semantic memory can be passed on to another person exactly by the use of language, while the information in episodic memory could be describe using words to other people to some degree, the information recipient cannot experience the exact same experience the person trying to convey. In this study, we will focus on episodic memory.

1.2.1 Episodic memory

Episodic memory is a memory of autobiographical events or a memory of personal events, times, places, associated with emotion and other contextual knowledge. With this kind of memory, a person can remember personal experience and consciously aware of the certain situation at a certain time of that event [83]. This episodic memory is a part of declarative memory, a category of long-term memory [84]. It is unique because it is often represented in form of visual information in order of event occurrence on personal timeline with memory owner as a perspective observer.

This cognitive function is important because it enables human to project oneself backward in time and recall several aspects of one experience. This ability becomes

the source of self-awareness and induces intelligence which set human apart from other animals.

1.3 Look into the Brain

Observing how information are organized in human brain is a challenging task, because our brains are situated inside solid skulls. In the past, the method of studying brain's structures and their functions are limited to study post-mortem brain, or observing behavior of patients with specific abnormality in specific region of the brain. While these approaches yield large body of proven useful knowledge, and the approaches still viable event in the present day, it is difficult to perform a controlled observation or design specific experiment paradigm around those limitations.

With the advancement of present day technology, several methods are available to observe brain function in non-invasive fashion. This open the opportunity for studying brain function in a more controlled manners. The example of one such technology is electroencephalogram (EEG). EEG is one of the most well-used method to record brain activity non-invasively. It detects brain activity through a matrix of electrodes placed along the scalp. Its main advantages are its ease of use and transportation, and its high temporal resolution. However, it also susceptible from contamination originated from non-cerebral sources, such as, eye-movement, or muscle activity. The major weakness of EEG is its poor spatial resolution, since the current are measure on the scalp. Determine the cerebral source of current measure on scalp require intense and solid assumption.

Considering merit and demerit of the EEG in regard to the condition of this study, we concluded that EEG is not suitable for our brain function study on memory-related task. Memory is a cognitive function that is hard to observe and verify externally, being able to clearly identify specific area where the activity occurs would give us better data for intepretation. Thus, we looked into another well-accepted approach of brain activity monitoring, the functional magnetic resonance imaging, or fMRI.

1.3.1 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) is a technology that detect brain activity by observing changes in blood flow. It is a extension of MRI technology developed for radiological use similar to x-ray imaging. It primary purpose is to construct images of anatomy of the body. It is considerably safe compared to other alternative method such as x-rays, or CT and PET scan, which both relying of ionizing radiation. MRI works by detect radio frequency emitted by atomic nuclei when it is subjected to an external magnetic field. The most often used nuclei is hydrogen atom because it abundant in human body in forms of water and fat. This structural MRI (sometime called medical MRI) can produce high resolution 3-dimensional image of the inside of human body.

Functional MRI differs from structural MRI by the target of the scan. While the structural focuses on reconstruction of body structure, functional MRI focuses on detecting change of physiological activity over time. In the field of brain function study, fMRI is used to detect the relative change in blood concentration in area across the brain. The basis assumption is that the area with higher activity required more oxygen for energy, thus induced the accumulation of oxygen-rich blood in that area.

Several aspects of the fMRI technology help push the advancement in brain function research field. It relatively safe so there is no worry that the scan will affect the subject's health, which is open up the opportunity to collect more data needed for the research. The quality of the scan image is also high, which in turn improve the quality of results interpretation. However, fMRI technology also has its own weakness, namely, low temporal resolution, or in a simpler term, low response time.

fMRI detect changes in blood flow, which required physical displacement of blood. This displacement process takes time, usually up to 2 seconds. While it might now constitute to analytical problem in a experiment design where the task is long and slow, for reactive cognitive function such as memory, it may poses a problem to the analysis where the actual neuronal activity cannot be picked up by the scanner. We also have to keep in mind that the measurement of blood-oxygen level is an indirect

effects of actual neuronal activity.

1.4 Motivations and objectives

Episodic memory is the main topic of this study because it is hypothesized to enable human to project oneself backward in time and recollect many aspects of their previous experience resulting in self awareness. Brain connectivity model is a tool that can be used to model particular brain function. The model can help us comprehend the brain mechanism of interest. Therefore, the objective of this study is to derive connectivity models that explain several aspects of episodic memory.

Chapter 2

Brain Analogy

In this chapter, I would like to discuss about how we can try to comprehend brain function. What we can observe when the brain is working is limited, without any specialized tool. We can hardly observe observe any activity of the brain visually even if we were to surgically open the skull to look at the brain. I would like to give the introduction to the tools currently used to observe brain function and concepts that we can utilized to help us understand the mechanism of the brain.

2.1 Brain activity data acquisition

Now that we have estimated idea of how we will model our brain function of interest, we can begin discussing about how to acquire the data. While acquiring structure data is as simple as have a subject lay inside the scanner and run the scan for around 5-10 minutes, acquiring functional data requiring experiment design and protocol for an optimal scan data.

2.1.1 Modes of acquisition

Current MRI scanners are capable of acquiring several mode of scanned data. Most commonly used are structural and functional scan. Most of the time, both mode are required for the analysis.

The sole purpose of structural scan is to product a high resolution 3-dimensional image of the brain. The structural scan is a time-consuming process, usually takes around 5-10 minutes to finish. The subject have to stay still (at least the head) during the scan, or else the subject run a risk of introducing movement artifacts into the final scan data. The structural data will be used in conjunction to functional data for the analysis.

Functional scan is difference from structure scan in that its objective is not focus to produce high quality 3-dimensional model of the brain, but to detect the relative change in blood level across the brain over time. The signal recorded in functional scan is called blood-oxygen-level-dependent signal or BOLD for short. This BOLD signal is an indirect measurement of neuronal activity of the brain. The basic assumption is that the increase in neuronal activity requires more energy from oxygen in blood. The area that consume more energy by actively working induces blood to accumulate at that area to provide enough oxygen to maintain ongoing neuronal activity. By observing those changing in blood-level we can infer neuronal activity of that region.

The strongest point of fMRI data is high spatial resolution image provided by structural scan. In conjunction with the functional data, we can map functional information onto 3-dimensional brain model, thus identify the exact location where the activity has occurred. However, the fMRI approach is not without a weakness. Since the BOLD signal measure the fluctuation of blood level and blood is a physical substance, it takes time for blood displacement to occur. In short, BOLD signal has low temporal resolution.

2.1.2 Acquisition protocols

The main concern of this topic is the experiment design. Conventional fMRI experiment using has a subject perform a task alternate with rest repeatedly in a block design. This is done in order to collect two set of data. One is the data during the task performing, another is a neutral state. With these two set of data, we can contrast them against one another to isolate the brain area where it is related to our task of interest. This acquisition protocol is usually called *task-related protocol*.

In recent years, there is an alternative protocol introduced to increase analytical option of fMRI study. In this protocol, a subject is asked to stay completely still and to refrain from performing any cognitive function during the whole length of the scan session. This is commonly called *resting-state protocol*. This base assumption of this protocol differs from task-related protocol in that it assume that there are a possibility that certain cognitive function is rely on intrinsic brain activity.

The contrast of resting-state protocol is usually determined by behavioral profiling test perform either before or after the scan session. The use of behavioral profiling does not limited to only with resting-state protocol, it can be incorporated into task-related design to increase analytical option as well.

2.2 fMRI data analysis

In this section, we will discuss several analytical option what can be used with the data we acquired.

2.2.1 Functional segregation

Functional segregation, also known as activation pattern is an analysis focuses on localized that activated area during the cognitive function of interest. The localization of the activated brain region can be analyzed using statistical testing or model-based regression. Usually, the analysis is divided into 2 steps, individual-level and group-level. In the individual-level analysis step, only a set of data collected from a single individual subject are analyzed. The resulting activation pattern is a generalized representative pattern of that individual. The process is then repeated for each every individual subjects included in the dataset.

In the group-level analysis, the result of the each individual-level analysis are combined and is analyzed again to produce a group-level result that is a representative pattern that can be applied across population. The group-level result is more preferable to individual-level result because an individual-level result is over-specified to that individual. There is no guarantee that that result will be valid for other people.

Human brain has been observe to has an ability called neuro-plasticity or brain plasticity. This ability allows brain to adapt itself based on experiences, and it change continuously throughout one's life. Because of this ability, each individual brain characteristic varies from person to person. If the group-level analysis contains too many variation, we may encounter an over-genralization problem. This problem is an opposite to the oversimplification problem where the result is specific to only one person, this over-generalization problem means that the results is generalized to the point where it lost any meaningful interpretability.

2.2.2 Functional integration

Functional integration, also known as connectivity is an analysis aim to illustrate relationship between active brain regions. It usually depicted in a form of a graph, where nodes represent brain regions and edges represent connections. The region-of-interest included in this analysis usually range from a selected group of region based on activation pattern analysis up to every single region of the brain defined by anatomical atlas.

The purpose of this analysis is to model brain interaction during the cognitive task of interest. Any correlation or causality discovery algorithm can be applied on localized BOLD signal to generate the connectivity model. However, we have to be careful with the characteristic of the BOLD signal in general. BOLD signal is an indirect measurement of actual neuronal signal, it may mask and convolute actual neuronal signal with may lead to faulty result. Furthermore, the problem with the cognitive function study in general is that there is no ground truth that can be used to validate the result. Faulty connectivity model leads to faulty interpretation of the brain function. BOLD signal also highly susceptible to movement artefacts and physiological artefacts such as heart beat. These artefacts could cause spurious connection to appear in our model. So, before applying any correlation or causality discovery algorithm to the BOLD signal, it must be properly preprocessed to remove noises as much as possible.

2.2.3 Functional and effective connectivities

Here I will briefly introduce the concept of functional and effective connectivities, however we will discuss this topic in more details later in chapter 3.

There connectivity model can be divided into 2 groups based on the property of the connection. A connectivity model where its connections do not contain directional information is a functional connectivity model, whereas the model where its connection contain directional information is a effective connectivity model. The functional model generally represents correlation and the effective model represents causation. This distinction is important in terms of interpretability of the result. Several time these 2 terms are used interchangeably, which we highly disagree in mixing these two terms together as they are not equivalent in property.

Consider a functional relationship between region A and B in functional connectivity model. There are only 2 possibilities for the information to be included in the model which is either the connection exist or does not exist. In contrast to effective connectivity, there are 4 possibilities for the information to be included in the model. One is the connection does not exist, the second is it is a unidirectional connection from A to B, the third is it is a unidirectional connection from B to A, and the fourth is it is a bidirectional connection between A and B. These additional information can improve the interpretability of our resulting model.

Another important difference between function and effective connectivities is that most correlation analyses do not take temporal order into account, while the temporal order of the connection is essential to causality discovery algorithm. Considering the scenario where there are 3 regions X, Y, and Z in our connectivity model. If the activity in region Z cause both activation of region X and Y, most correlation algorithm is prone to detect a synchronization of region X and Y as a connection, while the causality discovery algorithm has a higher chance to detect the source activity at region Z.

2.3 Modeling brain mechanism

In the previous chapter, we had discussed about the functional magnetic resonance imaging (fMRI), the main method of observing brain activity in this study. Briefly, this technique observe the change in blood flow in each region of the brain, which implies that the regions with larger amount of blood flow consume more energy, thus more active in comparison to the area with lesser blood flow. From this information, we can create a localization map of activated region during the task of interest. This is an activation pattern or functional segregation. However, higher brain functions are likely result from several regions of the brain working in tandem. By first isolating the regions that are activated during the task then study how each of those regions interact with each other, we can derive a brain connectivity.

When we what to describe how any particular system works, we compare that system to some form of simplified representation, either it be an equation, a graph, or a model. In case of brain function., what is its appropriate form of representation?

Brain can be divided anatomically based on cellular structure into several regions. We also partially know that each regions responsible for a specific set of cognitive function based on the observation and study by the prior researchers. Simpler task such as motor movement can be identified to be a product of a certain area, appropriately called motor area. This is a result of activation pattern study. However, for the higher cognitive function, there are a possibility that in order to produce that function, a single brain area is not enough. When the result of activation pattern analysis show several activated regions spread across the brain, it is suggested that those region are working together to produce those cognitive function.

If there is an evidence suggested that several regions of the brain working together, it is reasonable to assume that those regions must exchange some form of information among each other. It is well-documented that there exist forms electrical and chemical pathway between several regions of the brain. With current technology, it is impossible to measure *what* information they are exchanging, but we can observe the *flow* of the information by tracing the change cascading throughout the brain. There

are several correlation and causality discovery analysis capable to undermining those kind of information from the collected signals. The result can be model into a graph describing the relationship between each brain region. Nodes represent brain regions, and edges represent connections or links the regions have.

2.3.1 Activation pattern

fMRI neuro-imaging analysis can produce a contrast image showing the activated brain regions during the task-of-interest. The basic idea is to contrast the images during the task with the images from outside the task. This is called subtraction analysis. There are several framework and software developed to analyze and produce the contrast images. There are 2 prominent software suite that utilized different mathematical framework to achieve the same result. One of them is a software suite called SPM. SPM (Statistical Parametric Mapping) constructs and assesses spatially extended statistical processes that is used to test hypotheses about functional imaging data [2]. Another software suite is FSL (FMRIB's Software Library). FSL is a model-based fMRI data analysis based on General Linear Modeling (GML) or multiple linear regression [1].

2.3.2 Connectivity

With the current technology, we can observe live brain activity. The next question is how we would interpret those information. Conventional fMRI study can show us the localization of brain activity in relation to the cognitive function of interest. Knowing which area of the brain active during which cognitive task does not give us the full understanding of the mechanism of the brain. Understanding the interaction between those active brain region will give us deeper understanding in dynamic of the brain function. The concept of brain connectivity model was developed to represent those interaction between brain regions. There are 3 types of brain connectivity models, anatomical, functional, and effective connectivity models. Anatomical connectivity model represents the actual physical connection based on brain cellular structure

and organization [90], the knowledge mostly acquired from postmortem study of the brain. Functional models represents un-directed statistical relationship between brain regions, while effective model represents directed causal relationship between brain regions. These are usually constructed by analyzing brain activity data. We can interpret the information provided by these models to infer how brain mechanism works.

One of the most well-known framework is the Granger causality (GC), a linear auto-regressive causality modeling framework [33]. It is a mathematical framework commonly employed to model causality of the neuronal activity from fMRI BOLD data. The underlying assumption of this framework is that if $X \rightarrow Y$ if and only if a change in X has an effect on Y [66]. However, all we can imply from observational data are statistical dependencies. It is controversial to infer effective connectivity (directed connectivity) due to the low temporal resolution nature of the BOLD signal as Granger causality is prone to under-sampling signals.

There are several other mathematical frameworks and algorithms available for functional or effective connectivity model inference from recorded brain signal time-series. In recent years, several tools designed specifically for brain connectivity study using fMRI data, such as Dynamic Causal Modeling (DCM) [26] or CONN toolbox [92] have been developed. Each attempts to address aforementioned issue from different aspects. The DCM constructs the connectivity model by predicting neuronal activity using forward model, then it uses haemodynamic model to generate hypothetical BOLD time-series. Finally, it tests the hypothesis against the real BOLD time-series to choose the best model. The CONN toolbox performs temporal preprocessing on BOLD time-series in additional to conventional spatial preprocessing to remove noises that usually cause spurious connection in the model as much as possible. Each approaches has its own advantages and disadvantages. For example, the DCM needs concrete assumption of the driver that cause changes in the system, it usually suitable with task-based fMRI paradigm. The CONN toolbox, which is usually applied to resting-state fMRI, is only designed for functional connectivity that shows only correlation between brain region, in contrast to effective connectiv-

ity model which encoded more information in form of directed link. The additional information improves the model interpretablility.

In the context of fMRI analysis, DCM is a technique developed specifically for analyzing connectivity from fMRI BOLD time-series and it is arguably one of the most widely adopted method. This technique is a model-based approach where it constructs connectivity model by simulating hypothetical model supplemented by a haemodynamic forward model, then it estimated the model parameters from observed data [26]. DCM requires *a priori* knowledge about the structure of the network being estimated to test different specific hypotheses using Bayesian model comparison. For this reason, the classical DCM only suitable for task-based experiment paradigm where input functions are known. To extend the capability of DCM to cover resting-state analysis where input function is not well-defined, a DCM for resting-state fMRI (spectral DCM) was developed [28]. The new developed technique fits a model to the cross spectrum of the data. Cross spectra are second-order statistics of the original time-series under stationarity assumption. However, the resting-state analysis usually includes larger number of region of interest which can be a challenge for DCM in terms of computational cost. Razi textitet al. proposes a framework complimentary to spectral DCM by using functional models as priors to reduce computational complexity of large-scale network [68].

Tigramite (time-series graph-based measures of information transfer) is a time-lagged causal discovery framework based on conditional independence testing using the assumptions of time-order, *Causal Sufficiency*, the *Causal Markov Condition*, and *Faithfulness*, among others [73]. The inclusion of time-lag enable this framework to show changes in causal model over time, which is useful for pathway inference. The connectivity models can be visualized in form of *graphical model* [48] which is a summary model showing all existing connectivities, or *time-series graph* [20], a graph that shows causal relation along lagged-timeline. This visualization is useful for model interpretation. The detailed background of this framework will be discussed later in section 2.4.

2.4 Tigramite causal discovery framework

The development of this framework started with an attempt to escape the curse of dimensionality in estimating multivariate transfer entropy from observational climate data (sea level pressure) [74]. Transfer entropy (TE) is a model-free approach to detect directed transfer of information (causality) between stochastic process [78]. The main problems with the interpretation of causal influences in a system that the underlying mechanisms are poorly understood are the possibility of spurious causalities from indirect influences or common drivers [74]. When interpret the relationship between two process, it can be said to be a causal relationship if a statistical methods can (1) measure associations, (2) measure time delays, and (3) exclude other influences [66]. Existing model-based approach such as Granger causality fulfill requirements (1) and (2). The unfulfilled requirement (3) makes it controversial to infer causal relationship in this approach. There is no such model-based requirements in information theoretic framework [15]. The information-theoretic function utilized in this framework is conditional mutual information (CMI) [39] in the form of transfer entropy (TE) [78].

The main advantage of choosing TE over the conventional methods such as DCM is that it is model-free and also capable of detecting both linear and non-linear dependencies. DCM relies on correct prior knowledge of the network under investigation to define the optimal model space because the model space should reflect the possible causal connection between brain region in the network. [43], therefore it may not be optimal for exploratory analyses. Vicente *et al.* formulated four requirements for a new effective connectivity measure for it to be considered a useful addition to the established methods, such as GC and DCM, and showed that TE fulfills those requirements. [87]. The four requirements are as follows:

1. It should not require the *a priori*.

2. It should be able to detect non-linear interactions.

3. It should be able to detect effective connectivity even if there is a wide distri-

bution of interaction delays between two nodes.

4. It should be robust against linear cross-talk between signal.

The first requirement ensures that the new measure is useful for exploratory investigations. DCM was design specifically for fMRI data by including generative model based on haemodynamic function [13], which can be both a strength and a weakness because, while the model fits the data well, it depends on the accuracy of the current knowledge regarding haemodynamic response.[7]. There are new studies suggest that haemodynamic response varies across population based on physical condition of the individuals [36]. Nonetheless, the model-free measure could also be use in complement to DCM in large-scale analysis to create prior constraints to reduce model space of large network. The second and third requirements are dictated by observed characteristics of brain function. Brain exhibits strong non-linearities interaction across all level of brain function. Also, the signal traveling from one brain region to another involve several pathways where delays could be varied according to anatomical structure [82]. The fourth requirement ensures quality of the analysis using signal from electroencephalography (EEG) or magnetoencephalography (MEG), however this property could still benefit analysis using fMRI signal.

There are several studies that utilize TE to investigate brain connectivity. The studies by Wibral *et al.* investigate brain connectivity using *multivariate transfer entropy* [63] in both task and resting-state paradigms [94] [93]. On the other hand, Tigramite framework proposed the use of graphical causality in combination with information theoretic measure i.e. TE. The Tigramite utilizes PCMCI algorithm [73], which was proposed to address the shortcoming of the Peter and Clark (PC) algorithm [81]. The PC algorithm is a graph-based causal discovery algorithm where it starts with a complete undirected graphical model [48], then the links are adjusted based on conditional independence test [81]. The PCMCI algorithm has main two step. In the first step, a version of PC algorithm is used to estimate parent sets of each variable. Then, in the second step, it performs the *momentary conditional independence* (MCI) test for each pair of variables and condition on the aforementioned parent sets. This

reduces number of independence test it needs to perform. The important advantage of PCMCI over PC is that the MCI test accounts for autocorrelation which keeps the false-positive rates at the expected level [75]

To obtain causal information from measured variables, some assumptions is needed. This framework focuses on three main assumptions under which the time-series graph represents causal relation [73]. The first assumption is *Causal Sufficiency*, which assumes that there exist no other unobserved variable that influence any other pair of our set of variable, either directly or indirectly. We need this assumption because it is impossible to ensure that we have measured all possible variables [66]. The second assumption is the *Causal Markov Condition*. This condition dictates relationship between process X and its associated graph G. It implies that once we know the value of a node's parent at time τ, all other variables in the past become irrelevant for predicting state of the current node [80]. The third assumption is *Faithfullness*. *Faithfullness* guarantees that the graph entails all conditional independence relations that are implied by the Markov condition [80].

Subsequently for the Causal Markov condition to hold, the assumption that there is no *instantaneous (contemporaneous) causal effects* is needed. While it may seem counterintuitive to consider the instantaneous effect between dynamical systems because the physical speed of information transfer, i.e. speed of light, is finite. The problem arise when the time-series cannot be sampled with sufficient resolution. [73].

Causal discovery algorithms used in this framework is PCMCI. This approach was implemented in this framework to address some of the shortcoming of the PC (Peter and Clark) algorithm [81]. The PC algorithms was invented for random variables without assuming a time order [48]. It's process consisted of several phases where first an undirected graphical model is estimated, then it's links are adjusted using a set of logical rules [81].

Tigramite defines time-series graph of a stationary multivariate discrete-time stochastic process $\mathbf{X}$ of dimension N as graph structure $\mathcal{G} = (V \times \mathbb{Z}, E)$ of $\mathbf{X}$ where the set of nodes in the graph consists of the set of components V at each time $t \in \mathbb{Z}$. The links in graph $\mathcal{G}$ are defined as a connection between variables $X^i_{t-\tau}$ and X^j_t connected by

a lag-specific directed link "$X^i_{t-\tau} \to X^j_t$" $\in \mathcal{G}$ *for* $\tau > 0$ *if and only if*

$$X^i_{t-\tau} \not\perp\!\!\!\perp X^j_t | \mathbf{X}^-_t \backslash \{X^i_{t-\tau}\}, \tag{2.1}$$

where $\mathbf{X}^-_t = (\mathbf{X}_{t-1}, \mathbf{X}_{t-2}, ...)$. $\mathbf{X}$, $\mathbf{X}_t$, and $\mathbf{X}^-_t$ are considered as sets of random variables. The symbol $\backslash$ denotes set difference [73].

The *stationarity* is assumed for process $\mathbf{X}$. The process $\mathbf{X}$ is casually stationary over a time index set $\mathcal{T}$ *if and only if for all links* $X^i_{t-\tau} \to X^j_t$ *in graph* [73]

$$X^i_{t-\tau} \not\perp\!\!\!\perp X^j_t | \mathbf{X}^-_t \backslash \{X^i_{t-\tau}\} \; holds \; for \; all \; t \in T. \tag{2.2}$$

The framework constructs a time-series graph of a multivariate stochastic process $\mathbf{X}_t$ by evaluating the conditional mutual information (CMI) from subprocesses $X_{t-\tau}$ to Y_t for $\tau > 0$

$$I(X^i_{t-\tau}; Y_t | \mathbf{X}^-_t \backslash \{X_{t-\tau}\}), \tag{2.3}$$

with infinite past $\mathbf{X}^-_t = (\mathbf{X}_{t-1}, \mathbf{X}_{t-2}, ...)$. If $Y \neq X$, the link $X_{t-\tau} \to Y_t$ is considered as a *coupling or cross-link at lag* τ. If $Y = X$, then the link is considered an *autodependency or autolink at lag* τ [71].

The CMI for multivariate random variables X, Y, Z is defined as

$$\begin{aligned} I_{X;Y|Z} &= \iiint dxdydz \, p(x,y,z) log \frac{p(x,y|z)}{p(x|z) \cdot p(y|z)}, \\ &= H_{X|Z} + H_{Y|Z} - H_Z - H_{X,Y|Z}, \end{aligned} \tag{2.4}$$

where H denotes the Shannon entropy and densities $p(\cdot)$ is assumed to exist [72]. The framework test the conditional independence hypothesis

$$H_0 : X \perp\!\!\!\perp Y | Z, \tag{2.5}$$

against the general alternative. $I_{X;Y|Z} = 0$ if and only if $X \perp\!\!\!\perp Y | Z$, provided that densities are well-defined [72]. Tigramite utilizes a permutation-based generation of the distribution under H_0 for hypothesis testing in graph structure construction. The

conditional independence testing used in this framework is CMI as defined in equation 2.4 are model-free method, therefore in principle can handle non-linear dependencies [73].

Then the framework measures information transfer from the past of a process X at times $t' < t$ to the target variable Y at time t and exclude common information in history shared by X and Y. TE is defined as [71]

$$I(X_t^-; Y_t | \mathbf{X}_t^- \backslash X_t^-), \tag{2.6}$$

$$I(X_t^-; Y_t | \mathbf{X}_t^- \backslash X_t^-) = \sum_{\tau=1}^{\infty} I(X_{t-\tau}; Y_t | \mathbf{X}_t^- \backslash X_t^-, X_{t-\tau}^-), \tag{2.7}$$

To overcome the *curse of dimensionality* of the condition in each term, TE is estimated using decomposed transfer entropy (DTE) [74] utilizing theory of graphical models [48] [20] which implies that

$$I(X_{t-\tau}; Y_t | \mathbf{X}_t^- \backslash X_t^-, X_{t-\tau}^-) = I(X_{t-\tau}; Y_t | \mathcal{S}_{Y_t, X_{t-tau}}), \tag{2.8}$$

for a certain finite subset $\mathcal{S}_{Y_t, X_{t-tau}} \subset \mathbf{X}_t^- \backslash X_t^- \cup X_{t-\tau}^-$ of the conditions. The suitable set $\mathcal{S}_{Y_t, X_{t-tau}}$ can be determined from the constructed time-series graph. The DTE is calculated by

$$I_{X \to Y}^{TE} \approx I_{X \to Y}^{DTE} = \sum_{\tau=1}^{\tau^*} I(X_{t-\tau}; Y_t | \mathcal{S}_{Y_t, X_{t-tau}}), \tag{2.9}$$

where τ^* is the chosen smallest τ [74].

The conditional independence test needed to compute CMI and TE in Tigramite is CMIknn based on conditional mutual information estimated with k-nearest neighbor entropy estimator developed by [46]

$$\hat{I}_{XY|Z} = \Psi(k) + \frac{1}{n} \sum_{i=1}^{n} [\Psi(k_i^z) - \Psi(k_i^{xz}) - \Psi(k_i^{yz})] \tag{2.10}$$

with the logarithmic derivative of the Gamma function $\Psi(x) = \frac{d}{dx} ln\Gamma(x)$. Free

parameter k is the number of nearest neighbors in the joint space of $\mathscr{X} \otimes \mathscr{Y} \otimes \mathscr{Z}$ around each sample point i at maximum norm distance ϵ_i. The k_i^{xz}, k_i^{yz}, and k_i^z are computed by the number of points with distance smaller than ϵ_i in the subspace $\mathscr{X} \otimes \mathscr{Z}$, $\mathscr{Y} \otimes \mathscr{Y}$, and $\mathscr{Z}$ to get k_i^{xz}, k_i^{yz}, k_i^z respectively [75].

The appropriate maximum time delay τ_{max} usually depends on the nature of signal being investigated. We can estimate the τ_{max} by observe the lagged unconditional dependencies decay. In this study, we observed that the dependencies decay beyond a lag of 15. For the significance level α, in the context of this framework it takes the role of a regularization parameter for model-selection, since precise assessment of uncertainty is not possible in iterative hypothesis testing.

To quantify causal interaction between subprocess, this framework proposed a measure I to quantify linear causal effect (CE) of perturbation [71]

$$I_{i \to j}^{CE}(\tau) = \Psi_{ji}(\tau) \tag{2.11}$$

where $\Psi(\tau)$ is iteratively computed matrix products of estimated coefficient matrices $\Phi(\tau)$ by [76]

$$\Psi(\tau) = \sum_{s=1}^{\tau} \Psi(s)\Phi(\tau - s). \tag{2.12}$$

The mediated causal effect (MCE) through a component k is the sum over the products of path coefficients only along causal paths through k.

$$I_{i \to j}^{MCE}(\tau) = \Psi_{ji}(\tau) - \Psi_{ji}^{(k)}(\tau) \tag{2.13}$$

where $\Psi^{(k)}(t)$ is a computed from equation 2.12 with mmodified path coefficient matrices $\Phi^{(k)}(t)$ where all links towards component k are set to zero

$$\Psi_{ki}^{(k)}(\tau) = \begin{cases} 0, \ for\ all\ links\ X_{t-\tau}^i \to X_t^k \\ \Phi_{ki}(\tau), \ otherwise \end{cases} \tag{2.14}$$

which blocks all paths though component k at any lag [76].

Aggregated causal effect (ACE) and aggregated causal susceptibility (ACS) measures on the lag with maximum effect [76]:

$$I_{i\to j}^{CE,\max} = \max_{0<\tau\leq\tau_{max}} |I_{i\to j}^{CE}(\tau)| \tag{2.15}$$

$$I_{i\to j}^{ACE} = \frac{1}{N-1}\sum_{j\neq i} I_{i\to j}^{CE,\max} \tag{2.16}$$

$$I_{i\to j}^{ACS} = \frac{1}{N-1}\sum_{i\neq j} I_{i\to j}^{CE,\max}. \tag{2.17}$$

The average mediated causal effect (AMCE) is calculated based on causal paths through a given node

$$I_{k}^{AMCE} = \frac{1}{|\mathcal{C}_k|}\sum_{(i,j)\in\mathcal{C}_k} \max_{0<\tau\leq\tau_{max}} |I_{i\to j|k}^{MCE}(\tau)| \tag{2.18}$$

where $\mathcal{C}_k$ is the set of interactions between all non-identical pair $i, j \neq k$ at all lags $0 < \tau \leq \tau_{max}$ where k is an intermediate component (at any lags) and $|\mathcal{C}_k|$ denotes its cardinality [76].

2.4.1 Computational cost and consistency

The computational complexity of the PCMCI used in Tigramite depends on the complexity of the condition selection step and the momentary condition independence (MCI) test step. The complexity of the conditional selection step depends on the network structure where in the worst case is a complete graph, the number of conditional independence tests for N variables is

$$N\sum_{p=0}^{N\tau_{max}-1} N\tau_{max} = N^3\tau_{max}^2 \tag{2.19}$$

tests with iteratively increasing cardinality [75]. The number of test in MCI step are $N^2\tau_{max}$ tests for $\tau > 0$ of a maximal dimensionality of $2 + |\hat{\mathscr{P}}(X_t^j)| + |\hat{\mathscr{P}}(X_{t-\tau}^i)|$ where $\mathscr{P}$ denotes the causal parents [75]. Thus, the overall complexity of the PCMCI

is $N^3\tau_{max}^2 + N^2\tau_{max}$ which is polynomial. The current implementation of the PCMCI does not yet support parallelization, however, it is a planned feature. There are several processes that have potential for parallelization, so the framework's performance may improve in the future.

Consistency is a property of causal discovery method indicates whether the method is able to converges to the true causal graph in the limit of infinite sample size [73]. Consistency of PCMCI is proven by Runge *et al.* [75].

2.4.2 Advantages and disadvantages of Tigramite

Graph theory is a classical tools for brain function modeling, usually based on pairwise association measures among nodes in the graph [12]. In contrast, Tigramite uses CE which is a dynamical and causal alternative to classical measures, and has been found to have higher predictive power [76]. The problem such as common driver, where X and Y are driven by common Z process with difference time lag, reduces the validity and interpretability of the connectivity model in the framework where only correlation between two variable is considered at a time such as Granger causality [52]. The implementation of Tigramite allows more detail pathway analysis by investigating CE of each nodes along lagged time. It mitigates common driver problem by discovering hidden pathways and drivers.

However, the limitation of this approach has to be considered when interpret the model. This method is a data-driven approach, thus it needs to rely on several assumptions. For example, causal sufficiency assumes that all variables are available and taken into account [80]. When interpreting resulting CEs, it is important to consider it only in relative to variables that were taken into account [76].

While we have shown that this approach is applicable in individual level, to interpret brain mechanism for general population, the method to construct a group connectivity is needed because modeling connectivity from data across individuals is controversial [19]. Causal analysis is sensitive to temporal noise and variance. The variation in time-order of neuronal activity across individual due to brain plasticity may cause misinterpretation of the causal effect. The fact that BOLD signal is an in-

direct measurement of the actual neuronal activity further confound the connectivity inference.

2.5 Case study: motor-task fMRI connectivity using Tigramite

Here I would like to demonstrate the basic of brain connectivity study using motor-task fMRI data. As a primary study using novel tools, the motor-task is relatively simpler comparing to memory-related task or resting-state because we can physically observe the subject performing the task. The brain networks related to motor function had also been extensively studied, thus we can validate the results of this study by comparing them with the previous studies by other researchers.

2.5.1 Materials and method

The dataset used in this study is obtained from Human Connectome Project (HCP), a project conducted by the Washington University-University of Minnesota Human Connectome Project Consortium (WU-Minn HCP). This project provides exceptional spatiotemporal resolution fMRI dataset of well-characterized large group of healthy individuals [85].

We utilize the HCP motor task-fMRI dataset for this particular case study. This motor task was adapted from design developed by Bucholz *et al.* [10]. Subjects are asked to perform following actions, tapping left or right fingers, squeezing left or right toes, or moving tongue in according to visual cue being presented. The session is organized in blocks of movement type, each preceded by a 3 second cue and lasted for 12 seconds with 10 movements. Overall, the session contains 13 blocks in total, with 4 foot movements (2 right and 2 left), 4 hand movements (2 right and 2 left), and 2 tongue movements. The rest 3 blocks are 15-second fixation blocks [85].

Figure 2-1 shows the process overview of this connectivity study. Univariate group subtraction analysis was done on the aforementioned HCP motor task using FSL

6.0.2 (FMRIBs Software Library, www.fmrib.ox.ac.uk/fsl) software suite (figure 2-1b). The preprocessing step consisted of image reconstruction, distortion correction, motion correction, and slice timing correction. The HCPs structural MRI and fMRI were preprocessed using FSL 5.0.6 according to HCP preprocessing pipeline [31]. Individual- and group-level univariate group subtraction analysis were done using FEAT (FMRI Expert Analysis Tool, v.6.00). 50 subjects were randomly selected from HCP dataset for this analysis.

Usually, a set of region-of-interest (ROI) will be selected based on an univariate group subtraction analysis, however, additional ROIs can also be included if they are known to involve in the function of interest based on the prior related literatures. In this case, the ROIs included are the activated region from the univariate group subtraction analysis (figure 2-2). Additionally, frontal lobe, cerebellum, left and right thalamus, are included based on prior studies [53] that they play roles in motor related task. All ROIs are listed in table 2.1.

BOLD time-series were extracted using FSL's average time-series calculation tool (fslmeants). Time-series of each area were extracted in according to Juelich histological atlas, Harvard-Oxford cortical structural atlas, and MNI structural atlas (table 2.1). Slice timing correction was performed using FSL. The masks of the aforementioned ROIs used as input for fslmeants were created using FSLeyes software (figure 2-1c). Each masks have been checked that there is no overlapping between different regions. For connectivity model construction, we propose the use of Tigramite causal discovery framework (figure 2-1d).

In our motor task-fMRI application, the algorithm's parameters we used are as follow: maximum time lag $\tau_{max} = 15$ time point, significance level $\alpha = 0.01$ (Student's t-test).

2.5.2 Results

Table 2.1: All region of interest included in connectivity model.

No.	Area Name	Abbreviation	Atlas
1	left thalamus	PmcBA4pL	MNI structural
2	right thalamus	PmcBA4pR	MNI structural
3	left premotor cortex Brodmann area 6	PcBA6L	Juelich histological
4	right premotor cortex Brodmann area 6	PcBA6R	Juelich histological
5	left anterior primary motor cortex Brodmann area 4	PmcBA4aL	Juelich histological
6	right anterior primary motor cortex Brodmann area 4	PmcBA4aR	Juelich histological
7	left posterior primary motor cortex Brodmann area 4	PmcBA4pL	Juelich histological
8	right posterior primary motor cortex Brodmann area 4	PmcBA4pR	Juelich histological
9	left visual cortex V1 Brodmann area 17	V1BA17L	Juelich histological
10	right visual cortex V1 Brodmann area 17	V1BA17R	Juelich histological
11	left visual cortex V2 Brodmann area 18	V1BA18L	Juelich histological
12	right visual cortex V2 Brodmann area 18	V1BA18R	Juelich histological
13	cerebellum	Cereb	Harvard-Oxford cortical structural
14	frontal lobe	FL	Harvard-Oxford cortical structural

Table 2.2: Area identified by univariate group subtraction as defined by Juelich histological atlas.

Area Name	Abbreviation
left anterior primary motor cortex Brodmann area 4	PmcBA4aL
right anterior primary motor cortex Brodmann area 4	PmcBA4aR
left posterior primary motor cortex Brodmann area 4	PmcBA4pL
right posterior primary motor cortex Brodmann area 4	PmcBA4pR
left premotor cortex Brodmann area 6	PcBA6L
right premotor cortex Brodmann area 6	PcBA6R
left visual cortex V1 Brodmann area 17	V1BA17L
right visual cortex V1 Brodmann area 17	V1BA17R
left visual cortex V2 Brodmann area 18	V1BA18L
right visual cortex V2 Brodmann area 18	V1BA18R

While the localization of the motor-related brain region had been well studied, we performed univariate group subtraction analysis on this data to verify that this

dataset is consistence with prior finding.

The resulting main cluster of all the task blocks are shown in figure 2-2, and the areas cover the activated brain region are listed in table 2.2. The left and right foot tasks show clusters at right and left premotor cortex (Brodmann area 6) respectively. The left and right hand tasks show clusters at right and left primary motor cortex (Brodmann area 4). The tongue block shows cluster in both left and right primary motor cortex. The visual cue block shows large cluster covers both left and right visual cortex V1 (Brodmann area 17) and V2 (Brodmann area 18).

In the following, we show a constructed connectivity model and its associated parameter of a random HCP subject. In this framework, in addition to studying causal effects between adjacent nodes in the connectivity model, we can also study total causal effect (CE) along indirect causal paths. The matrices of CEs between all ROIs are shown in figure 2-3. The CE between two components i and j at lag τ can be denoted as $I^{CE}_{i\to j}(\tau)$.

We can observe CE becomes stronger as the lag (τ) is increasing at node 12, 8, and 4 or area V1BA18R, PmcBApR, and PcBA6R (table 2.1) respectively. From this observation, we can further investigate the interaction between these area by plotting their mediation graph. The figure 2-4 is a mediation graph between V1BA18R and PmcBA4aL. We choose to investigate this pair because it has highest CE, $I^{CE}_{12\to 5}(15) = 0.82$. Time-series graph in figure 2-4b shows the effects propagate from V1BA18R to other visual areas in the early process, then the strongest CE propagates to PmcBA4aL in the left hemisphere and weaker CE propagates to PmcBA4aR in the right hemisphere. After that, the CE propagates from PmcBA4aR to PcBA6R. Left Thalamus only receives CE from PcBA6R and show negative CE to several visual areas and PmcBA4aL. The negative CE means that it counteract the effect of other areas.

By calculating average causal effect (ACE), a column-mean of the CE matrices, and average causal susceptibility (ACS), a row-mean of the CE matrices, we can observe how much effect a specific ROI has on the rest of the brain and how sensitive a specific ROI is to perturbations from other parts of the brain. An average mediated causal effect (AMCE) measures how strong a subprocess mediates CEs propagating

throughout the system [76].

In figure 2-5, we show ACE, ACS and AMCE for this HCP subject. The figure 2-5a shows that this particular subject's right visual cortex (Brodmann area 18) has strong effect to the rest of the brain. This is reasonable since in HCP motor task-fMRI protocol, the subject's actions were initiated by visual cue. In figure 2-5b, we can see that the left primary motor cortex (Brodmann area 4) has high susceptibility with the change from other area. We can infer the reason behind this observation to be due to the fact that this task focuses on motor function, thus most changes in the system affect motor-related area the most. In figure 2-5c, right visual cortex (Brodmann area 17) is shown to be the strongest mediator of the CE spreading. This area acts as the main pathway to this system is correspond to the experiment paradigm where there visual cue initiate the action.

2.5.3 Discussions

Correctly interpreting brain mechanism is difficult, especially in higher cognitive function such as memory or self-awareness, because there is no ground truth, and some cognitive function cannot be physically observed. In this study, we want to show that in addition to conventional connectivity model construction approaches such as Granger causality, Tigramite is also one of the viable approaches with its own benefits. We choose to show its application with motor task-fMRI dataset because mechanism of brain motor function is well studied. The available knowledge can be used to compare and verify the validity of the resulting connectivity model.

The brain areas involve in controlling body's voluntary movement is the motor cortex. This area can be further divided into primary motor cortex (Brodmann area 4), premotor cortex (Brodmann area 6), and supplementary motor area [58]. The primary region of the motor system is the primary motor cortex. It works in association with the rest of the motor area to control muscle movement. Visual area 1 (V1), or Brodmann area 17 (BA17), in visual cortex functions primarily in pattern recognition in the visual field [32]. It processes visual information in association with other region inside visual cortex, such as, Broadmann area 18 (BA18). Frontal cortex

in frontal lobe has been found to play roles in mediating movement-related brain signal [57] through thalamus and cerebellum [9]. According to these knowledge, we use Tigramite to construct a connectivity model involving these regions.

The Tigramite framework shows not only the statistical dependency between brain regions, but also causal effects among the regions. In addition to the topological information of the resulting graphical model, ACE, ACS, and AMCE provide information about the overall characteristic of the interaction inside the model.

ACE shows how much effect a ROI has on the rest of the brain. The ACE of the random subject depicted in result section shows that the major driver of the system is right visual area (BA17), followed by right premotor cortex (BA6) and right primary motor cortex (BA4) respectively (figure 2-5a). It is reasonable to expect visual cortex as a major driver to the system due to the fact that the motor task performed by the subject was initiated by visual cue. Inside the motor cortex, ACE shows that premotor cortex is the major driver to the system. It reflects the fact, founded by studying brain activity of monkey, that the premotor cortex is involved in planning and preparing for movement, in which the movement is then executed by the primary motor cortex [91].

The level of ACS shows how susceptible a ROI is to the perturbations from other part of the brain. In our sample case, the brain areas with high ACS are left primary motor cortex (BA4) and left premotor cortex (BA6) respectively (figure 2-5b). Considering that the right motor cortex is shown to be one of the major driver, the high susceptibility of the left motor cortex may be the evidence of inter-hemispheric coupling in brain activity observable even during uni-lateral motor task [16].

AMCE measures the subprocess that mediates the propagation of CEs throughout the system. Figure 2-5c demonstrates that the most dominant causal mediators is right visual area (BA17), which means that this region is a major causal pathway of this system. The presence of dominant mediation and driver in right hemisphere may related to the handedness of the subject, unfortunately the HCP dataset does not included this information in subject's profile, so we cannot confirm or deny this conjecture.

In figure 2-4, we shows a connectivity model of pathway between right visual area (BA18) and left primary motor cortex (BA4) at lag 15. While we expected a mediation pathway in frontal lobe that caused by motor movement planning activity [4], we could not detected it. The absence of this connection might be due to the fact that if the CEs are faster than the lag resolution, the repetition time (TR) in the case of fMRI which is 2.8 seconds for this dataset, it will appear in the analysis as contemporaneous links, which are not regarded as causal links [76].

2.6 Issues with fMRI data for brain connectivity modeling

The low temporal resolution of fMRI BOLD signal poses a challenge to connectivity modeling because the causal inferring process is temporal sensitive. Moreover, fMRI images are constructed from several scan slices acquired at the different time in orderly fashion. Despite the slice-timing correction process usually applied in the preprocessing step, there is a chance that the error or deviation in correction may result in spurious connectivity, or incorrect order of causality. This issue will be further discussed in chapter 3

2.7 Validation and interpretation

While most conventional fMRI studies rely on pool of data collected across individuals, modeling of the connectivity from data across individuals is controversial [19]. Nonetheless, a method to establish a general model that represents brain connectivity across individuals is essential. We propose a method of constructing a representative graph based on graph structure by using median aggregation of the weight of corresponding edges and nodes of each individual graphs which will be discussed in detail later in chapter 4.

2.8 Generalizing brain connectivity model

As we have discussed functional segregation section, the generalized group-level result is more preferable to individual result. This poses a problem with the connectivity model analysis because currently there is no established method to compute and validate the connectivity model. We will discuss this problem in more details in chapter 4.

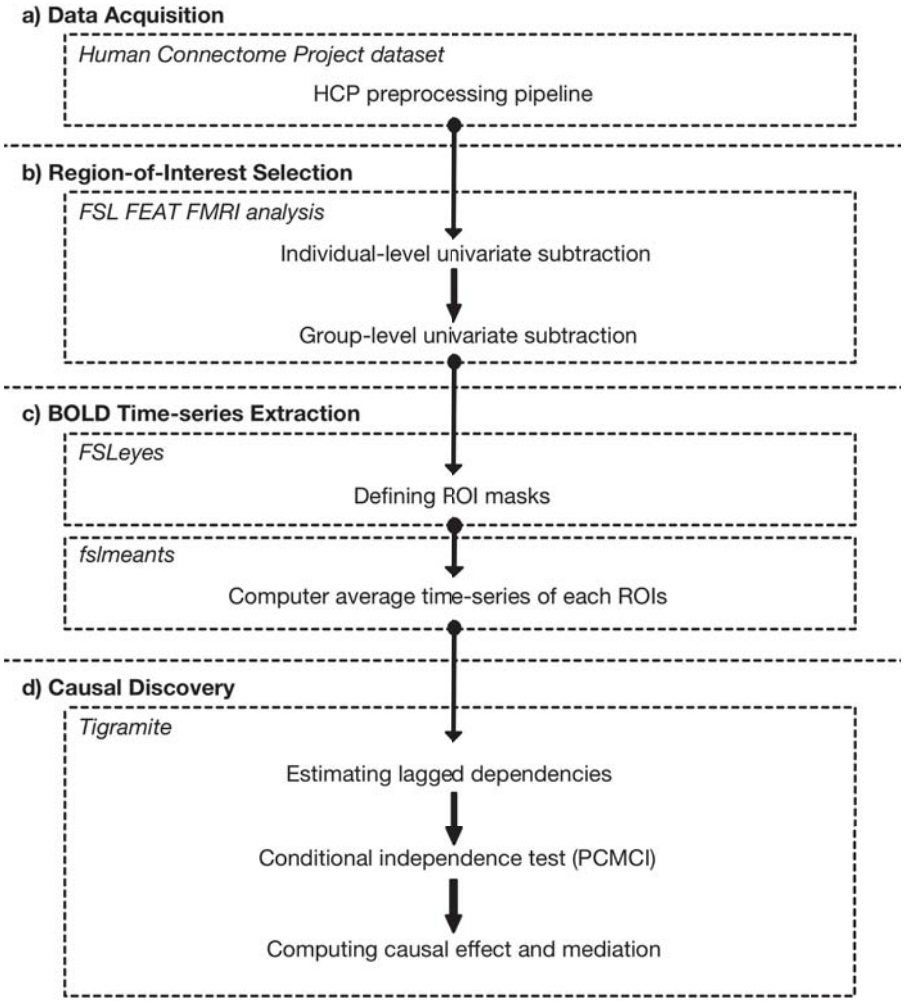

Figure 2-1: Summary of processing pipeline from fMRI data to connectivity using Tigramite. a) Here, we use motor task-fMRI dataset provided by Human Connectome Project (HCP). The data were preprocessed by the HCP using the HCP preprocessing pipeline [31] which includes image reconstruction, distortion correction, motion correction, and MNI nonlinear volume registration. b) We performed localization of activated brain region during the task using *FSL FEAT fMRI analysis*. Group-level analysis were done using randomly selected 50 individuals. c) Then we defined masks for BOLD time-series extraction based on the aforementioned localization results using *FSLeyes*. Additional regions that are known to play roles in motor-related function were included. Then the average BOLD time-series of each regions of interest were extracted using *fslmeants* tool. d) Finally, Tigramite was used to construct a connectivity from the extracted time-series. The first step is to estimate the lagged dependencies to determine maximum lag (τ_{max}). Then we performed the conditional independence test to estimate the causal link between each ROIs. After that, the estimated time-series graph were used to evaluate causal effect and causal mediation.

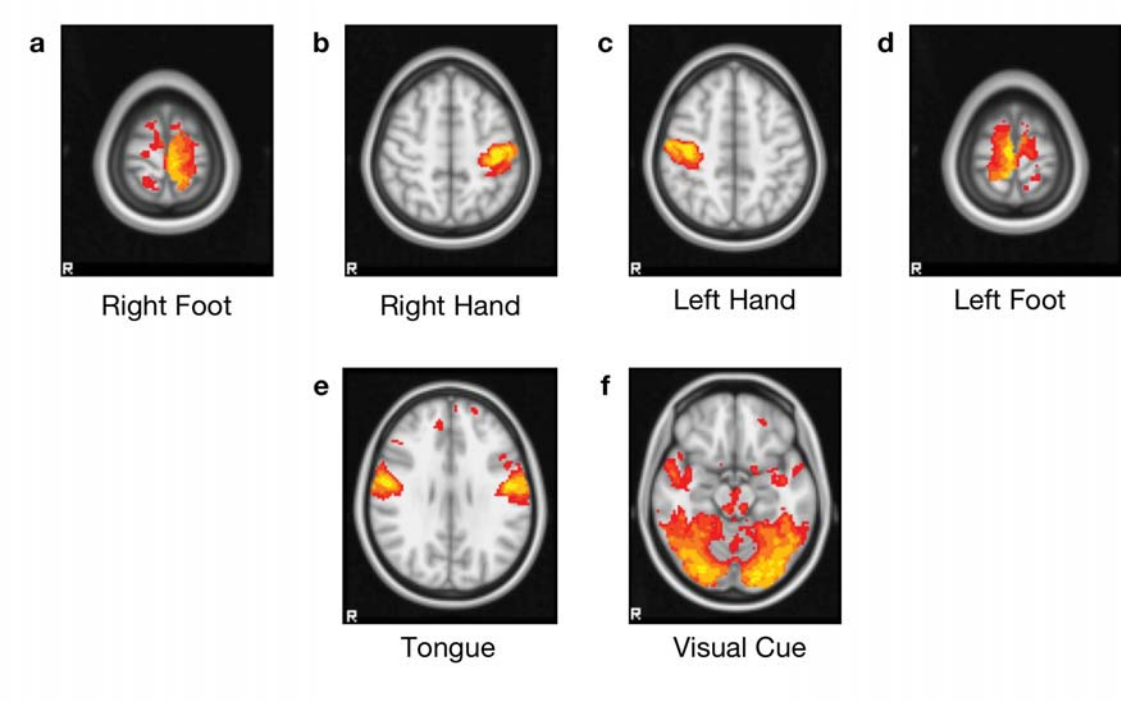

Figure 2-2: Group-level clusters of each task blocks from randomly selected 50 subjects of HCP motor task-fMRI dataset. Z statistic images were thresholded using clusters determined by Z>3.1 at cluster significance threshold of P=0.05 (corrected). FEAT (FMRI Expert Analysis Tool, v6.00) was used for the analysis. The General Linear Model was used to model 6 blocks (5 task blocks, 1 cue block). Task blocks consisted of tapping left or right fingers, squeezing left or right toes, or moving tongue, preceded by visual cue block. The brain areas covers by these clusters are listed in table 2.2.

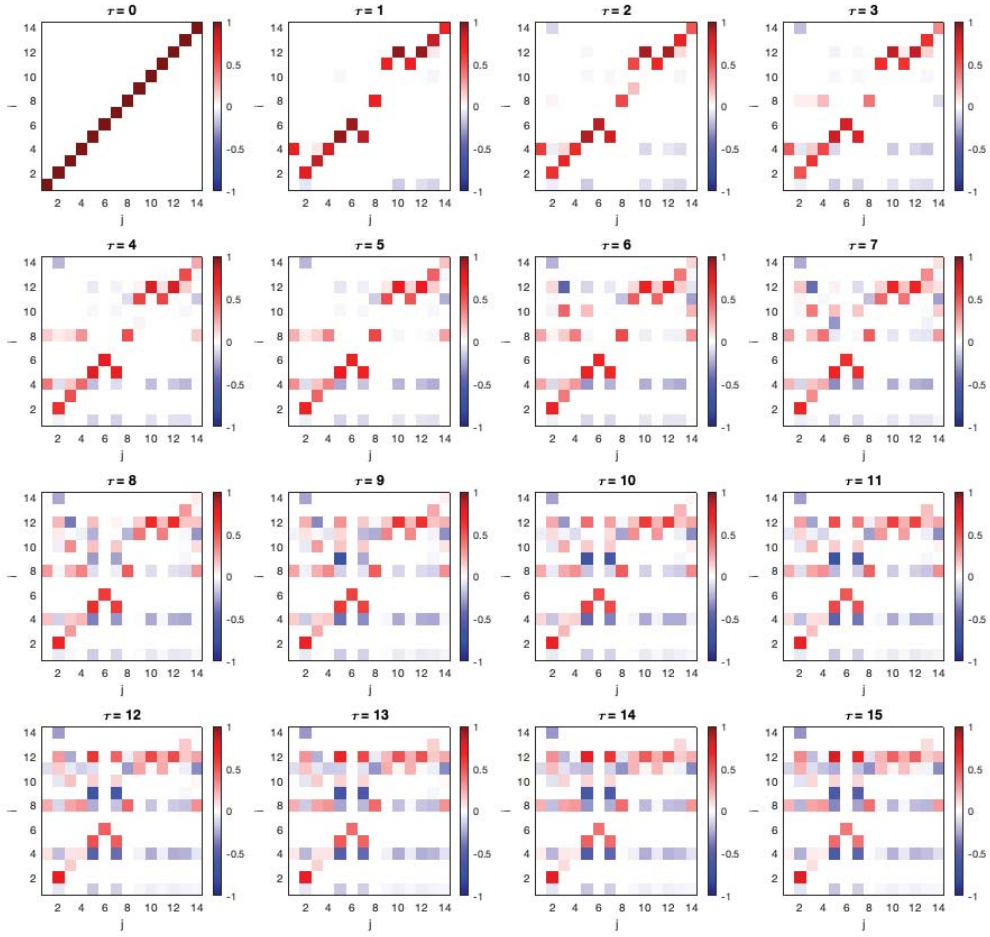

Figure 2-3: Causal effect of all ROI pairs and lags. An entry in the matrix shows causal effect $I^{CE}_{i\to j}(\tau)$ calculated using equation 2.12 where i and j correspond to ROI listed in table 2.1. The strength declines in the longer lags.

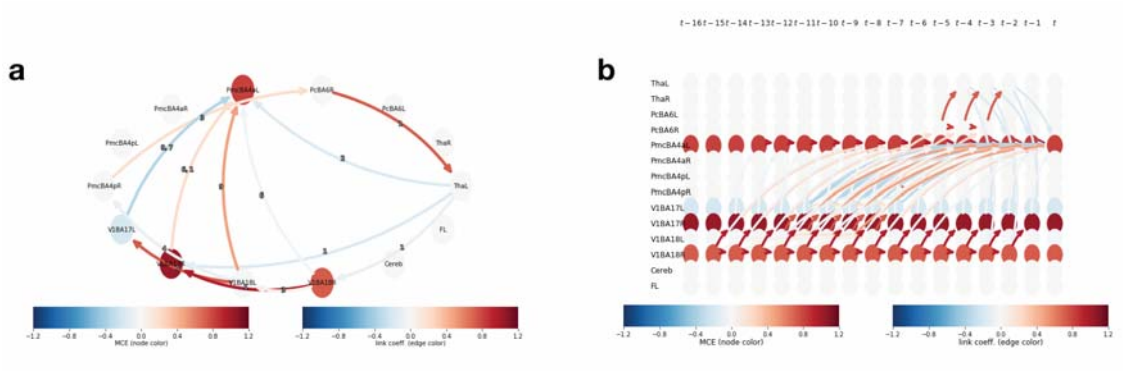

Figure 2-4: a) Aggregated graphical model from V1BA18R to PmcBA4aL at lag 15 $I^{CE}_{12\to5}(15)$. It is a summary graph represents time-series graph in figure 2-4b. The edge color shows link coefficient and node color shows the MCE. b) Time-series-graph of V1BA18R to PmcBA4aL pair at lag 15 $I^{CE}_{12\to5}(15)$ depicts links in relevant causal paths between V1BA18R and PmcBA4aL at lag 15. The edge color shows link coefficient and node color shows the MCE.

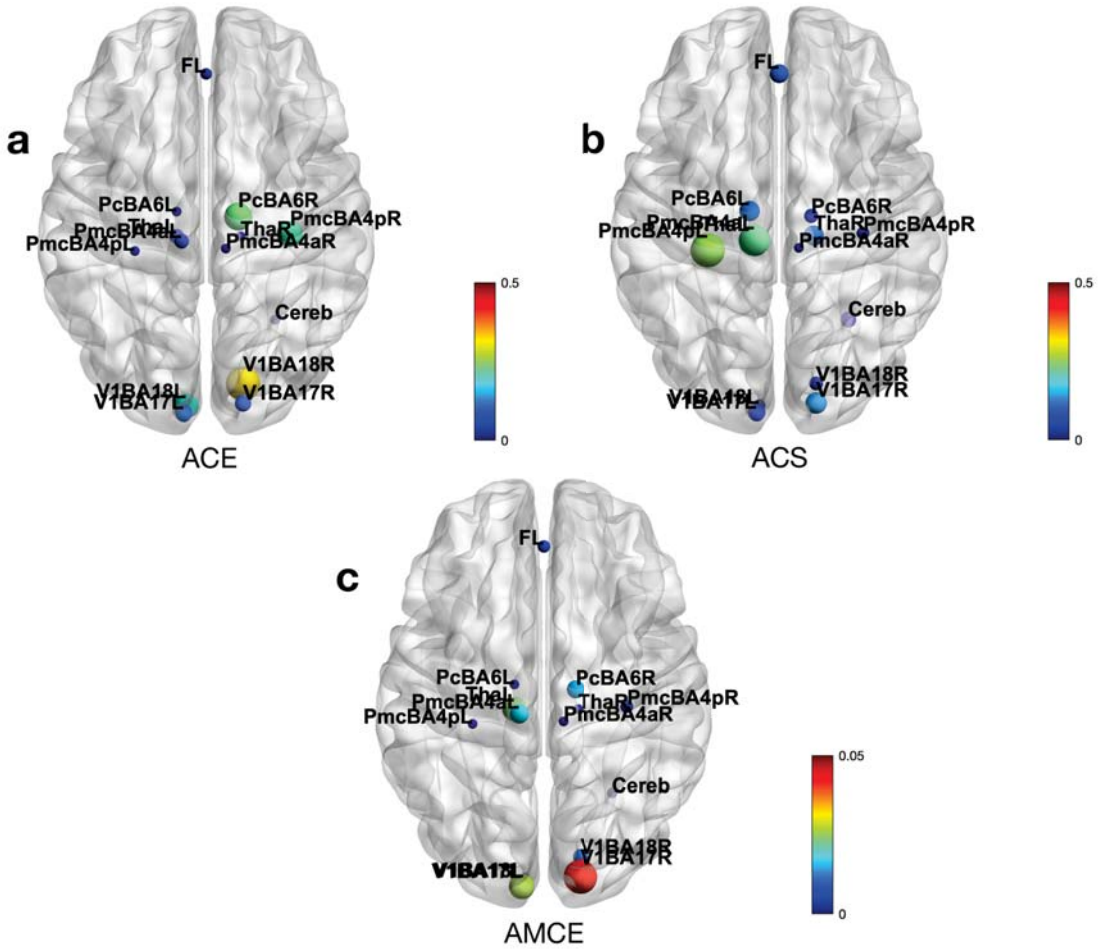

Figure 2-5: a) Depicts average causal effect (ACE) of each brain regions (nodes) in HCP motor task-fMRI connectivity model. The values (size of the nodes) reflect how much particular region effects the rest of the brain. b) Average causal susceptibility (ACS) shows how sensitive the region is to the change from the rest of the system. c) Average mediated causal effect (AMCE) shows how strong the region mediate the effect propagation.

Chapter 3

Functional and Effective Connectivities

How can we describe brain mechanism? In the simplest form, we can consider brain as a information processing unit, thus it is logical to illustrate brain function using a model that represents information flow. That is a connectivity model. The connectivity model consists of nodes and edges, where nodes represent brain regions and edges represent information pathway between regions their are connected to. Using this concept, we can find which areas are active during the task and measure the flow of information by tracing a series of activation over time, then construct a graph describe that mechanism. We can combine the model with the prior knowledge of function of each regions involved in the model, then trying to interpret the meaning of the model.

Nonetheless, illustrating how brain works for a specific cognitive function is a challenging task. Currently available technologies for observing brain function non-invasively is limited, and the signal acquired is indirect. One of the most prominent technology in this field is functional magnetic resonance imaging (fMRI). The fMRI technology has enabled the observation of regional brain activation by detecting the amount of oxygen presence in blood in each particular part of the brain, on the principle that the region that is working is consuming oxygen for energy. This allows the chronological observation of brain regional activations, and by plotting those

regional activations through time, we can assume information pathways from region to region inside the brain during any particular cognitive task. These pathways are the brain connectivity.

3.1 Deriving connectivity model from BOLD signals

Since brain activity cannot be observed physically, the brain connectivity is a useful tool to model its mechanism. A connectivity model or a network is a mathematical representation of a real-world complex system denoted by a collection of nodes and links between pairs of nodes [70]. Nodes usually represent brain region, and links represent connection between regions. The model illustrate how each regions of the brain interact with each other and show how information, in form of neuronal signal, flow through them. Combine with the background knowledge of each particular region responsibility to certain lower cognitive function, the mechanism of higher cognitive function can be inferred. There are 3 types of connection, anatomical, functional and effective connection. The anatomical connection is an actual physical link between regions by biological pathway.

Functional connectivity is a type of connectivity that represents the *undirected* link or *correlation* between the node. It is defined as the temporal coincidence of spatially distant neurophysiological events [27]. We need to be careful when interpreting this type of connectivity. For example, when the analysis shows that the region A has functionally connected with region B, it might be incorrect to conclude that there are information transfer from region A to region B. There is a possibility that both region A and B have the common influencer region C, so they both A and B seems to be coupled. Moreover, correlated activity in two regions may be mediated by other area relaying the information from the first to the second area, which will resulting in the correlation presence even in the absence of real physical connection. Thus, the function connectivity does not imply any causal relationship between brain regions.

Effective connectivity is a type of connectivity model that the *directed* link between nodes represent *causation* between the node. It is defined as the influence one

area exert over another [25]. This type of connectivity allow for more sophisticated interpretation of the brain mechanism. Furthermore, the effective connectivity also considers time-dependent change, so we can trace the path that the signals, or informations, propagate. The Tigramite framework use transfer entropy to measure this connectivity from signals.

The anatomical connectivity is the most straightforward of all 3 connectivity in terms of inferring and interpreting connectivity model, because there are physical evidences and measurable signal as ground truth, albeit postmortem pathological study of neuronal structure or invasive procedure on live patient are usually required. Contrarily, functional and effective connectivity usually derived from non-invasive measurement and they are hypothetical connections. It is usually controversial to infer solid conclusion from hypothetical connections as there is no ground truth to support the inference, thus limiting our ability to make meaningful interpretation of these connectivities. Confounding factors present due to limitation of non-invasive measurement further reduce the reliability of the resulting connectivity model.

There are several mathematical framework or algorithms that can be applied to construct both functional and effective connectivity from fMRI blood-oxygen-level-dependent (BOLD) signal. The example of such algorithm is Granger causality. Granger causality [33] is a mathematical framework commonly employed to model causality of the neuronal activity from fMRI BOLD signal. The underlying assumption of this framework is that if $X \rightarrow Y$ if and only if a change in X has an effect on Y [66]. However, all we can imply from observational data are statistical dependencies. Inferring and interpreting causal relationship is controversial. Moreover, the fact that fMRI BOLD signal is an indirect measurement of actual neuronal signal further confounds the inference. The detailed background about the development of other tools commonly used in this field is discussed in chapter 2.

Regardless of fMRI technological limitation, there are attempts and progresses in research and development of the framework to extract connectivity information from fMRI BOLD signal. CONN toolbox is a MATLAB toolbox designed for functional connectivity analysis using BOLD signals. This toolbox emphasis on preprocess the

signals to make it suitable for functional connectivity analysis. Primary concern of signal preprocessing for conventional fMRI analysis is spatial preprocessing, such as, slice-timing correction to correct time lag between each slice acquisition, or realignment to correct displacement between slices caused by subject's movement. However, in case of connectivity analysis, temporal aspect of the signal is also a concern, because connectivity analysis is temporal sensitive. Global signal regression can be used to remove temporal noise, but it is known to introduce negative correlation in the connectivity result which reduces result's interpretability. CONN toolbox avoid that issue by utilizing component-based noise correction method (CompCor) instead of global signal regression, which increase sensitivity and specificity of functional connectivity, thus allow for better interpretability [92].

Additional to a software designed specifically for fMRI connectivity analysis, any causal analysis framework has potential to carry out the task as well. Tigramite is a time-lagged causal discovery framework [71]. Compare to Granger causality, this framework relies on different set of assumptions to identify a causal graph. It performs conditional independence testing using the assumptions of time-order, *Causal Sufficiency*, the *Causal Markov Condition*, and *Faithfulness*, among others [73], hence improve causal interpretability in comparison to Granger causality. In chapter 2, we have discussed the detailed background and implementation of Tigramite framework.

Beside conventional fMRI analysis, resting-state fMRI is gaining more and more attention in recent year. In contrast to conventional fMRI, which the experiment design revolves around block- or event-related task, resting-state fMRI is a model-free analysis for any steady-state fMRI dataset. It increases analytic options for describing the functional organization of the brain [55].

In the study discussed in this chapter, we compare resting-state functional connectivity model from CONN toolbox and effective connectivity model using Tigramite framework. Functional connectivity models only consider temporal correlation (undirected connection) while effective connectivity models consider temporal causality (directed connectivity). Additional information obtained from directed connectivity may improve fMRI connectivity interpretability, which is a major controversial in the

field of brain connectivity modeling [19].

3.2 Method

3.2.1 Subjects

This study contains data from 120 subjects (of all 149 participants, 1 is removed for biased questionnaire responses, 3 are removed because data incompletion, and 12 participants voluntarily withdrew from the study). The subject group included in this study consists of 68 females and 52 males. Minimum age is 45 year-old and maximum is 65 year-old (mean: 55.03, SD: 6.07).

3.2.2 Experiment design

A behavioral test is used to evaluate episodic memory recollection capabilities of the subjects. Stimuli are presented to the subjects to invoke episodic recollection. Stimulus used in this study is 3-word tuple cue consisted of *descriptive time*, *place*, and *action*. This word combination is used to stimulate subject's episodic recollection because they are basic elements of episodic memory [83]. Each trial consists 30 cues. Each cue has 2 corresponding responses, *difficulty* of recollection and *confidence* of recollection.

There are 3 phases in a single resting-state fMRI data acquisition session, *pre resting-state fMRI*, *resting-state fMRI*, and *post resting-state fMRI*. In *pre resting-state fMRI* phase, a set of 30 stimuli is presented to the subject. The subject does not need to respond to any of the stimuli in this phase. The *pre* phase is then followed by 10 minutes resting-state fMRI acquisition session, where the subject is asked to lie still inside fMRI scanner and to refrain from performing any cognitive task. In *post* phase, the same set of stimuli presented to the subject during the *pre* phase is presented to the subject. In this phase, the subject responding to each stimulus by performing self-assessment of difficulty and confidence in episodic memory recollection of the corresponding scenario associated with each stimulus. The summary of the

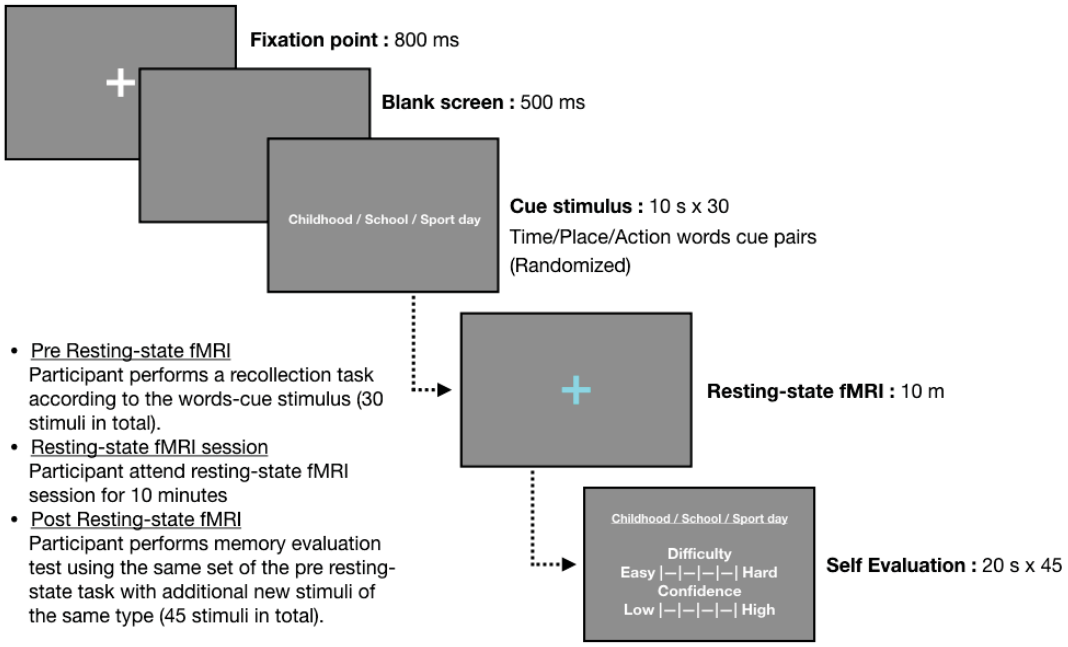

Figure 3-1: Resting-state fMRI session paradigm. Before the scan, participants were asked to perform recollection task using words-cue stimuli. The words-cue is a combination of words describing time, place, and action. Each stimuli was shown for a duration of 10 seconds with total of 30 stimuli. This session is followed by a 10 minutes resting-state fMRI scan session. After the scan, the participants were presented with the same set of stimuli with additional new stimuli. However, for this post-scan session, the participants were asked to evaluation the *difficulty* and *confidence* of the recollection of the memory corresponding to the stimuli.

paradigm is shown in figure 3-1.

3.2.3 Data acquisition

Stimuli and self-assessment questionnaires are presented to subjects using 'Presentation' stimulus delivery program (Neurobehavioral Systems Inc, Albany, CA, USA). In *pre* phase, a white fixate crosshair is displayed for 500 ms, followed by 500 ms blank screen, then word-combination cue is displayed for 10 s. During *resting-state fMRI* scan session, a blue fixate crosshair is displayed to the subject. The subject has not

been given any instruction to perform any physical or cognitive task. In *post* phase, word-combination cue is displayed along with self-assessment question for 20 s. The response is in 1 to 5 integer scale. The subject responds to the question by pressing corresponding numeric button on keyboard. In addition to 30 stimuli presented during *pre* phase, 10 novel stimuli and 5 attention checking stimuli are added to *post* phase.

Resting-state fMRI was performed on 3 T MR scanner (Siemens). Forty continuous axial slices (slice thickness 3.2 mm, 0.8 mm gap) were acquired in each volume using a T2*-sensitive gradient echoplanar imaging sequence (TR: 2,500 ms, TE: 30 ms, flip angle: 80°, FOV: 212 mm × 212 mm)

3.2.4 fMRI data preprocessing

The fMRI data in this study are preprocessed through CONN toolbox standard preprocessing pipeline. The pipeline utilizes SPM8 for spatial preprocessing which includes slice-timing correction, realignment, normalization, and smoothing (8-mm FWHM Gaussian filter). Temporal preprocessing is done using component-based noise correction (CompCor) implementation of CONN toolbox. The temporal covariates removed by linear regression are the estimated subject motion (three-rotation and three translation parameter, and another six parameters representing their first-order temporal derivatives), the BOLD time-series within the subject-specific white matter mask (three PCA parameters), and cerebrospinal fluid (CSF) mask (three PCA parameters). The resulting residual BOLD time-series are band-pass filtered at $0.01 \text{ Hz} < f < 0.10 \text{ Hz}$ [92].

3.2.5 ROI BOLD extraction

The region of interest (ROI) BOLD signals used in both CONN and Tigramite analysis are extracted using CONN toolbox's preprocessing pipeline. The ROI BOLD signals are average BOLD time-series computed across all the voxel within the ROI. The ROIs are defined by Harvard-Oxford Atlas. Ten ROIs are selected for connectiv-

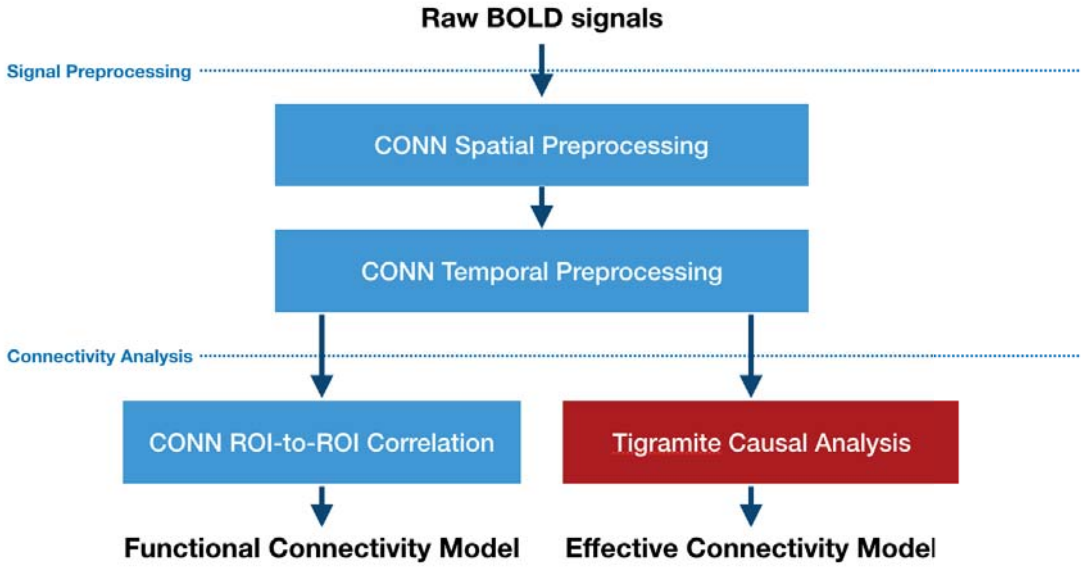

Figure 3-2: Data processing workflow. Raw BOLD signals of each region-of-interest were extracted and preprocessed using CONN toolbox. The CONN toolbox performs temporal preprocessing in addition to traditional spatial preprocessing to reduce temporal variance in fMRI BOLD signal in an attempt to avoid spurious connection in the connectivity analysis. The preprocessed signal were used to produce functional connectivity model using CONN ROI-to-ROI correlation analysis tool, and effective connectivity model using Tigramite causal analysis framework.

Table 3.1: Selected regions of interest (Harvard-Oxford cortical structural probability atlases).

Hemisphere	Regions	Abbreviation
Right	hippocampus	Hippocampus r
Left	hippocampus	Hippocampus l
Right	anterior parahippocampal cortex	aPaHC r
Left	anterior parahippocampal cortex	aPaHC l
Right	posterior parahippocampal cortex	pPaHC r
Left	posterior parahippocampal cortex	pPaHC l
-	medial prefrontal cortex Default Mode network	networks.DefaultMode.MPFC
Right	lateral parietal Default Mode network	networks.DefaultMode.LP (R)
Left	lateral parietal Default Mode network	networks.DefaultMode.LP (L)
-	posterior cingulate cortex Default Mode network	networks.DefaultMode.PCC

ity analysis (table 3.1). The selected ROIs consisted of Default Mode networks and area that are known to be responsible for episodic memory related cognitive functions [14]. Those regions are selected for this study to model the memory-related connectivity that shows the interaction among those region in relation to our memory-related cognitive function of interest.

3.2.6 Behavioral test

Self-assessment memory recollection test questionnaire is used to evaluate subject's episodic recollection ability. The assessment measures 2 parameters, *difficulty* in performing recollection, and *confidence* of the accuracy of the content of the recollection. The difficulty level indicates how much effort the subject has to assert in order to recall a memory of particular scenario specified by the stimulus. The confidence level indicates how certain the subject feel about the accuracy of the recalled memory. The assessment results are used as between-subject contrast for group-level analysis.

3.2.7 CONN ROI-to-ROI analysis

All aforementioned 10 ROIs (table 3.1) are used as seed for this analysis to estimate the ROI-to-ROI functional connectivity (bivariate correlation measure) among these ROIs. Between-subjects contrast is defined by behavioral results from memory

recollection test.

The second-level between subject contrast is determined by memory recollection self-assessment questionnaire with 2 parameters, recollection difficulty and confidence. The difficulty show how much effort the subject need to assert to recall the memory. The confidence shows how much confidence the subject has in regard of the accuracy of the recalled memory. The self-assessed confidence level is shown to be associated with episodic memory retrieval performance [38].

3.2.8 Tigramite analysis

We model causal relation among 10 ROIs (table 3.1) for each individual subjects using Tigramite causal time series analysis software package. It is a time-lagged causal discovery frameworks [73]. There are 2 free parameters for the algorithm, the maximum time lag τ_{max}, and the significance threshold α in the condition- selection step. To determine maximum time lag τ_{max}, we estimated lagged unconditional dependencies of the BOLD time-series and found the dependencies diminish beyond a lag of 8. The significance threshold α is set to 0.1. The α is a regularization parameter in model-selection techniques, and should not be seen as significance test level in the condition-selection step [75]. Group representative model was constructed by median aggregation of connection weight of corresponding link of each individual connectivity graph. We use median to reduce the effect of outliers.

3.3 Results

3.3.1 Behavioral results

The behavioral profile of each subjects is determined by self-assessed memory recollection questionnaire. The subject is presented with 3-word combination stimuli consisted of *descriptive time*, *place*, and *action*. Then subject is asked to recall the memory related to the stimuli and determine the *difficulty* and the *confidence* of the recollections.

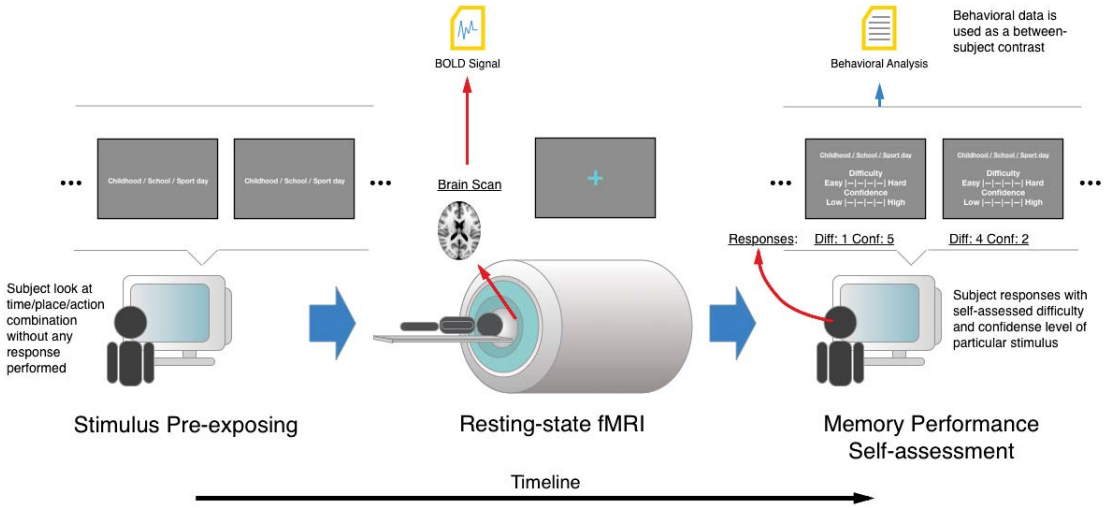

Figure 3-3: ImPACT data acquisition paradigm. The subject was pre-exposed to the words-cue stimuli in pre-scan phase (figure 3-1). Then the subject participated in resting-state fMRI scan session where the resting-state brain activity of the subject was acquired. In the resting-state session, the subject were asked to do nothing, both mentally and physically, throughout the scan session. After that in the post-scan phase, the subject was asked to perform the memory recollection task (figure 3-1) which the result will be used as behavioral profile in resting-state fMRI analysis.

Table 3.2: Category of subject based-on self-assessment memory recollection test

Group	Number of subjects
High Confidence Low Difficulty (Red)	79
Low Confidence High Difficulty (Blue)	41

The subjects are divided into 2 groups by Euclidean distance clustering based on episodic memory recollection performance obtained using self-assessment test during *post resting-state fMRI* phase. The self-assessment test asked the subjects to determine their *confidence* in the correctness of their recollections and *difficulty* in recalling those memories. Both assessments are quantify from low to high in 1 to 5 integer scale. The clustering is done in 2-dimensional plane where each dimensions represents each aforementioned *confidence* and *difficulty* parameters. The values of each paramenters for an individual subject are mean averages value of the test across all recollection stimuli. From the result of the clustering, the group with lower average *confidence* is considered a *low-confidence* group, and vice versa. Likewise, the group with lower average *difficulty* is considered *low-difficulty* group, and vice versa. Combining aforementioned 2 parameters, the groups can be categorized into 2 characteristic groups, *high-confidence-low-difficulty* group, and *low-confidence-high-difficulty* group, with 79 members and 41 members respectively (figure 3-4 and table 3.2). These categories are used as between-subject contrast for group resting-state connectivity analysis.

3.3.2 Functional connectivity

After the standard fMRI data preprocessing protocol and additional temporal preprocessing in preparation for connectivity analysis by CONN toolbox and Tigramite framework, the BOLD signal of each regions of interest are extracted. The ROI BOLD signals are average BOLD time-series aggregated across all the voxel covered within the ROI. The 10 ROIs are selected for the analysis based on the background knowledge that those areas are known to involve in memory related cognitive function (table 3.1). The purpose of including those area in the connectivity model is to model how those areas interact with each other in relation to our cognitive function of interest. The roles and functions of each individual regions will be discuss in detail

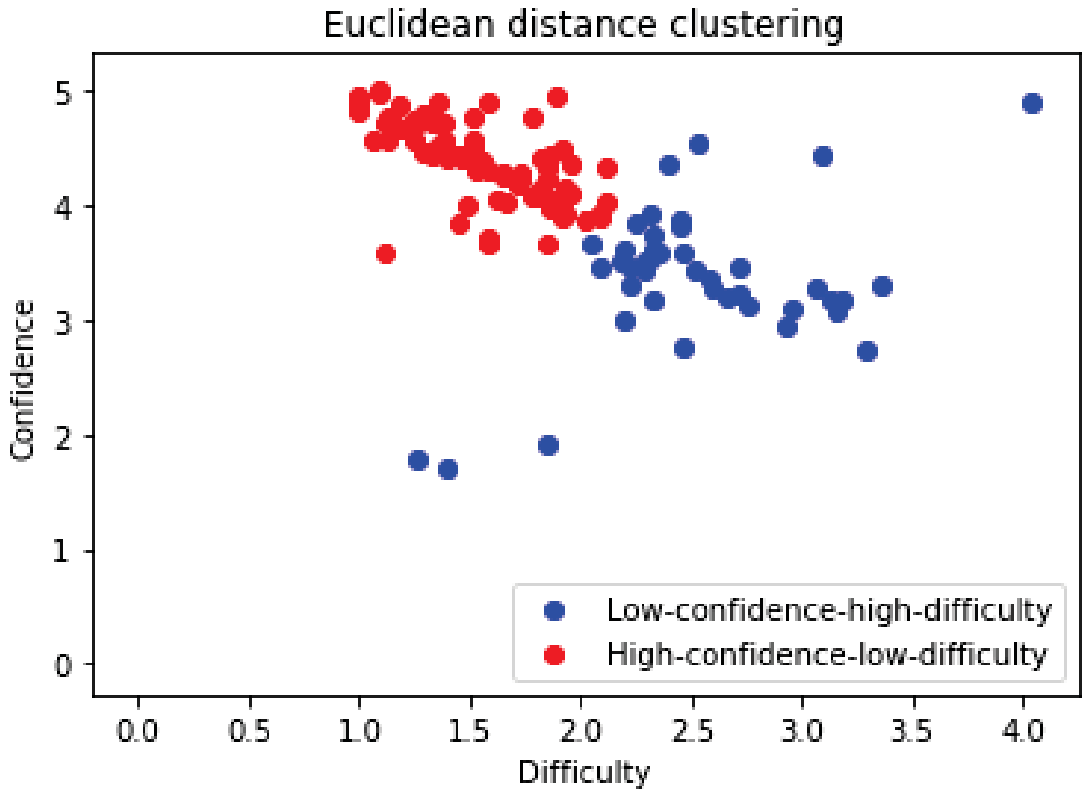

Figure 3-4: Euclidean distance clustering of episodic recollection performance. The group with lower average *confidence* is considered a *low-confidence* group, and vice versa. Likewise, the group with lower average *difficulty* is considered *low-difficulty* group, and vice versa.

Table 3.3: CONN ROI-to-ROI connection weight. (thresholded at FDR-corrected $p < 0.05$). A row represents source region and a column represent destination region.

	Hippo l	Hippo r	aPaHC l	aPaHC r	pPaHC l	pPaHC r	LP (L)	LP (R)	MPFC	PCC
Hippo l	0.0	36.82	15.96	12.99	24.17	19.55	10.58	9.48	14.55	7.07
Hippo r	36.82	0.0	15.03	16.29	20.32	21.38	8.98	8.92	13.65	6.26
aPaHC l	15.96	15.03	0.0	17.13	13.18	10.89	6.34	4.51	6.95	4.49
aPaHC r	12.99	16.29	17.13	0.0	12.74	13.58	6.4	7.05	9.03	5.16
pPaHC l	24.17	20.32	13.18	12.74	0.0	33.38	15.44	14.15	11.78	17.13
pPaHC r	19.55	21.38	10.89	13.58	33.38	0.0	13.04	12.19	8.13	13.35
LP (L)	10.58	8.98	6.34	6.4	15.44	13.04	0.0	30.37	10.36	21.72
LP (R)	9.48	8.92	4.51	7.05	14.15	12.19	30.37	0.0	14.4	26.78
MPFC	14.55	13.65	6.95	9.03	11.78	8.13	10.36	14.4	0.0	17.18
PCC	7.07	6.26	4.49	5.16	17.13	13.35	21.72	26.78	17.18	0.0

in the discussion section. The areas are defined using Harvard-Oxford Atlas.

Then the CONN toolbox ROI-to-ROI connectivity analysis is performed on the aforementioned ROI BOLD data.

The resulting connectivities are shown in table 3.3 and the highest 10 connectivities are listed in table 3.4. CONN toolbox constructs a connectivity graph using seed-based approach by iteratively considers each ROIs as seed, then combines the results of every seeds (ROIs) into one single graph. This approach is acceptable for functional connectivity analysis since functional connectivity concern only correlation between seed and region-of-interest, the direction of the connection does not affect correlation measures. It can be observed in table 3.3 that swapping a specific pair of seed region and ROI does not yield different connectivity measure. This is completely different from effective connectivity which a pair of regions has different connection measure depends on the direction of the connections.

Table 3.4 shows consolidated highest 10 connections by intensity. Figure 3-6 is a connectivity plot of the aforementioned consolidated connections (full connectivity plot is included in Figure 5 in Supplementary materials section). The highest 3 connections are the hemisphere pairs of the identical regions. The most intense connectivity following those pairs is a connection between posterior cingulate cortex Default Mode network and right lateral parietal Default Mode network, followed by connections between hippocampus and anterior parahippocampal cortex on the left hemisphere, left lateral parietal Default Mode network and posterior parahippocampal cortex and hippocampus on the right hemisphere, left posterior parahippocampal

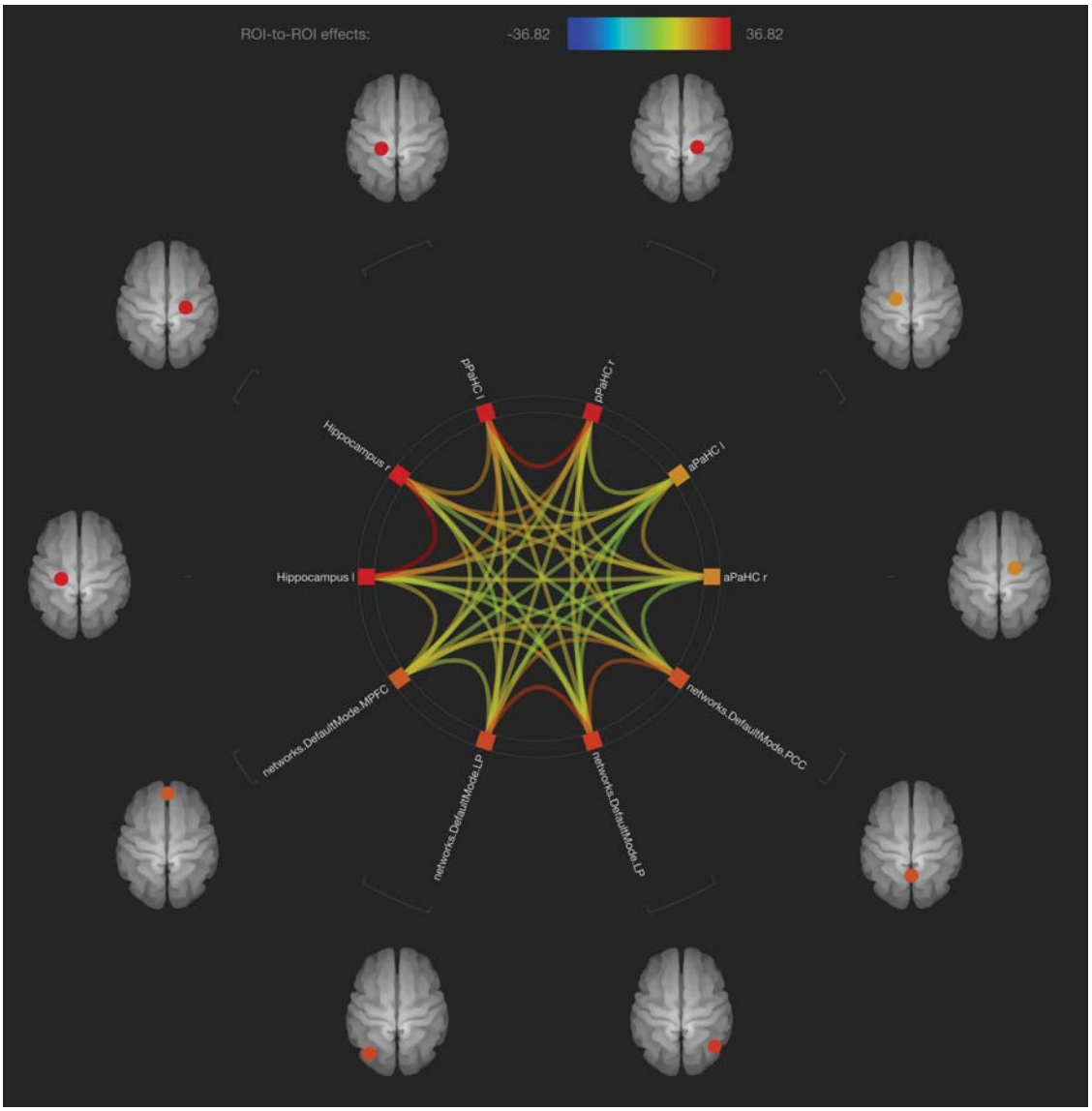

Figure 3-5: CONN toolbox graphical model of resting-state fMRI connectivity with 10 seed area (table 3.4). Results are thresholded at FDR-corrected $p < 0.05$.

Table 3.4: Consolidated top 10 ROI-to-ROI connections by intensity. (thresholded at FDR-corrected $p < 0.05$)

ROI	ROI	Intensity
Hippocampus l	Hippocampus r	36.82
pPaHC r	pPaHC l	33.38
networks.DefaultMode.LP (L)	networks.DefaultMode.LP (R)	30.37
networks.DefaultMode.PCC	networks.DefaultMode.LP (R)	26.78
Hippocampus l	pPaHC l	24.17
networks.DefaultMode.LP (L)	networks.DefaultMode.PCC	21.72
pPaHC r	Hippocampus r	21.38
pPaHC l	Hippocampus r	20.32
pPaHC r	Hippocampus l	19.55
networks.DefaultMode.MPFC	networks.DefaultMode.PCC	17.18

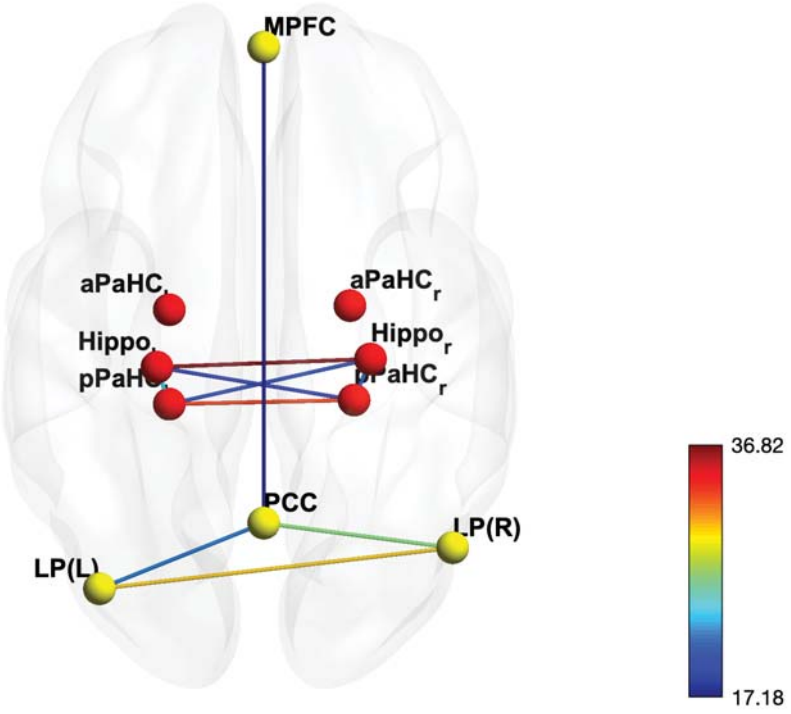

Figure 3-6: CONN toolbox ROI-to-ROI simplified graphic model with 10 highest connections (table 3.4) of resting-state fMRI connectivity with 10 seed area (table 3.4). Results are thresholded at FDR-corrected $p < 0.05$.

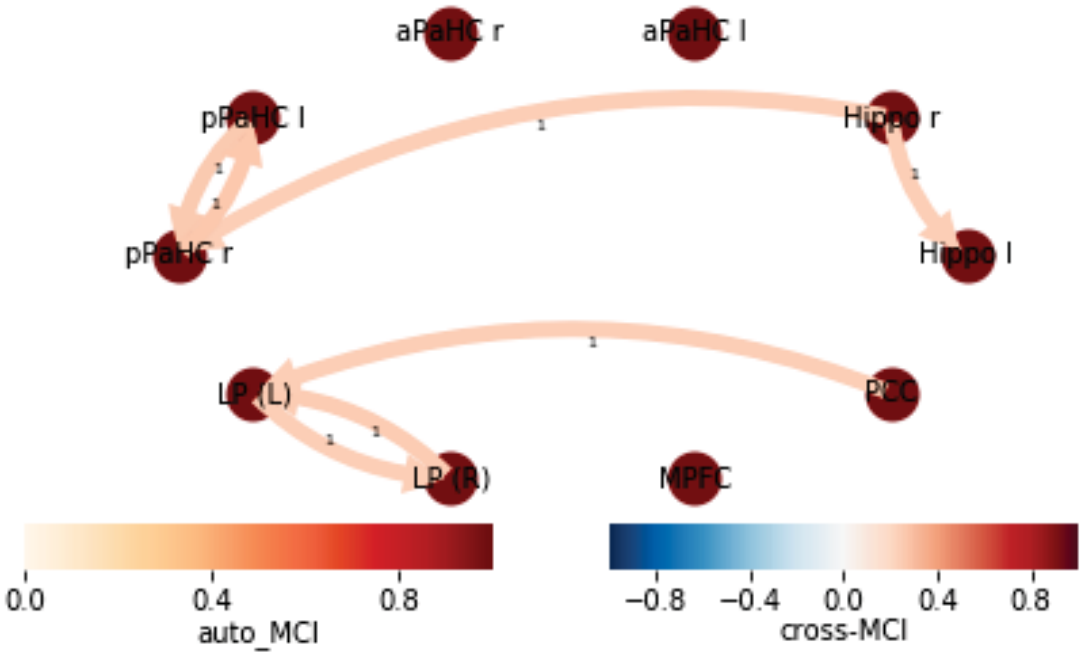

Figure 3-7: Tigramite graphic model of resting-state fMRI connectivity with 10 seed area (table 3.4). Results are thresholded at FDR-corrected $p < 0.05$.

cortex and right hippocampus, right posterior parahippocampal cortex and left hippocampus, and finally medial prefrontal cortex Default Mode network and posterior cingulate cortex Default Mode network.

3.3.3 Effective connectivity

The effective connectivity analysis is performed using the exact same data with the functional connectivity analysis in previous section. The exact same preprocessing protocol is performed on the data, so that any discrepancy in the resulting connectivity model is a result of capability of the analytic algorithms, since one of the goal in this study is to compare two models from different modal of analysis.

The resulting effective connectivity shows 7 connectivities among the selected ROI (figure 3-9). Five out of 7 connections are interaction between two identical region of difference hemisphere. The rest 2 connections are connection from right hippocampus to right posterior parahippocampal cortex, and from posterior cingulate

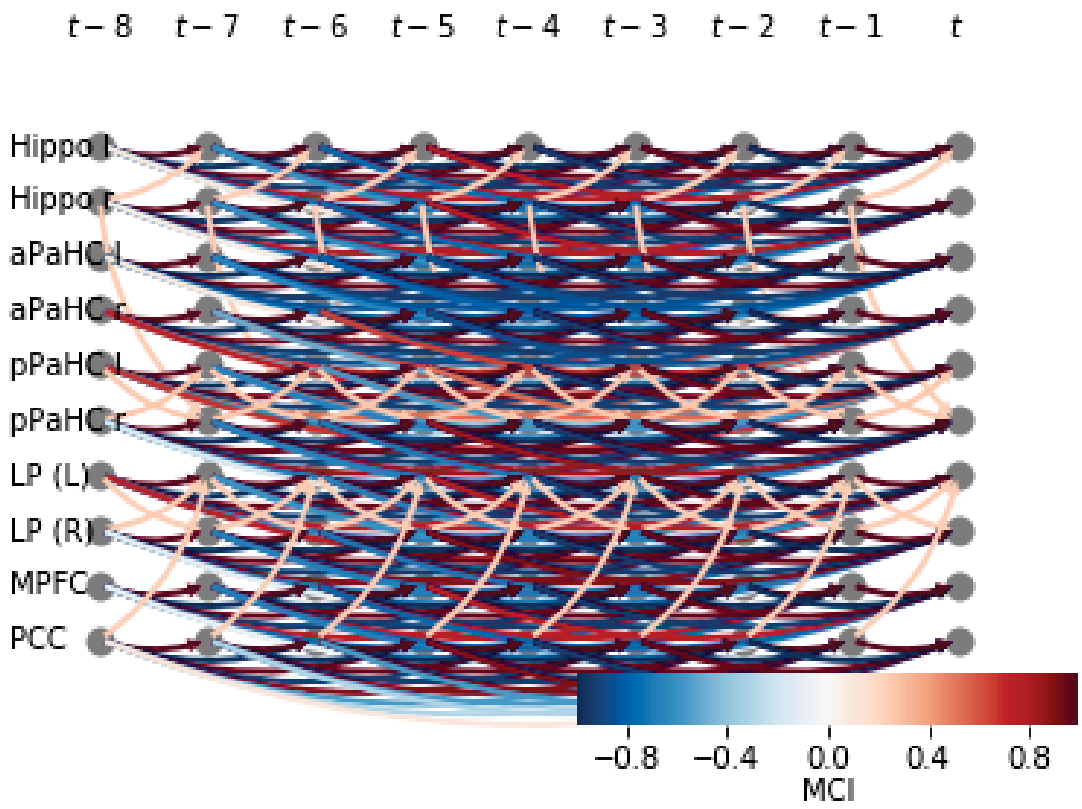

Figure 3-8: Tigramite time-series model of resting-state fMRI connectivity with 10 seed area (table 3.4). Results are thresholded at FDR-corrected $p < 0.05$.

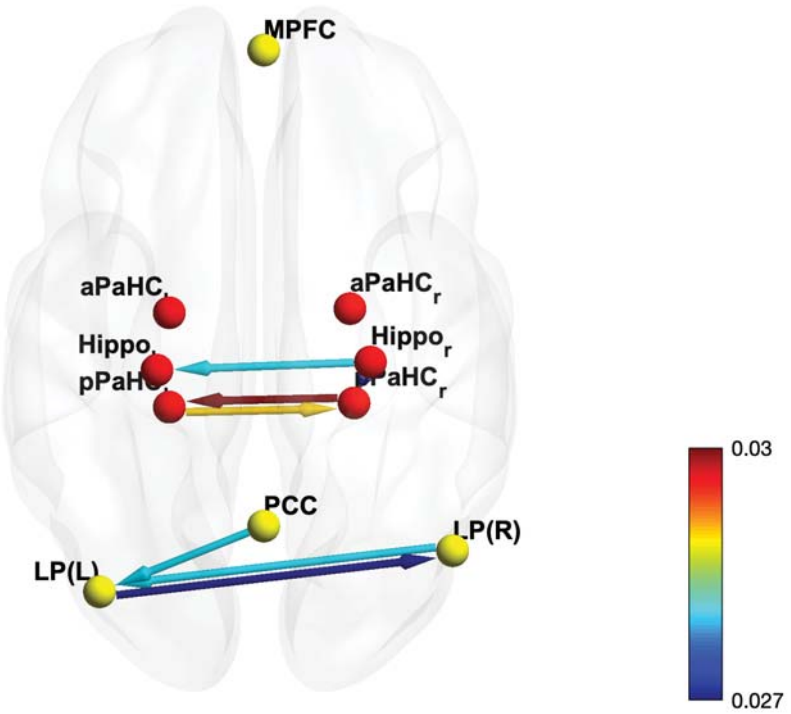

Figure 3-9: Tigramite simplified graphic model of resting-state fMRI connectivity with 10 seed area (table 3.4). Results are thresholded at FDR-corrected $p < 0.05$.

Table 3.5: Group Tigramite connection weight. (thresholded at FDR-corrected $p < 0.05$). A row represents source region and a column represent destination region.

	Hippo l	Hippo r	aPaHC l	aPaHC r	pPaHC l	pPaHC r	LP (L)	LP (R)	MPFC	PCC
Hippo l	-0.051	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Hippo r	0.028	-0.052	0.000	0.000	0.000	0.027	0.000	0.000	0.000	0.000
aPaHC l	0.000	0.000	-0.239	0.000	0.000	0.000	0.000	0.000	0.000	0.000
aPaHC r	0.000	0.000	0.000	0.007	0.000	0.000	0.000	0.000	0.000	0.000
pPaHC l	0.000	0.000	0.000	0.000	0.004	0.029	0.000	0.000	0.000	0.000
pPaHC r	0.000	0.000	0.000	0.000	0.030	-0.067	0.000	0.000	0.000	0.000
LP (L)	0.000	0.000	0.000	0.000	0.000	0.000	0.034	0.027	0.000	0.000
LP (R)	0.000	0.000	0.000	0.000	0.000	0.000	0.028	-0.055	0.000	0.000
MPFC	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	-0.079	0.000
PCC	0.000	0.000	0.000	0.000	0.000	0.000	0.028	0.000	0.000	0.022

cortex Default Mode network to left lateral parietal Default Mode network. All connection weights (mutual conditional information measure), including auto mutual conditional information measure, is shown in table 3.5. Tigramite's graphic model and time-series graph model are included in Supplementary material as Figure 6 and 7 respectively.

3.4 Findings

In this chapter, we have constructed functional and effective connectivity models from the same resting-state fMRI BOLD data. By comparing these two models, we illustrate the practical advantage of effective connectivity over functional connectivity. The Tigramite framework used to derived effective model provides performance advantage in comparison to CONN toolbox by eliminating trivial connection from the connectivity model, in addition to connections' directional information of the connectivity model. These advantages increase intepretability of the model. Currently, a large body of studies in brain connectivity focuses on only functional connectivity analysis. As the result of this study has shown, we would like to emphasize the limitation of functional connectivity analysis in terms of interpretability, and would like to encourage brain connectivity study with effective connectivity model as it improves interpretability of the actual brain function.

Nonetheless, the Tigramite framework is a novel framework and the application on fMRI BOLD data is scarce. Further study need to be done to confirm its validity

on BOLD data application.

We would like to also emphasize the importance of BOLD data noise reduction, since these connectivity analysis frameworks are temporal sensitive and prone to generate spurious connection from BOLD signal noise. The preprocessing pipeline established in CONN toolbox is crucial to successful connectivity modeling in both case.

3.4.1 Spontaneous BOLD fluctuations in resting-state connectivity model

The spontaneous BOLD fluctuations or spontaneous neuronal activity is brain activity that is not associated to any specific input or output. It is usually observable in resting-state fMRI data since the resting-state data acquisition protocol attemps to minimize both sensory input and subject response, the subject is also asked to refrain from performing cognitive task. Thus, the spontaneous BOLD fluctuation represents intrinsic neuronal activity generated by brain [22]. In traditional task-related fMRI study, this fluctualtion is eliminated by process of averaging across many trials along with other physiological artefacts, such as cardiac or respiratory activity, and non-physiological artefacts, such as scanner instability.

It is reasonable to eliminate spontaneous BOLD fluctuation from tradition task-related fMRI study because it increases confidence that the effect being studied is related to the task. However, in resting-state connectivity study, eliminating the fluctuation along with other artefacts poses a potential risk of decreasing validity. Thus, spontaneous BOLD fluctuation is crucial to resting-state connectivity modeling. The major concern of spontaneous BOLD data acquisition is to ensure that the results are not contaminated by or originated from spurious sources of variance BOLD, or other artefacts. CONN toolbox [92] address this issue by proposed and implemented an anatomical component-based noise correction method (aCompCor) [6], which not only increase the validity, but also the sensitivity and specificity of the connectivity analysis.

Several studies have show that many neuro-anatomical systems is coherent in their spontaneous activity [22]including task-negative/default mode [47] [23] [34] [24], hippocampus or episodic memory [88] [69]. The evidence of coherent of spontaneous BOLD fluctuation is also observable in functional connectivity analysis of this study, the temporal correlations between spatial coherence are shown by connections of hippocapus, anterior parahippocampal cortex, and lateral parietal Default Mode network (table 3.4). The coherent connections of hippocampus, and lateral parietal Default Mode network also presence in resulting effective connectivity analysis. Additionally, coherent connection of posterior parahippocampal cortex is also in the effective connectivity model with the absence of connection of anterior parahippocampal cortex. We will discuss about the difference of resulting functional and effective connectivity in the next section.

Chapter 4

Group Connectivity

In this chapter, I would like to discuss about the group connectivity modeling from fMRI BOLD signal of subsequence memory task using Tigramite causal discovery framework.

4.1 Individual- and group-level validation and interpretation problem

Observing how information are organized in human brain is a challenging task. However, in recent years, the progress in functional Magnetic Resonance Imaging (fMRI) technology has allowed the study of brain connectivity, the statistical dependencies between localized regional brain activity. In this context, we can model how information flows in the brain by analyzing brain connectivity during the memory-related cognitive task.

Currently, one of the problem in brain connectivity research is how to derive a connectivity that represents the mechanism of the group of population. The difficulty stems from the fact that there is the possibility that the order of activity between each regions of the brain may varies across individual. While the temporal variation may not affect the group brain activity localization analysis, those variation may affect the precision of temporal-sensitive analysis such as connectivity analysis. This cause the

problem to the validation of brain connectivity analysis where the connectivity model that is a represent of a population rather than individual in preferable. Furthermore, without the way to validate the connectivity model across the population, it is hard interpret the generalized brain mechanism from the connectivity model.

To address this problem, this chapter will discuss about a proposed framework to derive a group representative connectivity model using Tigramite framework.

4.2 Causal discovery analyses

Granger causality [33] is a mathematical framework commonly employed to model causality of the neuronal activity from fMRI BOLD data. The underlying assumption of this framework is that if $X \rightarrow Y$ if and only if a change in X has an effect on Y [66]. However, all we can imply from observational data are statistical dependencies. It is controversial to infer effective connectivity (directed connectivity) due to the low temporal resolution nature of the BOLD signal as Granger causality is prone to under-sampling signals. To avoid that issue in this study, we utilize Tigramite time-lagged causal discovery framework [71]. This framework relies on different set of assumptions to identify a causal graph. It performs conditional independence testing using the assumptions of time-order, *Causal Sufficiency*, the *Causal Markov Condition*, and *Faithfulness*, among others [73]. The detailed background and implementation of the Tigramite framework is discussed in chapter 2.

While most conventional fMRI studies rely on pool of data collected across individuals, modeling of the connectivity from data across individuals is controversial [19]. Nonetheless, a method to establish a general model that represents brain connectivity across individuals is essential. We propose a method of constructing a representative graph based on graph structure by using median aggregation of the weight of corresponding edges and nodes of each individual graphs.

4.3 Methods

4.3.1 Human Connectome Project

Human Connectome Project is a project conducted by the Washington University-University of Minnesota Human Connectome Project Consortium (WU-Minn HCP) [85]. We utilize this dataset because it provides access to large exceptional spatiotemporal resolution of well-characterized samples of healthy individuals.

This study made use of 376 subjects available in HCP data. Of all available 511 subjects, 52 subjects are excluded due to data incompletion, 83 subjects are excluded from the study due to biased responses in picture sequence memory test (subjects always respond to the stimuli in the test only either *remember* or *know*). Of the 376 subjects included in this study, 54 are between the ages of 22-25, 179 are between the ages of 26-30, 141 are between the ages of 31-35, and 2 are above 35 year-old.

4.3.2 Subsequent memory paradigm

The HCP dataset does not include a specific task related to episodic memory, hence, we employ a subsequent memory paradigm by combining HCP working memory task-fMRI and corresponding picture sequence memory test. Subsequent memory paradigm is a study of neural activity during an encoding phase of the stimuli that are later subsequently remembered in contrast to the stimuli that are forgotten [18].

In the encoding phase, a subject is given a chance to study a series of stimulus while their brain activity data are being collected. Later after the encoding phase is completed, the subject then performs a recollection test. In this test, the subject is shown a series of stimulus consists of both "old" stimuli presented during encoding phase and completely *new* unseen stimuli. During this phase, the subject is allowed to respond to the stimulus by indicating that they either *remember*, *know*, or seeing *new* stimulus.

The response is collected and evaluated for memory recollection quality. The correction and the confidence of the response is evaluated. If *remember* or *know*

responses are given to the old stimuli, it indicates the subject's correct recollection. The *remember* response indicates subject's confidence in their conscious recollection, and the *know* response indicates subject's doubt in their recollection, in which they may feel familiarity with the stimulus but fails to consciously recall it precisely. Then if the subject gives the *new* response to the *old* stimuli, it is considered that the stimuli have subsequently been forgotten by the subject, and if *remember* or *know* response is given to the *new* stimuli, that response is considered as a false recollection. If the *new* response is given to the *new* stimulus, it indicates that the subjects remember that the presented stimulus is not included in the set of stimuli previously shown during encoding phase.

4.3.3 Univariate group subtraction

The scanned images are processed and analyzed using FSL 5.0.7 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) software suite. The HCP's structural MRI and fMRI were preprocessed using FSL 5.0.6 software suite. The preprocessing pipeline is done by HCP using the pipeline derived from [31]. FEAT (FMRI Expert Analysis Tool, v6.00) was used to analyze first- and second-level analysis. The General Linear Model was used to model the event duration. The event-timing were specified in FSL's 3-column Explanatory Value file format. The explanatory file describes time when the interested events occurred, the duration of the events, and the value of the input during that time. The trial on which the stimuli are identified by the subjects as "remember" and "know" are selected for the analysis. The reasons are that this study wants to compare the condition where a subject encoded the memory of the stimuli that later successfully be recalled with one that failed to be recalled.

Additional Psychophysiological Interaction (PPI) Analysis is done using parahippocampal gyrus as a seed to identify additional memory encoding related region.

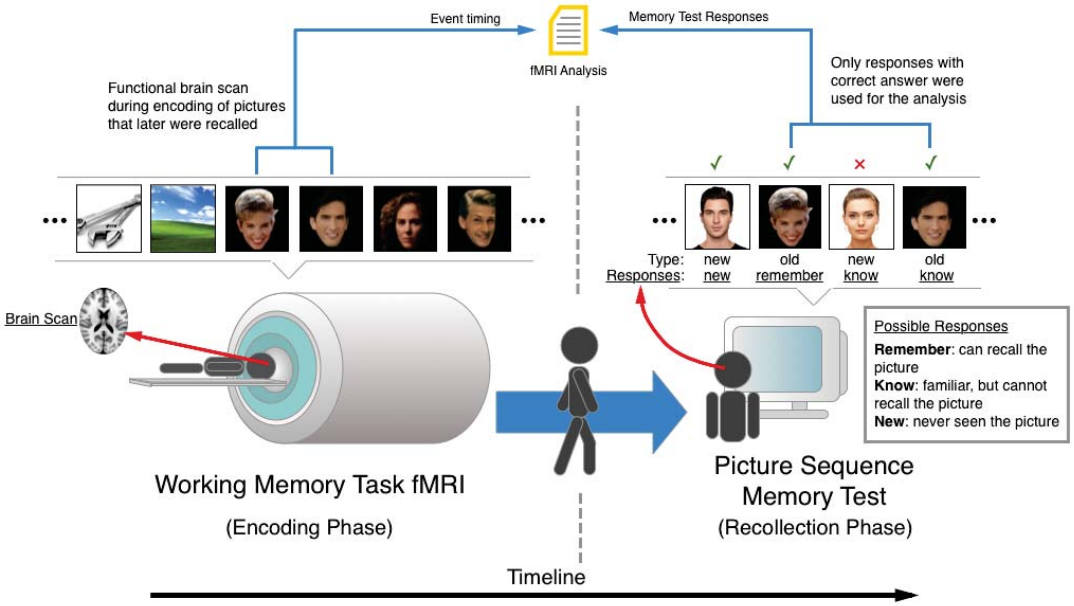

Figure 4-1: HCP subsequent memory analysis paradigm. Firstly, the subject was asked to perform working memory task during the fMRi scan session. The subject was presented with a sequence of image stimuli. The subject performed the task by recalling previously shown images. This is considered as memory encoding phase. Then after the scan, the subject were asked to perform picture sequence memory test. In this test the subject were presented with the image from the same set presented during the working memory task fMRI scan session mixed with some new additional images. The subject responded to each image with *remember*, *know*, or *new* to determine if the subject was able to remember images previously shown during the fMRI session correctly. This is considered as recollection phase.

4.3.4 Tigramite and Causal Modeling

To determine maximum time lag for the causal algorithm, we estimate lagged unconditional dependencies and found the dependencies diminish beyond a lag of 8.

We perform causal analysis on BOLD data from 4 regions of interest of each individual subjects to construct individual model of each subjects. Then, a representative model is constructed by aggregated all of each individual models using median operator.

4.4 Results

4.4.1 Univariate group subtraction and regions of interest

The peak activated region yielded by fMRI group subtraction analysis is large (17,529 voxels) and cover wide area of the brain (figure 4-2). Harvard-Oxford cortical and subcortical structural probability atlases are used to identify the activated region. The major activated regions are selected as regions of interest. Additionally, the PPI shows that lingual gyrus has significant correlation with parahippocampal gyrus. Therefore, 4 ROIs shown in table 4.1 are selected for connectivity modeling.

Table 4.1: Selected regions of interest (Harvard-Oxford cortical structural probability atlases).

Regions	Hemispheres
parahippocampal gyrus	Left and right
temporal occipital fusiform cortex	Left and right
occipital gyrus	Left and right
lingual gyrus	Left and right

4.4.2 Causal modeling and group representative model

The resulting group representative graphical model and time series graph are presented in figure 4-3 and 4-4, respectively. In the representative model, only 2 significant connections, a connection from occipital gyrus to temporal occipital fusiform

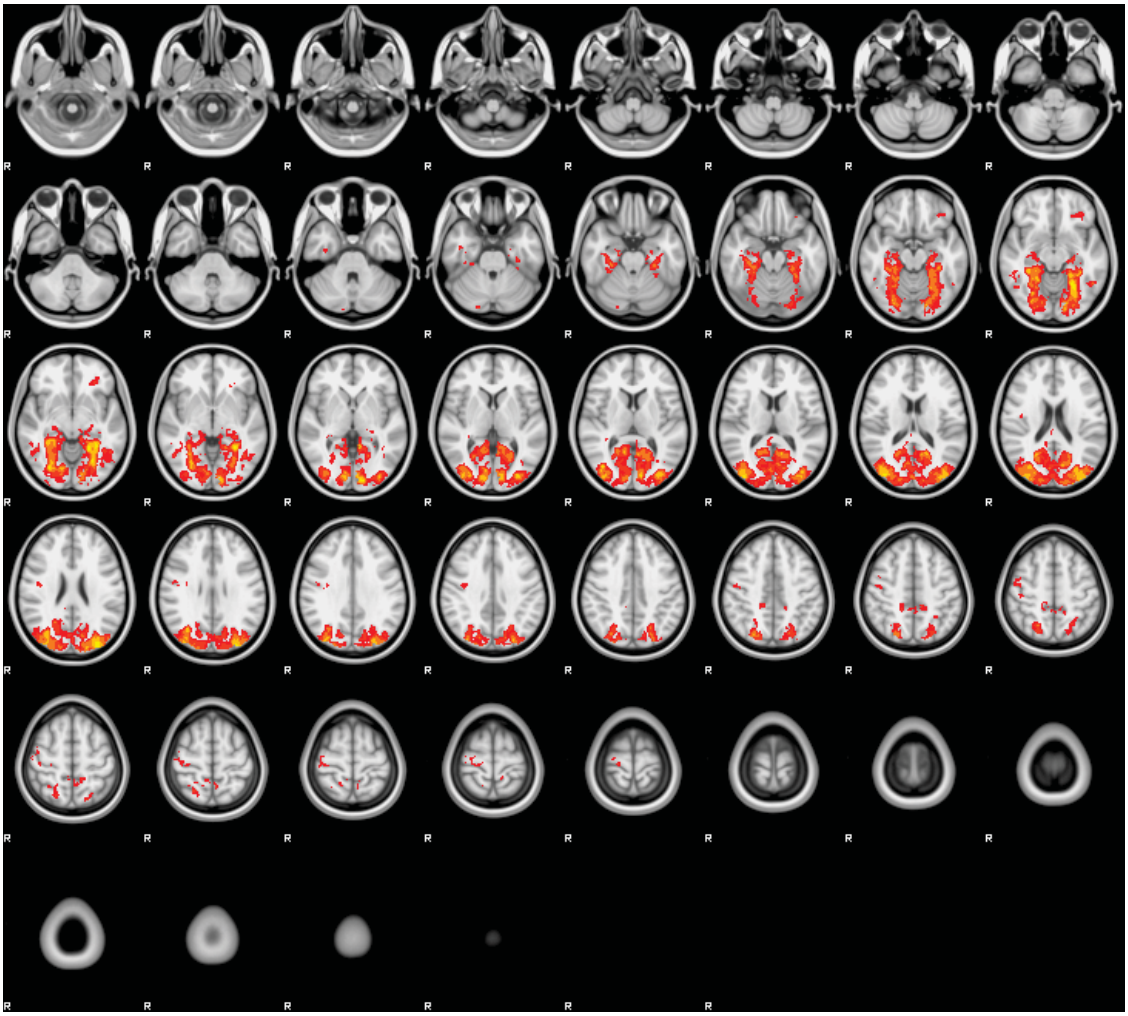

Figure 4-2: Activated cluster from univariate group subtraction analysis of all 376 subjects on Successful recollection > Failed recollection (threshold at $Z > 2.3, P < 0.05$).

cortex, and from lingual gyrus to parahippocampal gyrus, are presented. Its average Levenshtein distance from our test is 6.35 (SD: 0.28).

The main concern of connectivity measure derived from fMRI data is that movement and physiological noise sources, which vary from subject to subject and session to session, can potentially induce spurious correlations between ROIs, which could confound the interpretation of the results by increasing chance of false positive [92]. The effect of aforementioned spurious correlations may contribute to the variation among individual graphs. The number of connections in the individual graph varies

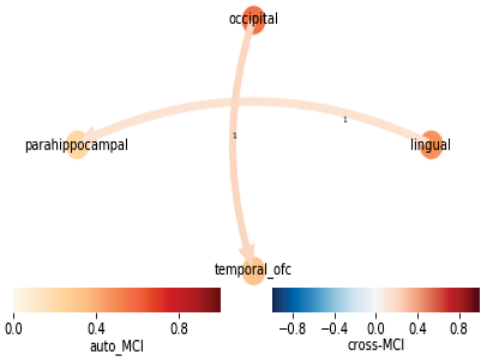

Figure 4-3: Representative connectivity graphical model of subsequent memory task.

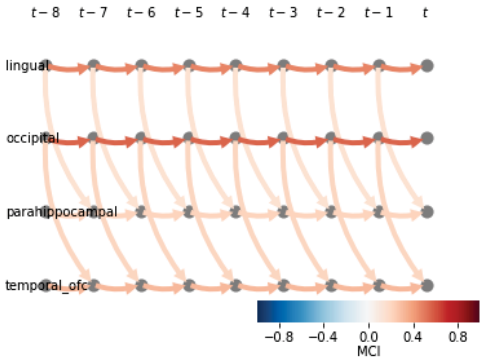

Figure 4-4: Representative connectivity resulting time series graph of subsequent memory task.

from only 1 to as many as 12 connections. Group model is calculated using median aggregation to reduce the effect of outlier. The Levenshtein distance is introduced to measure the reliability of the resulting group model by showing that the model is in the average distance among the population.

4.4.3 Univariate group subtraction and regions of interest

The peak activated region yielded by fMRI group subtraction analysis is large (17,529 voxels) and cover wide area of the brain (figure 4-2). Harvard-Oxford cortical and subcortical structural probability atlases are used to identify the activated region. The major activated regions are selected as regions of interest. Additionally, the PPI shows that lingual gyrus has significant correlation with parahippocampal gyrus. Therefore, 4 ROIs shown in table 4.1 are selected for connectivity modeling.

4.5 Findings

4.5.1 Episodic memory encoding

In the subsequent memory paradigm of this study, brain's activity is observed only during the encoding phase. Cognitive functions related to memory beyond memory encoding, such as, memory organization or memory recollection are not addressed.

According to previous studies, the resulting peak activated regions are known to have roles in memory formation. A study by Ofen et al. [64] found that middle temporal gyrus, fusiform gyrus, and parahippocampal gyrus play significant role in development of declarative memory formation development from child to adult. Occipital area and fusiform gyrus are known to play important roles in face recognition [29] and declarative memory forming [64]. The protocol used by HCP may contribute to the activation of this region since images of human face are used as stimuli for working memory task fMRI [54]. Lingual gyrus is a part of declarative memory system [59] and also contributes to visual memory forming [77].

The results of this study agree with previous studies and affirm that the prior knowledges hold in large population since most of the previous fMRI studies included only small number of subject due to technical difficulty of fMRI experiment protocol.

Chapter 5

Connectivity Deduction

5.1 Functional vs effective connectivities

Functional connectivity is defined as the temporal correlation among the activity of different brain area. Effective connectivity is defined as the causal relation among the activity of different brain area [41]. The fundamental difference between functional and effective connectivity is the temporal implication of the source of the effect. Consider the simplified connectivity of brain regions X, Y, and Z, functional connection between X and Y implies region X's activity temporally correlated to activity of region Y. However, there is a possibility that this correlation is cause by region X and region Y react to the input from the region Z. The disregard of temporal order in functional connectivity analysis decreases the validity of the interpretation of the resulting connectivity. On the other hand, the effective connectivity considers temporal order of the source and destination of the connection, thus, improve the validity of the connectivity interpretation.

This aspect is especially important when analyzing the connectivity from fMRI BOLD signals because the low temporal resolution nature of the BOLD signal and other confounding factor, such as, movement and physiological artefacts. In [92], the authors emphasis the importance of temporal preprocessing step on BOLD signal in addition to traditional spatial preprocessing step of fMRI study to remove temporal confounding factor. Inadequate noise reduction of BOLD data may result in spurious

connection in both functional and effective connectivity which could lead to faulty interpretation of the connectivity of interest. Both functional and effective connectivity in this study use the same CONN toolbox preprocessing pipeline to preprocess BOLD signals before connectivity analysis.

In the study discussed in chapter 3, CONN toolbox was used to analyze functional connectivity. It utilizes seed-based correlation framework to determine functional connectivity in individual-level analysis, then the resulting measures are input into a second-level general linear model to obtain population-level result. The seed-based correlation analysis obtains a full connectivity model by iteratively input each ROI as a seed to analyzing correlation between it and other ROIs, then combine all of the seed connections together. This approach does not take temporal order relation between each seed into account.

In the same study, for effective connectivity analysis, we utilized Tigramite, a time-lagged causal discovery framework [71] to analyze effective connectivity from the preprocessed BOLD signals. This framework differ from CONN toolbox approach in that it consider time-lagged, or temporal order of each connectivity as shown in figure 3-9. The lagged unconditional dependencies of the BOLD time-series is estimated to determine the time point when the dependencies diminish. The framework then estimates the connectivity along the lagged time, thus achieving temporal-ordered connectivity, or effective connectivity. The population-level connectivity was calculated by median aggregation of individual subject's connectivity.

Comparing the resulting connections from these analyses (figure 3.3 and 3.5), we can clearly see that the effective connectivity yields more concise connectivity as most low intensity connections were eliminated and the result from Tigramite also provide directional (causal relation) information between the connected brain regions. For example, we can see that coherent connection of posterior parahippocampal cortex and lateral parietal Default Mode network are bidirectional (figure 3-6), while what we can inferred from functional connectivity as a coherent connection of hippocampus is just a connection from right hippocampus to left hippocampus (figure 3-6). The advantages of having directional information also apply to the connection from right

hippocampus (Hippo r) to right posterior parahippocampal cortex (pPaHC r), and from posterior cingulate cortex Default Mode network (PCC) to left lateral parietal Default Mode network (LP(L)), including coherent connection between 2 hippocampi (Hippo r and Hippo l). This additional information gives effective connectivity advantage in term of interpretability in comparison to functional connectivity, as these 3 aforementioned connections are not difference from other connections, however in effective connectivity model, these 3 connections are *unidirectional* while the rest are *bidirectional*.

5.2 Individual- and group-level connectivities

The goal of brain research is to describe biological mechanic of the brain that responsible for any particular cognitive function. Most researches identify brain function in forms of active region and pathway. Sensory pathways is one of the well-known example. However, the knowledge of higher cognitive function's pathway, such as, consciousness or memory organization is limited since these functions lack physical interaction that can be observed. Causal interaction analysis on fMRI BOLD timeseries is a common way to study said brain functions.

Granger causality [33] is a popular approach among numerous techniques developed to analyze causal interactions in fMRI data [55]. However, inferring causal relationship (effective connectivity or directed connection) using this framework on fMRI BOLD data is controversial because low temporal resolution nature of the BOLD signal may confound its statistical dependencies implication. Without the temporal order integrity, the framework shows only correlation (functional connectivity or undirected connection). Consequently, we use Tigramite framework [73] for our studies to avoid temporal sensitivity issue of Granger causality framework.

In fMRI study, the localization of specific brain function is observed across individuals using statistical inference, and therefore the location can be generalized across population. However, fMRI statistical framework does not account for temporal order of activation. We have no statistical basis that guarantee temporal order of activation

or activation time lag across individual to be able to infer general causal model of a group of individuals. Nonetheless, the general representative model is needed for drawing a general conclusion.

To address this issue, we compare difference between the resulting representative model with model of random sub-groups using Levenshtein distance. The average distant is 6.35 (SD: 0.28), with the maximum distance at 11, and the minimum at 1. While structure of individual subject's model varies, ranged from a graph with only one connection to a complete graph, our test shows that the representative graph is balanced.

Therefore, we conclude that the graph is a general representative model of this sample population. However, it is important to emphasize that this method only concerns structural similarity, the connection weights are ignored.

5.3 Interpreting connectivity models

Even after we have the connectivity model from our analysis, we need to interpret those model to be able to describe the underlying mechanism of our brain function of interest. Usually, we need to compile knowledges about brain regions involved in the connectivity then infer the mechanism from the relationship represented by the connectivity model.

For example, consider the study in chapter 3. Hippocapus is known to play crucial role in both memory encoding [65], and memory recollection [50] [60]. Considering our experiment paradigm where the subject is presented with memory recollection stimuli during *pre resting-state fMRI* phase, the hippocampus is likely to active during *resting-state fMRI* scan phase even without the subject consciously perform the recollection task, as the hippocampus performs memory consolidation and strengthening of the recalled memories in *pre resting-state fMRI* phase [37]. Moreover, there also is an evidence shows that left and right hippocampi responsible for difference cognitive roles. The left hippocampus plays a critical role in episodic verbal memory while the right is more important for spatial memory processing [21]. This might in-

dicate that the right hippocampus is processing projected spatial memory in recalled episodic memory, then pass the information to the left hippocampus for it to process the information into abstract concept to be consolidated and reinforced. Considering the between-subject contrast of this study, which is *High-Confidence-Low-Difficulty - Low-Confidence-High-Difficulty*, it is reasonable to see this effect.

While the unique contribution of posterior parahippocampal cortex is unclear, several study suggest that it contributes to memory function as patients with lesions involving the parahippocampal cortex are impaired on a memory task [86]. From the resulting effective connectivity of this study, it suggests that activity in right hippocampus cause activity in right posterior parahippocampal area. Several studies suggest that the parahippocampal cortex is functionally dissociable from the hippocampus [8] [44] [96]. However, the dissociation does not eliminate the possibility of information exchange between hippocampus and parahippocampal cortex as shown in an fMRI study of incidental target detection task, the parahippocampal cortex was active only for novel scenes while the hippocampus was selectively active to changes in the spatial relationship between objects and their background context [42]. In case of the result of this study, the connection from right hippocampus to posterior parahippocampal cortex may suggest that posterior parahippocampal cortex is encoding memory that it recognizes as novel from information formerly processed by hippocampus.

Posterior cingulate cortex and lateral parietal Default Mode network are known to involve episodic memory retrieval function [62] [79]. While the functional relationship between these two network is unclear, there is a hypothesis stated that the posterior cingulate cortex is a central node in the default mode network of the brain [67] [11]. There are evidences show increase in activity in the posterior cingulate cortex during episodic recollection [35], and mental time-travelling [3]. Some study also suggests it regulate balance between internally and externally focused thought [49] as it active both during task-related and rest cognitive state [56]. Since the evidences of specific role of posterior cingulate cortex default mode network in response to specific cognitive function are inconclusive, this particular connection may only reflect the

intrinsic default mode network activity of the brain.

5.4 Results summary

In chapter 3, we have compared 2 types of connectivity models, the functional and effective connectivity. In the study, we have discussed that the effective connectivity yields more concise and comprehensive model that improve the interpretability of the brain function of interest. In chapter 4, we have discussed a framework for constructing group connectivity model and shown that the group with higher episodic memory recollection performance has an active network in hippocampus and posterior parahippocampal area. Within-region interaction and coherent connection may also contribute to the performance gain of the group, but it is outside the scope of this study.

Chapter 6

Conclusion

We have been discussing about how we study brain mechanism using connectivity modeling concept. In chapter 1, I have introduced the basic anatomy of human brain showing that there are distinction among different region inside the brain, both in term of cellular formation and their corresponding function. I have pointed out the important aspect of one of the function of the brain, the episodic memory. I have discussed by episodic memory is an interesting aspect of study, namely it is considered to be the basic of human self awareness and consciousness, the very distinct cognitive function. I have given a brief introduction to the technology that can be used to observe brain activity non-invasively in real-time. The fMRI technology yields high spatial resolution brain image which benefits our understanding of how each region of the brain activated during a given task. However, the drawback of fMRI is that it relies on detecting the movement of blood, which is slow, thus gives it low temporal resolution characteristic.

Now that we can measure brain activation, how could we extract the knowledge out of that data? In chapter 2, I have discussed about how the data acquisition paradigm can help us make the brain activity data more informative when we aim to extract some useful information out of it. From fMRI data, we can observe the localization and temporal order of the brain activation. From those information, we can construct a connectivity model that illustrate the working mechanism of the brain. I have introduced several frameworks that can be used to extract connectivity model

from fMRI data, and discussed their advantages and disadvantages with each others. I have pointed out the Tigramite is one of the framework that could be useful in brain connectivity study, and demonstrate its application with motor task-fMRI data. The results show that Tigramite can construct an informative effective connectivity model from fMRI dataset.

Next, I have discussed about the difference between functional and effective connectivity in chapter 3. A large body of research in brain connectivity mostly concerns only with functional connectivity. In the chapter, I have explained what is functional and effective connectivity, and discussed about why we should aim for more use of effective connectivity in this field. The effective connectivity is more informative in comparison to the functional one, which will improve the interpretability of the connectivity model resulting in deeper understanding of the brain function. I have demonstrate the difference between the functional and effective connectivity by comparing the functional model from CONN tool box and effective model from Tigramite framework using the same resting-state fMRI dataset of memory recollection behavioral task. The result of the comparison shows that the effective connectivity model is more concise and informative that the functional one.

To be able to imply brain mechanism across broad population, the group-level connectivity analysis is needed. However, there is no established method for general group-level connectivity analysis. In chapter 4, I propose the use of topological aspect of the connectivity graph to create a group-level connectivity framework by comparing graphs with Levenshtein distance to see how similar or how difference one graph to others. I have demonstrate the proposed framework using the graph generate by Tigramite framework from subsequent memory task-fMRI dataset, and the result is supported by the other memory-task related researches.

Finally in chapter 5 I have discussed about how we can extract useful information from the connectivity model using the result models from chapter 3 and chapter 4. While the connectivity models are proved to be useful in aiding our understanding of brain mechanism, there are some obstacles in interpreting the connectivity model due to characteristic of fMRI data, such as low temporal-resolution. In interpreting the

higher cognitive function such as episodic memory, the temporal variable, along with other confounding factor common for fMRI BOLD signal may lead to inconclusive interpretation of the brain function of interest.

6.1 Going forward

There are a lot of areas in this study where they can be improved. For one, we can find a way to improve quality of fMRI signal just like the CONN tool box applying additional preprocessing step discussed in chapter 3.

The group-level connectivity algorithm is also still need further improvement. The framework we discussed in chapter 4 concern only topological aspect, or shape of the graph while disregard the weight of each individual connection. Currently, there is no standardize measure of brain connection weight and there is no guarantee that the weight might be vary across individual. This aspect warrant further investigation in the future.

Bibliography

[1] "FSL - FslWiki", 2019. [Online; accessed 5-November-2019].

[2] "SPM - Statistical Parametric Mapping", 2019. [Online; accessed 5-November-2019].

[3] Donna Rose Addis, Alana T Wong, and Daniel L Schacter. Remembering the past and imagining the future: Common and distinct neural substrates during event construction and elaboration. *Neuropsychologia*, 45(7):1363–1377, January 2007.

[4] Richard A Andersen and He Cui. Intention, Action Planning, and Decision Making in Parietal-Frontal Circuits. *Neuron*, 63(5):568–583, September 2009.

[5] R C Atkinson and R M Shiffrin. Human Memory: A Proposed System and its Control Processes. pages 89–195. Elsevier, 1968.

[6] Yashar Behzadi, Khaled Restom, Joy Liau, and Thomas T Liu. A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, 37(1):90–101, August 2007.

[7] Natalia Z Bielczyk, Sebo Uithol, Tim van Mourik, Paul Anderson, Jeffrey C Glennon, and Jan K Buitelaar. Disentangling causal webs in the brain using functional magnetic resonance imaging: A review of current approaches. *Network Neuroscience*, 3(2):237–273, January 2019.

[8] Véronique D Bohbot, John J B Allen, Alain Dagher, Serge O Dumoulin, Alan C Evans, Michael Petrides, Miroslav Kalina, Katerina Stepankova, and Lynn Nadel. Role of the parahippocampal cortex in memory for the configuration but not the identity of objects: converging evidence from patients with selective thermal lesions and fMRI. *Frontiers in human neuroscience*, 9:431, August 2015.

[9] Clémentine Bosch-Bouju, Brian Hyland, and Louise Parr-Brownlie. Motor thalamus integration of cortical, cerebellar and basal ganglia information: implications for normal and parkinsonian conditions. *Frontiers in Computational Neuroscience*, 7:163, 2013.

[10] K K Bucholz, R Cadoret, C R Cloninger, S H Dinwiddie, V M Hesselbrock, J I Nurnberger, T Reich, I Schmidt, and M A Schuckit. A new, semi-structured

psychiatric interview for use in genetic linkage studies: a report on the reliability of the ssaga. *Journal of Studies on Alcohol*, 55(2):149–158, 1994. PMID: 8189735.

[11] Randy L. Buckner, Jessica R. Andrews-Hanna, and Daniel L. Schacter. The brain's default network. *Annals of the New York Academy of Sciences*, 1124(1):1–38.

[12] Ed Bullmore and Olaf Sporns. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience*, 10(3):186–198, March 2009.

[13] Richard B Buxton, Eric C Wong, and Lawrence R Frank. Dynamics of blood flow and oxygenation changes during brain activation: The balloon model. *Magnetic Resonance in Medicine*, 39(6):855–864, June 1998.

[14] Suzanne Corkin. What's new with the amnesic patient H.M.? *Nature Reviews Neuroscience*, 3(2):153–160, February 2002.

[15] Thomas M. Cover and Joy A. Thomas. *Elements of Information Theory (Wiley Series in Telecommunications and Signal Processing)*. Wiley-Interscience, USA, 2006.

[16] Felix Darvas and Adam O. Hebb. Task specific inter-hemispheric coupling in human subthalamic nuclei. *Frontiers in Human Neuroscience*, 8:701, 2014.

[17] F Deng, X Jiang, D Zhu, T Zhang, K Li, L Guo Brain structure and, and 2014. A functional model of cortical gyri and sulci. *Brain Structure and Function*, 219:1473–1491, July 2013.

[18] Florin Dolcos, Kevin S LaBar, and Roberto Cabeza. Dissociable effects of arousal and valence on prefrontal activity indexing emotional evaluation and subsequent memory: an event-related fMRI study. *NeuroImage*, 23(1):64–74, September 2004.

[19] Andrea Duggento, Luca Passamonti, Gaetano Valenza, Riccardo Barbieri, Maria Guerrisi, and Nicola Toschi. Multivariate Granger causality unveils directed parietal to prefrontal cortex connectivity during task-free MRI. *Scientific reports*, 8(1):5571, April 2018.

[20] Michael Eichler. Graphical modelling of multivariate time series. *Probability Theory and Related Fields*, 153(1-2):233–268, 2012.

[21] Ali Ezzati, Mindy J Katz, Andrea R Zammit, Michael L Lipton, Molly E Zimmerman, Martin J Sliwinski, and Richard B Lipton. Differential association of left and right hippocampal volumes with verbal episodic and spatial memory in older adults. *Neuropsychologia*, 93:380–385, December 2016.

[22] Michael D Fox and Marcus E Raichle. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, 8(9):700–711, September 2007.

[23] Michael D Fox, Abraham Z Snyder, Justin L Vincent, Maurizio Corbetta, David C Van Essen, and Marcus E Raichle. The Human Brain Is Intrinsically Organized into Dynamic, Anticorrelated Functional Networks. *Proceedings of the National Academy of Sciences of the United States of America*, 102(27):9673–9678, July 2005.

[24] Peter Fransson. Spontaneous low-frequency BOLD signal fluctuations: An fMRI investigation of the resting-state default mode of brain function hypothesis. *Human Brain Mapping*, 26(1):15–29, 2005.

[25] K J Friston, C D Frith, and R S J Frackowiak. Time-dependent changes in effective connectivity measured with PET. *Human Brain Mapping*, 1(1):69–79, January 1993.

[26] K J Friston, L Harrison, and W Penny. Dynamic causal modelling. *NeuroImage*, 19(4):1273–1302, August 2003.

[27] Karl J Friston. Functional and effective connectivity in neuroimaging: A synthesis. *Human Brain Mapping*, 2(1-2):56–78, January 1994.

[28] Karl J Friston, Joshua Kahan, Bharat Biswal, and Adeel Razi. A DCM for resting state fMRI. *NeuroImage*, 94(C):396–407, July 2014.

[29] Paolo Fusar-Poli et al. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of psychiatry & neuroscience : JPN*, 34(6):418–432, November 2009.

[30] Michael S Gazzaniga. Forty-five years of split-brain research and still going strong. *Nature Reviews Neuroscience*, 6(8):653–659, August 2005.

[31] Matthew F Glasser et al. The minimal preprocessing pipelines for the Human Connectome Project. *NeuroImage*, 80:105–124, October 2013.

[32] Christopher G. Goetz. *Textbook of Clinical Neurology (Third Edition)*. W.B. Saunders, Philadelphia, third edition edition, 2007.

[33] C W J Granger. Investigating Causal Relations by Econometric Models and Cross-spectral Methods. *Econometrica*, 37(3):424, August 1969.

[34] Michael D Greicius, Ben Krasnow, Allan L Reiss, and Vinod Menon. Functional Connectivity in the Resting Brain: A Network Analysis of the Default Mode Hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, 100(1):253–258, January 2003.

[35] D A Gusnard, E Akbudak, G L Shulman, and M E Raichle. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proceedings of the National Academy of Sciences*, 98(7):4259–4264, March 2001.

[36] Daniel A Handwerker, Javier Gonzalez-Castillo, Mark D'Esposito, and Peter A Bandettini. The continuing challenge of understanding and modeling hemodynamic variation in fMRI. *NeuroImage*, 62(2):1017–1023, August 2012.

[37] Caroline Harand, Françoise Bertran, Renaud La Joie, Brigitte Landeau, Florence Mézenge, Béatrice Desgranges, Philippe Peigneux, Francis Eustache, and Géraldine Rauchs. The Hippocampus Remains Activated over the Long Term for the Retrieval of Truly Episodic Memories. *PloS one*, 7(8):e43495, August 2012.

[38] R N Henson, M D Rugg, T Shallice, and R J Dolan. Confidence in recognition memory for words: dissociating right prefrontal roles in episodic retrieval. *Journal of Cognitive Neuroscience*, 12(6):913–923, November 2000.

[39] Katerina Hlaváčková-Schindler, Milan Paluš, Martin Vejmelka, and Joydeep Bhattacharya. Causality detection based on information-theoretic approaches in time series analysis. *Physics Reports*, 441(1):1 – 46, 2007.

[40] William Hodos. *Evolution of Cerebellum*, pages 1240–1243. Springer Berlin Heidelberg, Berlin, Heidelberg, 2009.

[41] Barry Horwitz. The elusive concept of brain connectivity. *NeuroImage*, 19(2 Pt 1):466–470, June 2003.

[42] L R Howard, D Kumaran, H F Olafsdottir, and H J Spiers. Double Dissociation between Hippocampal and Parahippocampal Responses to Object-Background Context and Scene Novelty. *Journal of Neuroscience*, 31(14):5253–5261, April 2011.

[43] Joshua Kahan and Tom Foltynie. Understanding DCM: Ten simple rules for the clinician. *NeuroImage*, 83(C):542–549, December 2013.

[44] Stefan Köhler, Stacey Danckert, Joseph S Gati, and Ravi S Menon. Novelty responses to relational and non-relational information in the hippocampus and the parahippocampal region: A comparison based on event-related fMRI. *Hippocampus*, 15(6):763–774, 2005.

[45] Daisuke Koshiyama, Masaki Fukunaga, Naohiro Okada, Fumio Yamashita, Hidenaga Yamamori, Yuka Yasuda, Michiko Fujimoto, Kazutaka Ohi, Haruo Fujino, Yoshiyuki Watanabe, Kiyoto Kasai, and Ryota Hashimoto. Role of subcortical structures on cognitive and social function in schizophrenia. *Scientific reports*, 8(1):1–9, January 2018.

[46] Alexander Kraskov, Harald Stögbauer, and Peter Grassberger. Estimating mutual information. *Physical Review E*, 69(6):S231–16, June 2004.

[47] H Laufs, K Krakow, P Sterzer, E Eger, A Beyerle, A Salek-Haddadi, and A Kleinschmidt. Electroencephalographic Signatures of Attentional and Cognitive Default Modes in Spontaneous Brain Activity Fluctuations at Rest. *Proceedings of the National Academy of Sciences of the United States of America*, 100(19):11053–11058, September 2003.

[48] S. L. Lauritzen. *Graphical Models*. Oxford University Press, Oxford, 1996.

[49] R Leech, S Kamourieh, C F Beckmann, and D J Sharp. Fractionating the Default Mode Network: Distinct Contributions of the Ventral and Dorsal Posterior Cingulate Cortex to Cognitive Control. *Journal of Neuroscience*, 31(9):3217–3224, March 2011.

[50] Hanne Lehn, Hill-Aina Steffenach, Niels M van Strien, Dick J Veltman, Menno P Witter, and Asta K Håberg. A specific role of the human hippocampus in recall of temporal sequences. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, 29(11):3475–3484, March 2009.

[51] Anna Manelis, Christopher A Paynter, Mark E Wheeler, and Lynne M Reder. Repetition related changes in activation and functional connectivity in hippocampus predict subsequent memory. *Hippocampus*, 23(1):53–65, January 2013.

[52] Michael Mannino and Steven L Bressler. Foundational perspectives on causality in large-scale brain networks. *Physics of Life Reviews*, 15:107–123, December 2015.

[53] Mario Manto, James M Bower, Adriana Bastos Conforto, José M Delgado-García, Suzete Nascimento Farias da Guarda, Marcus Gerwig, Christophe Habas, Nobuhiro Hagura, Richard B Ivry, Peter Mariën, Marco Molinari, Eiichi Naito, Dennis A Nowak, Nordeyn Oulad Ben Taib, Denis Pelisson, Claudia D Tesche, Caroline Tilikete, and Dagmar Timmann. Consensus Paper: Roles of the Cerebellum in Motor Control—The Diversity of Ideas on Cerebellar Involvement in Movement. *The Cerebellum*, 11(2):457–487, December 2011.

[54] Daniel S Marcus et al. Human Connectome Project informatics: quality control, database services, and data visualization. *NeuroImage*, 80:202–219, October 2013.

[55] Daniel S Margulies, Joachim Böttger, Xiangyu Long, Yating Lv, Clare Kelly, Alexander Schäfer, Dirk Goldhahn, Alexander Abbushi, Michael P Milham, Gabriele Lohmann, and Arno Villringer. Resting developments: a review of fMRI post-processing methodologies for spontaneous brain activity. *Magma (New York, N.Y.)*, 23(5-6):289–307, December 2010.

[56] Malia F Mason, Michael I Norton, John D Van Horn, Daniel M Wegner, Scott T Grafton, and C Neil Macrae. Wandering Minds: The Default Network and Stimulus-Independent Thought. *Science*, 315(5810):393–395, January 2007.

[57] Nikolaus R. McFarland and Suzanne N. Haber. Thalamic relay nuclei of the basal ganglia form both reciprocal and nonreciprocal cortical connections, linking multiple frontal cortical areas. *Journal of Neuroscience*, 22(18):8117–8132, 2002.

[58] Jeffrey D Meier, Tyson N Aflalo, Sabine Kastner, and Michael S A Graziano. Complex Organization of Human Primary Motor Cortex: A High-Resolution fMRI Study. *Journal of neurophysiology*, October 2008.

[59] Vinod Menon, Jesse M Boyett-Anderson, Alan F Schatzberg, and Allan L Reiss. Relating semantic and episodic memory systems. *Brain research. Cognitive brain research*, 13(2):261–265, April 2002.

[60] Maxwell B Merkow, John F Burke, and Michael J Kahana. The human hippocampus contributes to both the recollection and familiarity components of recognition memory. *Proceedings of the National Academy of Sciences of the United States of America*, 112(46):14378–14383, November 2015.

[61] P Morgane, J Galler, and D Mokler. A review of systems and networks of the limbic forebrain/limbic midbrain. *Progress in Neurobiology*, 75(2):143–160, February 2005.

[62] Finn Årup Nielsen, Daniela Balslev, and Lars Kai Hansen. Mining the posterior cingulate: Segregation between memory and pain components. *NeuroImage*, 27(3):520–532, September 2005.

[63] Leonardo Novelli, Patricia Wollstadt, Pedro Mediano, Michael Wibral, and Joseph T Lizier. Large-scale directed network inference with multivariate transfer entropy and hierarchical statistical testing. *Network Neuroscience*, 3(3):827–847, January 2019.

[64] Noa Ofen, Yun-Ching Kao, Peter Sokol-Hessner, Heesoo Kim, Susan Whitfield-Gabrieli, and John D E Gabrieli. Development of the declarative memory system in the human brain. *Nature neuroscience*, 10(9):1198–1205, September 2007.

[65] Gail O'Kane, Elizabeth A Kensinger, and Suzanne Corkin. Evidence for semantic learning in profound amnesia: An investigation with patient H.M. *Hippocampus*, 14(4):417–425, 2004.

[66] Judea Pearl. *Causality: Models, Reasoning and Inference*. Cambridge University Press, New York, NY, USA, 2nd edition, 2009.

[67] Marcus E Raichle, Ann Mary MacLeod, Abraham Z Snyder, William J Powers, Debra A Gusnard, and Gordon L Shulman. A default mode of brain function. *Proceedings of the National Academy of Sciences*, 98(2):676–682, January 2001.

[68] Adeel Razi, Mohamed L Seghier, Yuan Zhou, Peter McColgan, Peter Zeidman, Hae-Jeong Park, Olaf Sporns, Geraint Rees, and Karl J Friston. Large-scale DCMs for resting-state fMRI. *Network Neuroscience*, 1(3):222–241, October 2017.

[69] S A R B Rombouts, C J Stam, J P A Kuijer, Ph Scheltens, and F Barkhof. Identifying confounds to increase specificity during a “no task condition”. *NeuroImage*, 20(2):1236–1245, October 2003.

[70] Mikail Rubinov and Olaf Sporns. Complex network measures of brain connectivity: uses and interpretations. *NeuroImage*, 52(3):1059–1069, September 2010.

[71] Jakob Runge. Quantifying information transfer and mediation along causal pathways in complex systems. *Physical Review E*, 92(6):062829–18, December 2015.

[72] Jakob Runge. Conditional independence testing based on a nearest-neighbor estimator of conditional mutual information. *arXiv.org*, September 2017.

[73] Jakob Runge. Causal network reconstruction from time series: From theoretical assumptions to practical estimation. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, 28(7):075310–21, July 2018.

[74] Jakob Runge, Jobst Heitzig, Vladimir Petoukhov, and Jürgen Kurths. Escaping the curse of dimensionality in estimating multivariate transfer entropy. *Physical review letters*, 108(25):258701, June 2012.

[75] Jakob Runge, Peer Nowack, Marlene Kretschmer, Seth Flaxman, and Dino Sejdinovic. Detecting causal associations in large nonlinear time series datasets. *arXiv.org*, February 2017.

[76] Jakob Runge, Vladimir Petoukhov, Jonathan F Donges, Jaroslav Hlinka, Nikola Jajcay, Martin Vejmelka, David Hartman, Norbert Marwan, Milan Paluš, and Jürgen Kurths. Identifying causal gateways and mediators in complex spatio-temporal systems. *Nature communications*, 6(1):8502, October 2015.

[77] Christoph J Schankin, Farooq H Maniyar, Till Sprenger, Denise E Chou, Michael Eller, and Peter J Goadsby. The relation between migraine, typical migraine aura and "visual snow". *Headache*, 54(6):957–966, June 2014.

[78] Thomas Schreiber. Measuring information transfer. *Phys. Rev. Lett.*, 85:461–464, Jul 2000.

[79] C Sestieri, M Corbetta, G L Romani, and G L Shulman. Episodic Memory Retrieval, Parietal Cortex, and the Default Mode Network: Functional and Topographic Analyses. *Journal of Neuroscience*, 31(12):4407–4420, March 2011.

[80] P. Spirtes, C. Glymour, and R. Scheines. *Causation, Prediction, and Search*. MIT press, 2nd edition, 2000.

[81] Peter Spirtes and Clark Glymour. An Algorithm for Fast Recovery of Sparse Causal Graphs. *Social Science Computer Review*, 9(1):62–72, August 2016.

[82] H A Swadlow and S G Waxman. Observations on impulse conduction along central axons. *Proceedings of the National Academy of Sciences*, 72(12):5156–5159, December 1975.

[83] Endel Tulving. What Is Episodic Memory? *Current Directions in Psychological Science*, 2(3):67–70, 1993.

[84] Michael T Ullman. Contributions of memory circuits to language: the declarative/procedural model. *Cognition*, 92(1-2):231–270, May 2004.

[85] D C Van Essen et al. The Human Connectome Project: a data acquisition perspective. *NeuroImage*, 62(4):2222–2231, October 2012.

[86] Gary W Van Hoesen. The parahippocampal gyrus: New observations regarding its cortical connections in the monkey. *Trends in Neurosciences*, 5:345–350, January 1982.

[87] Raul Vicente, Michael Wibral, Michael Lindner, and Gordon Pipa. Transfer entropy—a model-free measure of effective connectivity for the neurosciences. *Journal of Computational Neuroscience*, 30(1):45–67, August 2010.

[88] Justin L Vincent, Abraham Z Snyder, Michael D Fox, Benjamin J Shannon, Jessica R Andrews, Marcus E Raichle, and Randy L Buckner. Coherent Spontaneous Activity Identifies a Hippocampal-Parietal Memory Network. *Journal of neurophysiology*, 96(6):3517–3531, December 2006.

[89] Setsu Wakana, Hangyi Jiang, Lidia M Nagae-Poetscher, Peter C M van Zijl, and Susumu Mori. Fiber Tract–based Atlas of Human White Matter Anatomy1. *Radiology*, 230(1):77–87, January 2004.

[90] Zheng Wang, Li Min Chen, László Négyessy, Robert M Friedman, Arabinda Mishra, John C Gore, and Anna W Roe. The Relationship of Anatomical and Functional Connectivity to Resting-State Connectivity in Primate Somatosensory Cortex. *Neuron*, 78(6):1116–1126, June 2013.

[91] M Weinrich and S P Wise. The premotor cortex of the monkey. *Journal of Neuroscience*, 2(9):1329–1345, September 1982.

[92] Susan Whitfield-Gabrieli and Alfonso Nieto-Castanon. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain connectivity*, 2(3):125–141, 2012.

[93] Michael Wibral, Conor Finn, Patricia Wollstadt, Joseph Lizier, and Viola Priesemann. Quantifying Information Modification in Developing Neural Networks via Partial Information Decomposition. *Entropy*, 19(9):494–16, September 2017.

[94] Michael Wibral, Viola Priesemann, Jim W Kay, Joseph T Lizier, and William A Phillips. Partial information decomposition as a unified approach to the specification of neural goal functions. *Brain and cognition*, 112:25–38, March 2017.

[95] J.L. Wilkinson. Chapter 5 - brainstem. In J.L. Wilkinson, editor, *Neuroanatomy for Medical Students (Second Edition)*, pages 82 – 109. Butterworth-Heinemann, second edition edition, 1992.

[96] Bianca C Wittmann, Nico Bunzeck, Raymond J Dolan, and Emrah Düzel. Anticipation of novelty recruits reward system and hippocampus while promoting recollection. *NeuroImage*, 38(1):194–202, October 2007.