A STUDY OF BRAIN NETWORKS ASSOCIATED WITH MOTOR SEQUENCE LEARNING FOOT TAPPING TASKS

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A STUDY OF BRAIN NETWORKS ASSOCIATED WITH MOTOR SEQUENCE LEARNING FOOT TAPPING TASKS

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Understanding the learning behavior of brain functional connectivity within motor sequence learning of foot tapping tasks is of great importance to help improving walking quality of elderly people. It is also of great interest to clinical and scientific communities. The role of functional connectivity in brain function has not yet been well understood. This study comprises of two parts. The first part is to investigate brain signal stationarity, while the other will look into brain interactions while performing motor learning sequence task. Functional magnetic resonance imaging (fMRI) was utilized to acquire data from twelve healthy adult participants to study brain functional connectivity and interactions during a sequence of motor learning foot tapping tasks. Tasks were divided into: two different learning blocks, two control blocks, and five blocks of resting states. In this condition, 90 percent of the subjects developed awareness of the sequence. The stationarity of fMRI time series needs to be understood as it has important implications on the choice of appropriate approaches for the analysis of complex brain networks. In this study, we first investigated the stationarity of fMRI time series acquired from twelve healthy participants while they performed a motor (foot tapping sequence) learning task. Since prior studies have documented that learning is associated with systematic changes in brain activation, a sequence learning task is an optimal paradigm to assess the degree of non-stationarity in fMRI time-series in clinically relevant brain areas. We predicted that brain regions involved in a "learning network" would demonstrate non-stationarity and may violate assumptions associated with some advanced analysis approaches.The participants

performed six blocks of learning, and six control blocks of a foot tapping sequence in a fixed order. The reverse arrangement test was utilized to investigate the time series stationarity. Our analysis showed some non-stationary signals with a time varying first moment as a major source of non-stationarity. We also demonstrated a decreased number of non-stationarities in the third block as a result of priming and repetition. The implication of our findings is that future investigations analyzing complex brain networks should utilize approaches robust to non-stationarities. Approaches such as graph theory can be sensitive to non-stationarities present in the data. Next, we choose to apply psycho-physiological interactions (PPI) to our data and we revealed some information about the degree to which components of large-scale neural systems were functionally coupled together to achieve and perform the designed learning sequence task. We have performed a recording of activation maps as a function of (Learning- control) conditions in 12 subjects in order to better understand how brain regions interact and contribute to functionally connected circuits. In this work, we will introduce the idea of psycho-physiological interaction (PPI), which explains the responses in one cortical region in terms of an interaction between the effect of other regions and learning task parameter. Here, we interpret this psycho-physiological interaction as the significant contribution changes of one brain region to another as participants perform the learning task. We can also look into those interactions as modulating the responses elicited by our pre-designed learning sequence task. We have found that the *Thalamus* was mostly involved and modulated with our pre-designed motor learning task. We also found that *Middle frontal Gyrus* and *left pre-central Gyrus* were the most interacting regions with the above mentioned cluster. This interaction can only be related to the interactions that are based on the experimental factors which are the psychological and physiological interactions. The current results have also supported PPI as a potential tool for understanding learning mechanism during foot tapping tasks.

Keywords: Functional magnetic resonance imaging fMRI, time series, stationarity, reverse arrangement test RAT, foot tapping, PPI.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

At first, I would like to thank my adviser for his support, patient and guidance during my masters studies. I would also like to thank my all colleagues in the iMED laboratory for their great co-operation in my data processing, participants for their time and others who helped me during the project. We thank all involved in the collection of data presented in this study. I want to express my great appreciation to the committee members for their time.

1.0 INTRODUCTION

1.1 HUMAN BRAIN

The human brain is considered to be the most interesting and complicated system in the globe. Its huge number of neurons (10^{11}) and connections (10^{14}) with an optimum and efficient network performance attracts researchers to understand the mechanism behind it [3], [4], [5]. It has been also considered to be a large-scale robust and interactive biological system with non-trivial topological properties such as hierarchy and small-world properties [6], [7]. This interesting biological system interacts and responds efficiently to external stimuli by transporting signals between specialized related brain regions. This response to mental or physical performance is becoming a key area in cognitive neuroscience research.

Therefore, the study of brain functional connectivity will greatly contribute to the understanding of the fundamental organization of processing systems in the human brain [8]. Figure 1.1 shows an explanation of human brain structure, regions distribution along with their tasks that people have previously defined [9].

1.2 BRAIN IMAGING TECHNIQUES

Investigating brain networks involved in complex cognitive, affective, or motor tasks are of great interest from scientific and clinical perspectives. To study brain interactions and brain networks, researchers have used various experimental modalities such as structural and functional magnetic

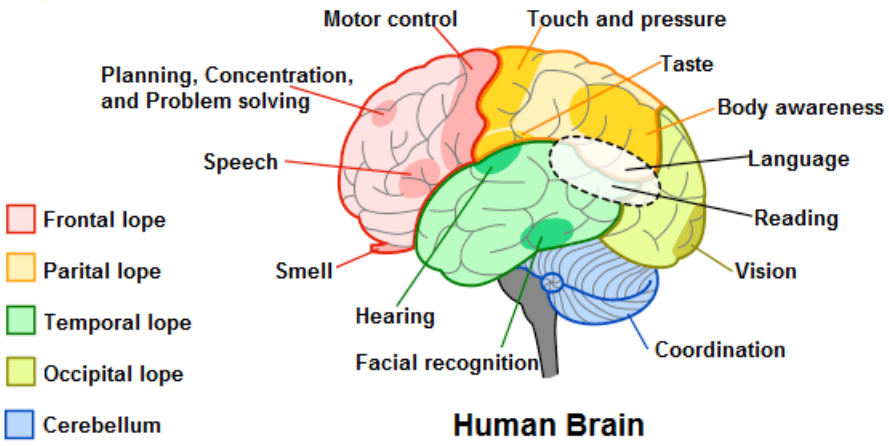

Figure 1.1: Human brain structure and regions distribution

resonance imaging (MRI) [10], [11], [12], positron emission tomography (PET) [12], diffusion tensor imaging (DTI) [10], electroencephalography (EEG) [13], magnetoencephalography (MEG) [14], single photon emission computed tomography (SPECT), computed tomography (CT) and near infrared spectroscopy (NIRS) [15]. All the above mentioned modalities have been used to to map the functional regional changes in brain activities from different perspectives: electrical activity, regional brain circulation, metabolism and etc [16].

However, The most common modality among those approaches is fMRI for many reasons: it is non invasive technique to acquire brain images, it has high spatial resolution and it has been proven since 1992 to be useful technique for exploring functional brain activity [17]. Since then, fMRI has been widely used to study brain networks involved in a variety of psychological and motor behaviors using several signal processing approaches [10], [11], [12], [14], [13]. fMRI has enabled us to understand the brain macroscopic organization by enabling us to study the structural and functional networks [18]. The use of fMRI to study brain activation patterns has several advantages over other methods such as PET, which requires radioactive ligands to be injected into the participants. FMRI: (1) is considered a non-invasive technology for acquiring brain images,

(2) can be used to examine task performance in less time, acquiring scan images more rapidly than the PET, and (3) the scans have high spatial resolution [19]. The blood oxygenation and flow is the fundamental basis for fMRI. Thus the brain activation signal increases around the area of blood vessels and brain tissues with higher blood oxygenation levels and blood flow [12], [20]; the more activated brain regions have higher blood flow and blood oxygenation than non-active regions [12], [20].

The idea behind choosing fMRI as good technique to study brain interaction is that blood flow changes at cerebral level serve to adjust both glucose and oxygen rates as a response to brain energy demands due to responses to cognitive tasks or certain stimulus [21]. As we all know that amino -acid called glutamate is the one that control cerebral blood flow in the brain which is also part of the neuronal activation for producing some agents such as (arachidonic acid metabolites, adenosine, and nitric oxide). These agents will be part of blood vasodilatation that stretches to surrounding regions through a local parallel fiber network [22]. Brain functional changes in local blood flow circulation within a mental arithmatic challenge was first introduced by Angelo Mosso who was able to find that brain activation increased when we continuously measure brain activity over the right prefrontal cortex through the defective skull of a subject [21], [23]. Since then, huge effort of neuroimaging research was put to focus on local changes of cerebral blood flow at the regions of brain activation.

Later on, fMRI was widely applied to investigate hemodynamic changes and responses in both healthy and disease which severly contributes to the expansion of a new promising scientific research sector called cognitive neuro-science [21]. To give broader idea of brain mapping history using fMRIand PET techniques, we introduce figure (1.2) below to show some of the events and concepts which have shaped brain functional imaging as we see it and know it nowadays [1].

In general, the measured signal by fMRI depends on the change of oxygenation which is referred to as the Blood Oxygen Level Dependent (BOLD) signal [20], [24]. Those BOLD signals will be taken to higher levels of analysis to investigate interactions between regional changes in cerebral per-fusion and neural activation using different approaches such as graph theory or psycho-physiological interaction PPI techniques etc.

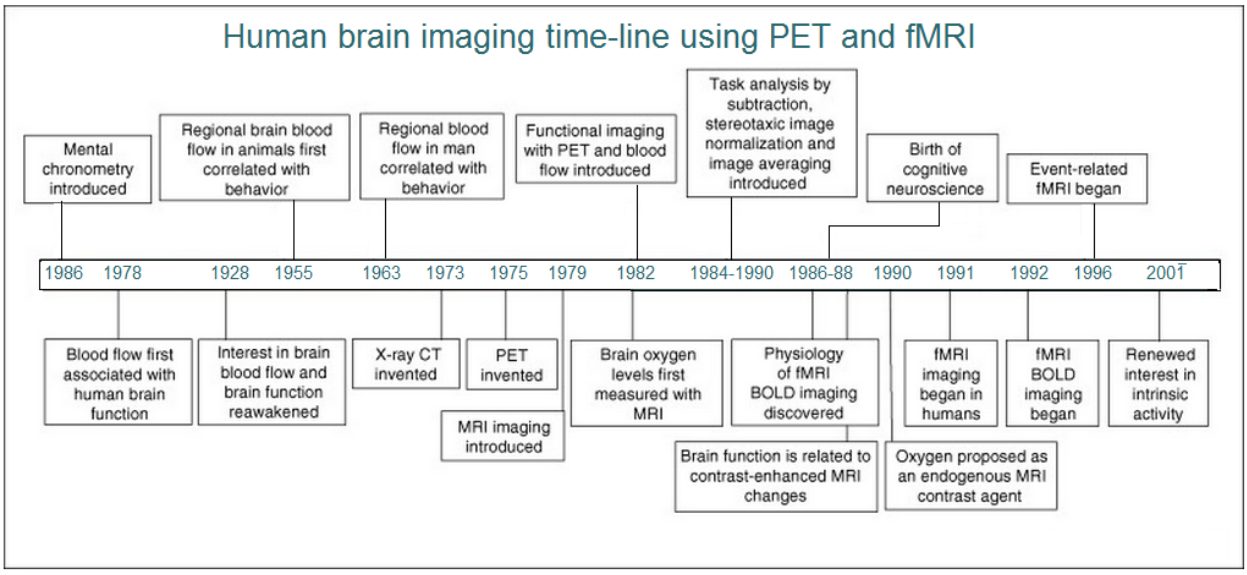

Figure 1.2: A chronology flowchart of major events associated with the development of human brain imaging using PET and fMRI techniques [1]

1.3 MOTOR LEARNING

Motor skill learning is a fundamental and mandatory adaptive mechanism in both human and animal life [25]. Researchers have paid great attention to the huge impact motor learning has on new acquired skills development and after brain injury recovery [26]. In order to define motor learning, we first start by defining its scope. In most occasions, motor learning consists of acquiring new novel movement patterns [27]. These patterns are natural and expected results as: responses to a stimulus, an actions being repeated, or cognitive task being performed [28]. Consequently, the involved muscles will gradually start to develop a stereotyped pattern of agonist and antagonist activity [28]. The more complex the skills are, the more number of joints and across-limb coordination are needed to be coordinated to achieve that task [27]. An example of complex task is the learning of skiing or skating sport activities which requires the establishment of novel simultaneous

and sequential action patterns. Keep in mind that the simplest type of motor learning necessitates practice related performance changes. Previous studies have shown that simply repeating a particular movement will be sufficient to change and manipulate the primary motor cortex output for tens of minutes [29]. Those studies have also demonstrated that repetitive motor behavior can produce changes in representational maps in motor cortex [30], [31], and [32], [33], [34], [35], [36] and [37]. That was not only for human brain, it has been also shown in animal studies that motor learning has impact in the production of functional changes in motor cortex [38], [39], and [40]. Motor skills, as we all know, are required by training; and based on task novelty and complexity, performance will plateau after certain number of training sessions. Simple skills can be learned as fast as one session, whereas complex skills will require more repetitive training sessions along with rest session included. The last type we call long term learning, which may or may not depend on short term learning. For more details on this, we refer to [41]. Here, we want ot mention that giving more time between training sessions is more efficient and showed better results than continuous (massed) training [42]. However, it is not clear yet which aspects of the motor behavior are responsible for producing functional plasticity in the brain.

1.4 RESEARCH OBJECTIVES

The primary objective of this study is to understand motor learning via advanced imaging techniques as fMRI. However, in order to make an informed decision regarding the analytical approach, we need first to understand whether the fMRI time series are stationary or not, i.e., if the statistical properties such as mean and variance of a time series are time-invariant [43]. The assumption of fMRI stationarity is especially important to understand whether the choice of an analytical approach needs to be robust to non-stationarities. The second objective is to apply the psycho-physiological interaction (PPI) technique to data processed in the first stage, and analyze interactions motivated with our pre-designed motor learning task. The ultimate goal is to see how the process of motor learning tasks would modulate brain regions and what kinds of interactions

between brain regions could occur during learning phase. We also want to see how the brain behaves after two different stages of learning; the first is [learning-control-learning] and the second is [Control-learning-control].

1.5 THESIS STRUCTURE

This thesis was comprised of two studies. The first study focuses on the stationarity of the extracted fMRI signals. We will also discuss and cover the effect of window size on the signal stationarity and sources of non-stationarity in this part. The second part, however, will mainly discuss the PPI analysis. Here, we will see the effect of motor learning tasks on the overall brain network and interaction between different brain regions.

2.0 BACKGROUND

2.1 MOTOR LEARNING

When we start discussing motor learning, we should first begins with defining its scope. Most commonly, motor learning entails acquiring novel movement patterns. Such novel patterns can be the straightforward result of a simple action being repeated and the involved muscles gradually developing a stereotyped pattern of agonist and antagonist activity [28]. However, If we want to develop a more complex skill that need to involve multiple joints and across limb coordination, for instance, training for sport or artistic activities, it will entail the establishment of novel simultaneous and sequential action patterns [27]. The category of motor learning also subsumes the acquisition of novel associations between environmental events and motor actions when, for example, learning to manipulate a tool or responding for the first time to a traffic signal [27]. The component actions (grasping, applying forces etc) and their sensory antecedents have already been acquired or experienced but not necessarily conjoined in a new context. Regardless of whether the learning necessitates adaptation or the formation of new sensory motor relationships, new patterns of neural activity or activation accompany these changes.

Motor skill learning can be also referred to the to the process of producing an auto movements [44]. It is also a process by which movements produced in a sequence that can be performed effortlessly through repeated task or practice and interaction with surrounding environment [45].

These kinds of motor behaviors are used on a daily basis, and are considered important for our everyday activities such as practicing sports and playing a musical instruments like Piano. However, in laboratories the cognitive tasks, processes and neural substrates, which mediate our capacity to learn such behaviors, have been studied using different experimental paradigms. One important category of these paradigms is to measure the incremental acquisition of tasks or movements into a well-excuted behavior which we call as (motor sequence learning MSL).

In the last two decades, we have witnessed a steady increase in the number of functional neuroimaging studies of motor learning. The application of functional connectivity methods to areas such as cognitive psychology, clinical diagnosis and treatment progression has yielded promising preliminary results, but is yet to be fully realized and understood due to the fact of methodological and interpretative issues that need to be solved [46]. Current investigations about motor learning have shown that repetitive motor behavior can produce changes in representational maps in motor cortex [30], [31]. It still unclear which specific aspects of the behavior are responsible for prducing such functional plasticity [32]. However, most of numerous noninvasive functional imaging studies in human subjects research conducted by: (Jenkins, Brooks, Nixon, Frackowiak, and Passingham [33]), (Pascual-Leone, Grafman, and Hallett [34]), (Zhuang, Dang, Warzeri, Gerloff, Cohen, and Hallett [36]) and (Seitz, Roland, Bohm, Greitz, and Stone-Elander [37]) etc., have found that the primary motor cortex or (M1) was involved in the operations of motor learning. Those learning tasks that were associated with M1 would be greater than the activity associated with simple motor use [47].

The above mentioned studies have proposed that the learning process itself might affect the functional organization of the motor cortex M1 in a way that is different way than the process when executing regular movement [32], this applies at least in human case. We still know little about the relative contribution of motor use and how it produces these plasticities in M1 although we have strong evidence that motor behavior associated with motor skill learning has a great impact on shaping the functional organization of M1 [32].

Trying to address this issue, Plautz et al in [32] have examined the effects of motor learning training on the representation of movements in M1. They have designed a task that basically promote consistent, repetitive use of a limited set of forelimb movements without the necessity of learning a new motor skill in order to perform the task. They have designed the task so that it only requires repetitive motor use alone with the absence of motor skill acquisition; this in order to be compared with the results from previous experiments that do require the learning of a new manual skill. They want to see whether the new task with a simple and repetitive motor activity alone is sufficient to produce representational plasticity in cortical motor maps. They found that repetitive motor activity alone does not produce functional reorganization of cortical maps. Instead, they propose that motor skill acquisition, or motor learning, is a prerequisite factor in driving representational plasticity in M1 [32]. Ungerleider et al. [48] have also found that the learning of sequential finger task generates slowly change of the primary motor cortex (M1) organization within the course of week or so. That change in M1 reorganization will generate a more rapid and dynamic changes in the striatum, cerebellum, and other motor related regions within the period of days [48]. Changes in M1 activity can be easily observed as fast as from the first scan session although the evolution of differential pattern of activation in the same region needs extra practice that lasts weeks to be noticed [49].

The learning process, in general, follows several distinct phases [44]. The first phase is a fast or early learning stage in which a considerable improvement in task performance can be seen within a single training session. The second is a slow phase in which further gains can be seen across several sessions of practice or tasks. The third stage or phase is a consolidation stage in which spontaneous increases in task performance can be experienced following the first and the second stages. This spontaneous increase in task learning should show a steady behavior of learning (i.e we do not expect to see major learning within this stage) where the participants should have already learned the task by that time. This was intuitive and confirmed by 90 percent of our participants who said they were able to recognize that there was a learning pattern and they were able to learn it. Another two stages we would like to mention here are an automatic stage during which the skilled

behavior is thought to require minimal cognitive resources and to be resistant to interference and the effects of time; and finally, a retention stage in which the motor skill can be readily executed after long delays without further practice on the task [44].

In addition, motor learning is highly correlated with time space between sessions and resting periods. Many researchers including Walkers et al. in [50] have found that there is a great performance improvement when subjects learned a sequence of finger tapping tasks and had resting periods of good sleep between training sessions [50]. In fact, they realized that additional performance gains occurred during the resting period phase. The idea here is activity during resting periods may reflect the on going processing of information which have been acquired from the early training sessions [51], [52], and [53]. The process of information and metabolic demands of consolidation have to be met by resting brain [51]. These interactions and process of information might be reflected in slow fluctuations of BOLD signal which are measured and detected as Resting State networks (RSNs). This would inform us that human motor system has the ability of " self rehearsal" during sleep sessions. We should keep in mind that it is the motor learning not the motor performance that modulate certain resting state network within the brain as Neil B. Albert et al. have shown in their study [54].

Another important concept we want to mention here is interference in motor learning. Interference refers to the occasions in which training a new task will lead to forgetting of earlier acquired skills. This will take place due to conflict of information processing in the brain. In this case, the new trained task will compete for the same information processing in the brain [55]. This concept of interference phenomenon is different way to inform us more specifically into the time-course of motor learning [55]. It was used to explore the time course of consolidation of a motor memory. Task consolidation has been shown to be disrupted by a secondary task being learned right after the first task [56]. Interference is also governed by the time factor. For example; if there was time gap between two training sessions (4 to 5 hours), there will probably be no interference. In fact, the interference will gradually reduce during these 4 or 5 hours of rest [57]. Consolidation

process is also performed in phases. It has been shown by Walker et al [50] that the first phase of consolidation is usually between 10 minutes and 6 hours after the end of the training session. This consolidation period will render the memory resistant to interference [58]. More consolidation will occur during the subsequent sleep sessions and will lead to more gain in task performance [58]. However, it not necessary that all forms of motor ability and skills will improve after sleep; this was shown by J Doyon, A Simard and others [59]. They have shown that the simple passage of time during daytime will be sufficient to engage the process of consolidation of a motor adaptation skill. They have also suggested that consolidation of a motor sequence learning after sleep should be associated with functional plasticity in the corticostriatal (CS) system, whereas consolidation of motor adaptation after a period of time, or sleep, should be associated with cerebral changes in the cortico-cerebellar (CC) system. But those suggestions require further experimental investigations to be confirmed.

Motor leaning composes of two important consolidations: motor adaptation skill and motor sequence. Doyon et al [44] have shown that the cerebellum is an important part for the consolidation of a new motor adaptation skill whereas the striatum plays an equally important role in the consolidation of a motor sequence [60]. However, till now there is no strong evidence that the striatum contributes to process of consolidation of a motor sequence after learning a new sequence of movements.

Another important section is the motor learning of patients who are suffering from brain disorder and deficiency or those who are recovering from brain damages like stroke. Patients with brain damage from stroke are estimated to be more than half million per year in the United States alone [61]. More than 70 percent of those who recover from this kind of brain damage have some level of neurological impairment and disability [61]. It has been shown that both cognitive and motor processes are required in order for us to acquire new motor skills. However, the degree of the relationship between cognitive deficits and stroke related motor and how cognitive deficit could affect the motor learning capability has not yet been fully understood [61]. Winstein et al. have

launched a study to examine and determine the degree to which stroke-related brain damage would impair the capability to acquire a novel motor skill [61]. It is important to understand how stroke affected brain will affect the acquisition of a new motor skill because it has great impact on the rehabilitation process where the motor skill is an important part of the functional motor recovery [61].

It has been well known that circuits which has being accessed by motor skill learning are ways different than those being accessed by control tasks. Continuous and consistent activation changes have been witnessed during the course of motor learning [55]. Many research and clinic studies have been launched to characterize brain activation pattern during the learning of motor skills using functional imaging techniques such as fMRI. The majority of those studies employed tasks that could be learned within the period of one session. However, a few of them have looked into differences between intersession and within-session activation changes using the same task [62], [63]. In a word, learning advances through separate stages of training [55]. Most of them will also suffer from Cognitive impairments. Both motor and cognitive impairments are considered to be main factors of functional disability such that 75 percent of all stroke survivors receive rehabilitative therapy which often focuses on the recovery of motor function.

2.2 SOME PREVIOUS CONTRIBUTION ABOUT MOTOR SKILL LEARNING

Motor skills as from experience, not from knowledge point of view, emerge as they easily escape our consciousness. Naturally, we acquire many motor skills and execute them without awareness [64]. The question is, how are motor learning acquired and processed in the brain? Many studies investigating the motor learning skills have been conducted from different points of view. Some have looked to the effect of motor learning on resting networks. Others have got a discrep-

ancy between the results of imaging studies where subjects learn motor sequences. For example, some experiments have shown decreases in the activation in some of the brain regions as learning increased; others have found that as learning progressed, learning related regions activation increases [65]. Some studies have demonstrated that motor learning, but not motor performance, modulates subsequent resting activity in specific task-relevant networks [54]. Changes in resting state activity were induced specifically by learning and were not limited to the time immediately after learning, but were measured after conscious processing has been redirected to an unrelated dummy task for a period of 4 min [54].

Salamoni et al. in their review have found that a remarkable number of evidence that support task practice with high relative frequency of feedback was mainly based on the performance improvement within the practice session but not on the effect from retention tests [66]. We want to mention here that few of brain studies have focused or used retention tests in their research design. What the majority of studies that Salamoni et al. reviewed suggested is that lower relative frequencies of feed back were seen better for learning than the higher frequencies. Most of recent studies have found that cognitive changes resulting from neuro-pathology could make differences in the process of cognitive tasks which will consequently affect the motor learning [67].

Another study on how are motor sequences acquired in the brain were done by Hikosaka et al. [68] who devised a sequential button press task, called the 25 task, in which the subject learned to press buttons in the correct order, by trial and error, and showed that the pre-supplementary motor area (preSMA), rather than supplementary motor area SMA, is crucial for learning new sequences [64]. One of the important achievements was the discovery of synaptic plasticity in single neurons [69]. However, it was still far from sufficient to explain and well understand motor skills. Recent integrative and multidisciplinary approaches have begun to suggest that essential features of motor skills reside in dynamic interactions between multiple neural networks. Such networks are composed of loop circuits formed by the frontoparietal cortices, the basal ganglia BG and cerebellum CB. These circuits acquire the same motor sequence in different coordinates, at

diverse speeds, with varying robustness, and with different levels of attention and awareness [70]. This operation is likely optimized by learning mechanisms, each unique to the BG and CB; and such dynamic interactions of neural networks would thus create the emergent and ever-changing properties of motor skills.

Daniel Margulies et al have used visualizations to arrive at understandings of their neurological data. They found that the complexity inherent in comprehending the structure and inter-individual variance of the connectome requires an awareness of the implications of available methods, as well as precision and sensitivity to analytic methods while developing new ones. They suggested that flashy graphic is insufficient to justify inclusion in a manuscript; the image should obviously first be loyal to the method and raw material it reflects, but clarity and intuitive design should also be a priority [71]. In general, motor skill learning accesses brain regions that are different from those that control already acquired movements [72]. Activation of these circuits changes during the course of motor skill learning. From the behavioral evidence presented earlier, one may hypothesize that association areas are preferentially activated in the early stages, when visuospatial to motor associations need to be formed. Later, cerebello- and striato-motor-cortex loops may improve movement efficiency [73]. Using functional imaging approaches and techniques, several studies have characterized brain activation patterns during motor skill learning. However, most of these studies have employed tasks that were learned over one session; few of them have compared within-session and intersession activation changes using the same task [62], [63].

Andreas Luft and Manuel Buitrago have found the behavioral, functional imaging, electrophysiological, and cellular/molecular studies provide good evidence that motor skill learning is basically a staged process [72]. Different mechanisms appear to be active at different times. For example, there is sequential demand for different circuitry during training compared to other stages; also consolidation (i.e., stabilization of novel motor memory) occurs both during and after training. So, task complexity may be an important determinant of how staged or segregated the process is. Complex motor tasks require several training sessions interspersed with periods of rest and sleep.

For these tasks, acquisition and consolidation processes are interlocked, forming a complex sequence of events. To better understand this process, future studies need to detail the time-courses of brain re-organization during motor skill learning. Researches have also been conducted to study the advances and pitfalls in the analysis and interpretation of resting-state fMRI data. These have discussed the resting state alone without cognitive tasks included [46]. They showed that in order to use RSNs to generate a comprehensive neuro-cognitive functional ontology, it may therefore be beneficial to adopt an approach combining both task- and resting-fMRI which is the case in this study.

Researchers have looked into motor learning from physical and psychological point of view. We have already covered some fo the previous studies related to the physical interaction. However, Wise et al. have looked into how motor experiences are consolidated from psychological point of view [74]. They recorded neuronal activity while monkeys adapted to visuomotor transforms between a joystick and the cursor on a screen it controlled. They were able not only to see changes in M1 and premotor cortex during motor adaptation, but they were also able to detect changes in activities which have continued for certain number of trials after performance reached its steady peak [48]. They were unable to see clear asymptote of this activity change up to the 30 in limit of the observation period. This finding suggest that the continued change of activity im motor cortex reflected the early stages of consolidation. [48]. Based on this finding, Lesliy et al. launched their study to look for evidence of consolidation by examining the reason of performance gain delay. They want to see whether delayed gains in performance could occur after training on a motor sequence task [48]. Additional psychological evidence can be supported by the study launched by Brashers-Krug et al. (1996). [56].

Researchers have also looked into patients with impaired brain ability and suffering from brain disorders such as Alzheimer Disease (AD). Paul et al have examined the learning and retention and in normal controls of three different types of information . In their study, they have found that this kind of patients were unable to learn series of frequent words and unfamiliar faces; however,

patients have shown a remarkable improvement in motor skills with learning curves that were similar to the control ones [75]. Paul et al have also noticed that patients did not lose much motor skills in a 20 minute delay trial. Although those kinds of patients have profound memory disorder, they were still able to learn and retain a variety of motor and perceptual skills [76], [77], [78], and [79]. Patients with Alzheimer disease (AD) actually get the benefit from the constant practice conditions. However, they do not learn a new motor task under a task that has changing practice conditions such as throwing a bean bag three different distances over different trials. That has been shown by Carolee et al in their work cited in [61]. The reason for patients with AD not being able to learn from tasks that include kind of problem solving is that they have brain regions damaged or some how affected. Those damaged or affected brain regions prevent the formation of a flexible representation of the motor task. Those findings lead us to the conclusion that different aspects of motor learning are performed by different regions and areas of the brain [61].

In the sense of motor learning and resting state, two major suggestions have been proposed. The first suggests that having resting periods between sessions of cognitive tasks will actively support introspective thought or support responses to future events [80]. The other perspective is that resting brain network could selectively and actively process information of previous sessions [51]. Albert et al have shown that motor learning can modulate subsequent activity within resting networks [54]. Future extensions should enable a more direct comparison of 'mental state' and resting-state network activity and will enable more definitive classification and diagnostic application of the latter, and thereby ultimately contributing to the thorough characterization of the human neural functional architecture.

3.0 PROTOCOL DESIGN AND DATA ACQUISITION

3.1 PARTICIPANTS

Twelve (6 males and 6 females) healthy young adult participants (age range from 19 to 48 years old, mean age 33 years old) participated in this experiment approved by the Institutional Review Board at the University of Pittsburgh. A written informed consent was obtained from all participants after the nature of the experiment had been explained. All participants were right handed.

3.2 DATA ACQUISITION

Motor learning traditional theory and research should be designed in away that would reduce errors in performance tremendously. So our data acquisition was conducted by an expert fMRI technician from the Department of Radiology, University of Pittsburgh, Pittsburgh, PA. The MRI scanning was acquired on a 3T Siemens TRIO scanner using a 12-channel parallel receive head coil. GE-EPI BOLD (FA=90 deg; TR=2000 ms; TE=29 ms) scans were collected with thirty-eight axial slices (3.4 mm thickness) with a 3.4 mm x 3.4 mm in-plane resolution (64x64). A T2-weighted

structural scan (FA=150 deg, TR=3000 ms, TE=11/101 ms) with voxel size 10.30 x 31.0 x 31.0 mm (matrix 256x224x256) was used to acquire 48 slices covering the whole brain which was collected prior to the functional scans. Head movement was minimized during the experiment by placing pillows around the head within the head coil. Each of the 60 second blocks consisted of a series of 7 tapping sequences as shown in Figure 3.1.

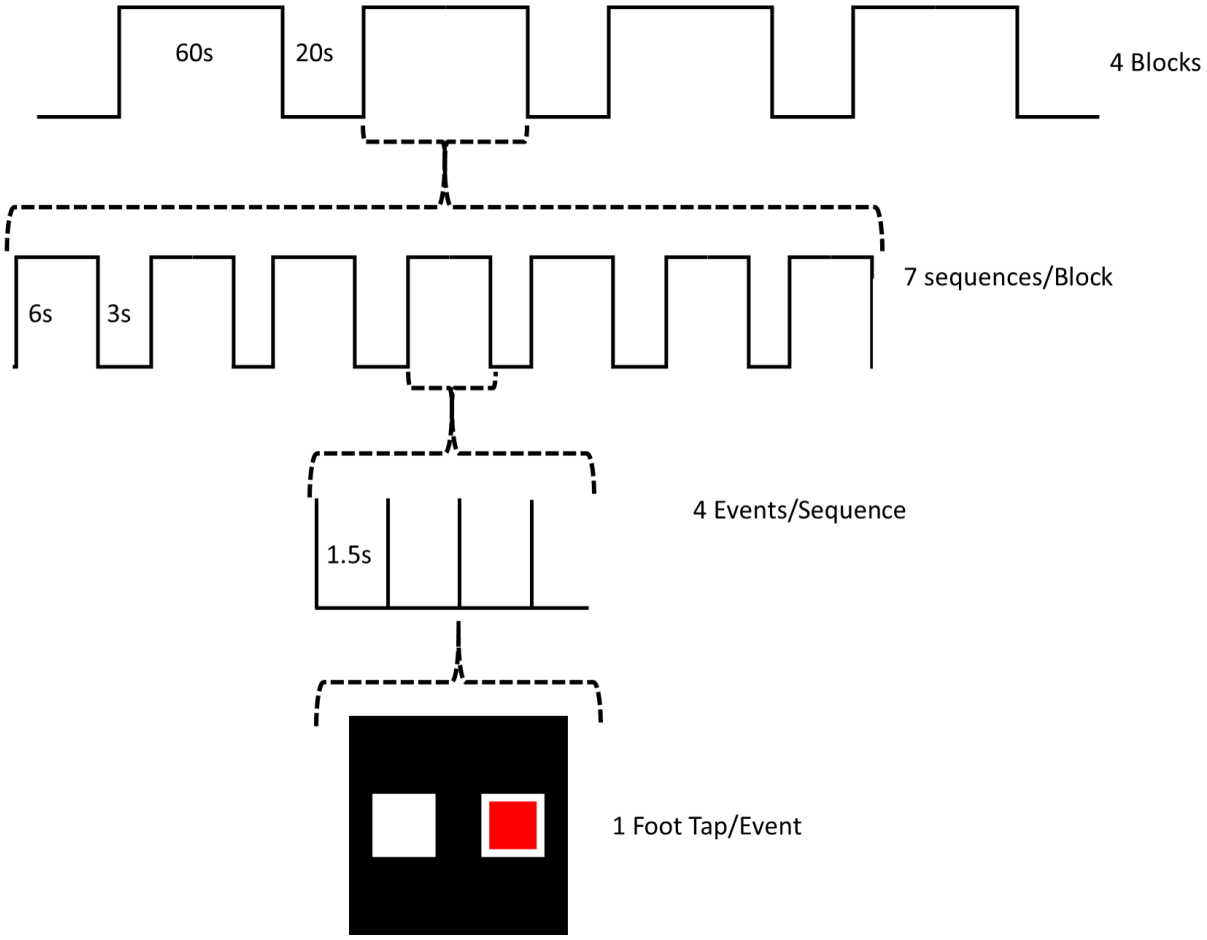

Figure 3.1: A flowchart depicting the fMRI protocol of the experiment.

Each sequence consisted of 4 directed movements (e.g. 7 sequences/block x 4 movements / sequence = 28 total movements/block). For the control blocks, 7 random tapping sequences were presented with no repeats. For the learning blocks, an identical tapping sequence was repeated 7 times. Each learning block used a different sequence so that each learning block required relearning the sequence. For each movement, participants were presented with a red box either on the left or right side of a display screen mounted at the head of the MR scanner, which was viewed using a mirror affixed above the head coil. Participants were told to perform ankle plantar flexion (foot tap) with either the right or left foot depending on if the box appeared on the right or left side, respectively. During the control sequence, the pattern of foot tapping was random and subjects were not expected to learn the sequence. During the learning sequence, subjects also repeated the same sequence 7 times per 60 second block; thus they were expected to learn the pattern, as demonstrated by a decrease in foot tap onset latencies. Participants were instructed to simply perform the foot tapping task as indicated by the position of the red box projected on the screen. They were not informed that the intent was to study motor sequence learning. An overall diagram of the experimental sequence is shown in Figure 3.2.

3.3 DATA PREPROCESSING

The Statistical Parametric Mapping (SPM) toolbox was utilized to preprocess and analyze the acquired fMRI data [24]. Data preprocessing steps included: realignment or (motion correction), coregistration, normalization, and smoothing. The realignment is performed using the least square method and a six parameter spatial transformation [81]. The movement artifacts and excessive head motion in the fMRI scans were removed in this procedure using a well known approach [82]. Next, the mean functional image generated from the previous realignment step is co-registered to a high resolution anatomical image and all of the other functional images are then resliced to

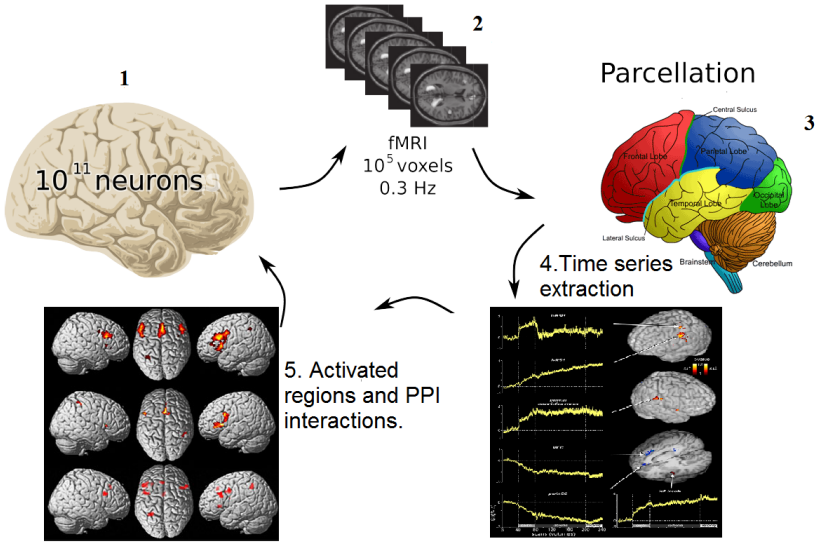

Figure 3.2: A flowchart showing sample procedure of the experiment starting from (1) the brain and (2) functional and anatomic magnetic resonance imaging fMRI scans. Time series need to be extracted from the scans; hence realignment, smoothing, co-registration and wrapping have been done. To get the time series, (3) anatomical parcellation using AAL template described in [2] was followed, it divided the brain region into 90 regions of interest ROIs which are time series we used for the analysis (4). These time series has been used for the PPI analysis to find regions of interest and regions of interactions (5) Region of interest have been detected and located on 3D brain map

align with the reference image. To normalize the scans between different subjects, we utilized the standard template image in MNI space (Montreal Neurological Institute) [83]. Unlike the rigid body realignment to correct for motion, normalization includes changing the size of the brain to match the size and position of the template. Hence, smoothing is performed to: increase the signal to noise ratio, increase inter-subject overlap, and to increase the validity of the analysis. Smoothing includes blurring the functional MRI images using a Gaussian filter (i.e data is convolved with a Gaussian kernel) [84]. After smoothing the images, each voxel becomes a weighted region of interest (ROI, the voxels under the kernel). The size of the new voxel can be obtained using the

full width half maximum technique (FWHM) [12], which is an indication of the distribution of the kernel values. Ideally, the FWHM kernel size should be chosen to match the size of the expected activation.

3.4 DATA ANALYSIS

We first preprocessed the fMRI data using a standard pipeline (described above). Then for each subject, 90 region of interest mean time series were extracted and processed. The time series were separated by task (rest, learning, control) described in detail below. The Statistical Parametric Mapping (SPM) toolbox was utilized to pre-process and analyze the acquired fMRI data [24]. Data preprocessing steps included: realignment or (motion correction), coregistration, normalization, and smoothing. The realignment is performed using the least square method and a six parameter spatial transformation [81]. The movement artifacts and excessive head motion in the fMRI scans was removed in this procedure using a well known approach [82]. Next, the mean functional image generated from the previous realignment step is co-registered to a high resolution anatomical image and all of the other functional images are then resliced to align with the reference image. To normalize the scans between different subjects, we utilized the standard template image in MNI space (Montreal Neurological Institute) [83]. Finally, smoothing is performed to: increase the signal to noise ratio and to increase inter-subject overlap; data is convolved with a Gaussian kernel [84]. After smoothing the images, each voxel becomes a weighted region of interest (ROI, the voxels under the kernel). The size of the new voxel can be obtained using the full width half maximum technique (FWHM) [12].

Next, we followed the parcellation schemes which have been previously used in network studies such as [82], [85], [86], and [87]. Network connectivity analysis is greatly affected by the

selection of links and nodes [88]. Our processed data were parcellated into 116 anatomical ROIs using the automated anatomical labeling (AAL) template [2]. This template segments the cerebrum into 90 cortical and subcortical anatomical ROIs (45 ROIs in each hemisphere) [2]. On the other hand, it divides the cerebellum into 26 ROIs (8 in the vermis and 18 in the cerebellar hemisphere, 9 in each side of the cerebellar hemisphere). In this study, we only considered the 90 regions of the cerebrum which we have included in table 3.1. This parcellation scheme provides non-overlapping segmentation of the entire brain volume such that each brain area depicted in AAL only points to one brain region in Table 3.1. We then parcellated the individual anatomical ROIs from the whole brain using the free accessed toolbox (MarsBaR) [89]. As a result, we got 90 time series each corresponding to an anatomical ROIs in table 3.1 for each participant. The mean time series is obtained by averaging the voxels for every time point in the time series. This procedure generated the mean time series with 170 time points.

Table 3.1: Cortical and sub-cortical regions of interest (45 in each cerebral hemisphere; 90 in total) as anatomically defined in the AAL template and their corresponding abbreviations used in the study

Region	Abbreviation	Region	Abbreviation
Precentral gyrus	PreCG	Supramarginal gyrus	SMG
Postcentral gyrus	PosCG	Precuneus	PCUN
Rolandic operculum	ROL	Superior occipital gyrus	SOG
Superior frontal gyrus, dorsolateral	SFGdor	Middle occipital gyrus	MOG
Middle frontal gyrus	MFG	Inferior occipital gyrus	IOG
Inferior frontal gyrus, opercular part	IFGoper	Cuneus	CUN
Inferior frontal gyrus, triangular part	IFGtri	Calcarine fissure and surrounding cortex	CAL
Superior frontal gyrus, medial	SFGmed	Lingual gyrus	LING
Supplementary motor area	SMA	Fusiform gyrus	FFG
Paracentral lobule	PCL	Temporal pole: superior temporal gyrus	TPOstg
Superior frontal gyrus, orbital part	SFGorb	Temporal pole: middle temporal gyrus	TPO
Superior frontal gyrus, medial orbital	SFGmedorb	Anterior cingulate and paracingulate gyri	ACP
Middle frontal gyrus, orbital part	MFGorb	Median cingulate and paracingulate gyri	MCP
Inferior frontal gyrus, orbital part	IFGorb	Posterior cingulate gyrus	PCG
Gyrus rectus	GRE	Hippocampus	HIP
Olfactory cortex	OLF	Parahippocampal gyrus	PHG
Superior temporal gyrus	STG	Insula	INS
Heschl gyrus	HES	Amygdala	AMY
Middle temporal gyrus	MTG	Caudate nucleus	CAU
Inferior temporal gyrus	ITG	Lenticular nucleus, putamen	PUT
Superior parietal gyrus	SPG	Lenticular nucleus, pallidum	PAL
Inferior parietal, but supramarginal and angular gyri	IPL	Thalamus	THA
Angular gyrus	ANG		

4.0 STATIONARITY OF FMRI TIME SERIES

The vast majority of recent contributions on complex brain networks are based largely on graph theory analysis [90]. The graph theoretical analysis of MRI data has been widely used to understand both normal brain networks and dysfunctional brain networks resulting from pathologies such as Alzheimer's disease [18], [91], [92], [93], schizophrenia [18], [94], [95], stroke [18], [96], epilepsy [18], [97] and tumors [18]. For example, Buckner et al. [93] were able to demonstrate a correlation between the site of the targeted regions and the location of major hubs in Alzheimer's disease. He et al. [91] have also shown different structural variation of brain small-world organization in individuals with Alzheimer's disease, which has been shown to accurately classify people with Alzheimer's disease. Similarly, Liu et al. [82] have shown the network properties in individuals with schizophrenia relative to controls.

In addition to understanding dysfunctional networks in pathological conditions, the brain networks involved in regulation, motor control and execution, and learning and memory are important for understanding normal brain development and function. Hence, researchers have used graph theoretical approaches to examine learning-related changes in network connectivity [98]. However, in order to establish a brain network using modern graph theory, many researchers using graph theoretical approaches for fMRI data have not closely examined whether their data violates the assumptions of graph-theory. In particular, in order to make an informed decision regarding the analytical approach we need to first understand whether the fMRI time series are stationary, i.e.,

if the statistical properties such as mean and variance of a time series are time-invariant [43]. The assumption of fMRI stationarity is especially important to understand whether the choice of an analytical approach needs to be robust to non-stationarities. Furthermore, the stationarity of fMRI time series is relevant when discussing simple meaningful statistics of fMRI time series such as means, variances, and correlations. These statistics are more useful as a description of the data if the time-series is stationary [99], [100]. The stationarity is also relevant to the frequency analysis of the fMRI time series as the Fourier transform is suitable for stationary signals [101]. In this chapter, we used reverse arrangement analysis to quantify the degree of non-stationarity in fMRI data in the context of network connectivity. Such investigation will help us define the most appropriate approaches that should be considered in the establishment of connectivity matrices and complex brain networks.

4.1 TIME SERIES AND STATIONARITY

A set of observations recorded at a specific time is usually denoted as a time series [99]. If the observations are recorded continuously with time, then we say it is a continuous time series. On the other hand, if $x(n)$ denotes observations made within time interval $0 \leq n \leq N-1$, where N represents the length of the signal, then $x(n)$ is a discrete time series since the observations are made at time intervals from the discrete set γ. This time series can be considered as a realization of random variables $\{X_n, n \in \gamma\}$ [99]. Stationarity is either strong stationarity (strict stationarity) or weak (wide sense) stationarity. If the statistical properties of a time series are time-invariant, then this time series is said to have strict stationarity [43] , i.e.:

$$F_{X_{n_1},\ldots,X_{n_k}}(x_1,x_2,\ldots,x_N) = F_{X_{n_1+h},\ldots,X_{n_k+h}}(x_1,x_2,\ldots,x_N) \tag{4.1}$$

for all positive integers h and for all $(n_1,\ldots,n_k) \in \mathbb{Z}$. In other words, strict stationary time series should express similar statistical properties in the graphs of two equal-length time interval of real-

ization [99]. A time series is considered to have weak or (wide-sense) stationarity if the only first two moments are time-invariant [100], such that the mean is constant, i.e.,

$$E(X_{n_1}) = E(X_{n_1+h}) \tag{4.2}$$

and the covariance only depends on the time lag between two observations [99], i.e.,

$$Cov(X_{n_1}, X_{n_2}) = Cov(X_{n_1+h}, X_{n_2+h}) \tag{4.3}$$

A usual first in the time series analysis is the visual inspection of the series in order potentially determine suitable analysis methods and/or statistical variables beneficial for summarizing information contained in the series [100].

To understand which mathematical approaches should be adopted, we need to understand the stationarity of the time series [102]. But, why do we need to examine the series stationarity? In previous contribution, no attention has been paid to the fundamental problem inherent in correlating any pair of time series, namely the nonstationarity and autocorrelation of the individual series being correlated. The problem is that, unless the stationarity issue is taken explicitly into account, correlations between such time series are most likely to be spurious, since they will reflect both the internal properties of the series as well as any true relation between the two series. In addition, it is likely that the regression errors (residuals) will be typically serially correlated, in violation of a fundamental assumption in least-squares regression analysis, namely that regression errors be independent, i.e. not serially correlated [103], [104]. Such a violation invalidates least-squares regression and is guaranteed to yield spurious correlations. So, to examine the time series stationarity, one of the following non-parametric tests is applied: a run test, a reverse arrangement test (RAT), or a modified RAT [101]. The RAT is a non-parametric test that has often been used to evaluate the wide-sense stationarity of a time series [105], [106], especially to investigate the weak stationarity of physiological and biomedical signals [14], [106], [107], [108], [109], [110]. Basically, the RAT test is used to search for monotonic trends in the mean square value calculated within non-overlapping intervals of a particular time series signal of interest [105], [111]. In this

study we performed the RAT test. Below are the steps we took to use the RAT test to examine the stationarity of the fMRI motor sequence learning task-related brain activation signal pattern.

1. A time series is divided into M equal non-overlapping segments. The number of segments M can be determined using the following equation:

$$M = \frac{N}{L} \tag{4.4}$$

where N is the length of the time series and L is the desired segment length.

2. Calculate the mean square value $Y(k)$ for each segment:

$$Y(k) = \frac{1}{L} \sum_{i=kL}^{(k+1)L-1} x^2(i) \text{ for } 0 \leq k \leq M-1 \tag{4.5}$$

3. The total number of reverse arrangements A is then counted within the sequence of mean square values $Y_0, Y_1, \ldots, Y_{M-1}$. A reverse arrangement occurs when the mean square value of one segment is greater than the mean square value of the subsequent segment, i.e. when: $Y_a > Y_b$ for $a < b$. Hence, using this condition, Y_k will form the indicator:

$$s(k,d) = \begin{cases} 1 & \text{if } Y(k) > \text{Y(k+d)} \\ 0 & otherwise \end{cases} \tag{4.6}$$

For $1 < d \leq D$, where $D = M - k - 1$; and therefore, for k^{th} time step, the reverse arrangement test is given by:

$$A(k) = \sum_{d=1}^{D} s(k,d) \tag{4.7}$$

and the total number of reverse arrangement test A is given by:

$$A_T = \sum_{k=0}^{M-1} A(k) \tag{4.8}$$

4. The calculated value of the total reverse arrangement A_T from the previous step is then compared to the value that would be expected from a realization of a weakly stationary random process. If we considered the sample as weakly stationary, then the expected value of (A) has a normal distribution [105] with the mean given by:

$$\mu_T = \frac{L(L-1)}{4} \tag{4.9}$$

and the variance:

$$\sigma_T^2 = \frac{L(L-1)(2L+5)}{72} \tag{4.10}$$

The null hypothesis that Y_k is weakly stationary is rejected if the calculated A_T falls outside the critical values defined by a significance level α. In this research, the critical values were determined from the calculation of the stationarity test statistic Z_T, which is given by:

$$Z_T = \frac{A_T - \mu_T}{\sigma_T} \tag{4.11}$$

where $Z_T \sim$ N(0,1), and the critical values of Z_T at the significant level α can be defined as $Z_{1-\alpha/2}$ and $Z_{\alpha/2}$, where Z is a standard normal variate. At 5% significance level, the values of Z are given by $Z_{1-\alpha/2} = -1.96$ and $Z_{\alpha/2} = 1.96$; and the values of the test statistics Z_T will have one of the following possibilities:

- $Z_{\alpha/2} < Z_T < Z_{1-\alpha/2}$: the null hypothesis that the time series is wide sense or weakly stationary is accepted.
- $Z_T \geq Z_{1-\alpha/2}$: this means that the number of reverse arrangements is greater than that expected of a stationary signal. This implies an existence of downtrend in the mean square sequence.
- $Z_T \leq Z_{\alpha/2}$: this means that the number of reverse arrangements is less than that expected of a stationary signal. This implies an existence of an upward trend in the mean square sequence.

4.2 RESULTS

4.2.1 Effects of window size

Once the 170 data points had been processed, we computed 90 fMRI time series that have been used for stationarity testing using the RAT Test. It can be clearly seen from Figure 4.1 (a)-(d) below that the greatest percentage of non-stationary signals were distinguished during the first and second runs of the fMRI task, while the least number of non-stationary signals were found within the last run.

The impact of a window size on stationarity is depicted in Figure 4.1(d). The percentage of non-stationary time series decreased with increasing window size; but this effect is not statistically significant due to a few window size increments ($p > 0.75$). At larger window sizes, a time series is divided into fewer segments and fewer comparisons between subsequent mean square values are carried out. This process will reduce the number of opportunities to detect a reverse arrangement. The boxplots on the other hand show the stationarity of the test statistics value Z_T at different window sizes for the three runs. In each of the three sub-figures, the two horizontal dashed lines represent the boundary between stationarity and non-stationarity of the data based on the value of Z_T defined by $|Z| < 1.96$.

From the boxplots in Figure 4.1 (a)-(c), we can observe the following:

- The fMRI time series were generally stationary since the median values of the stationary test statistic Z_T fell within the stationarity range at the 5% significance level previously defined and represented by the two dashed lines at each figure ; i.e. $|Z| < 1.96$.

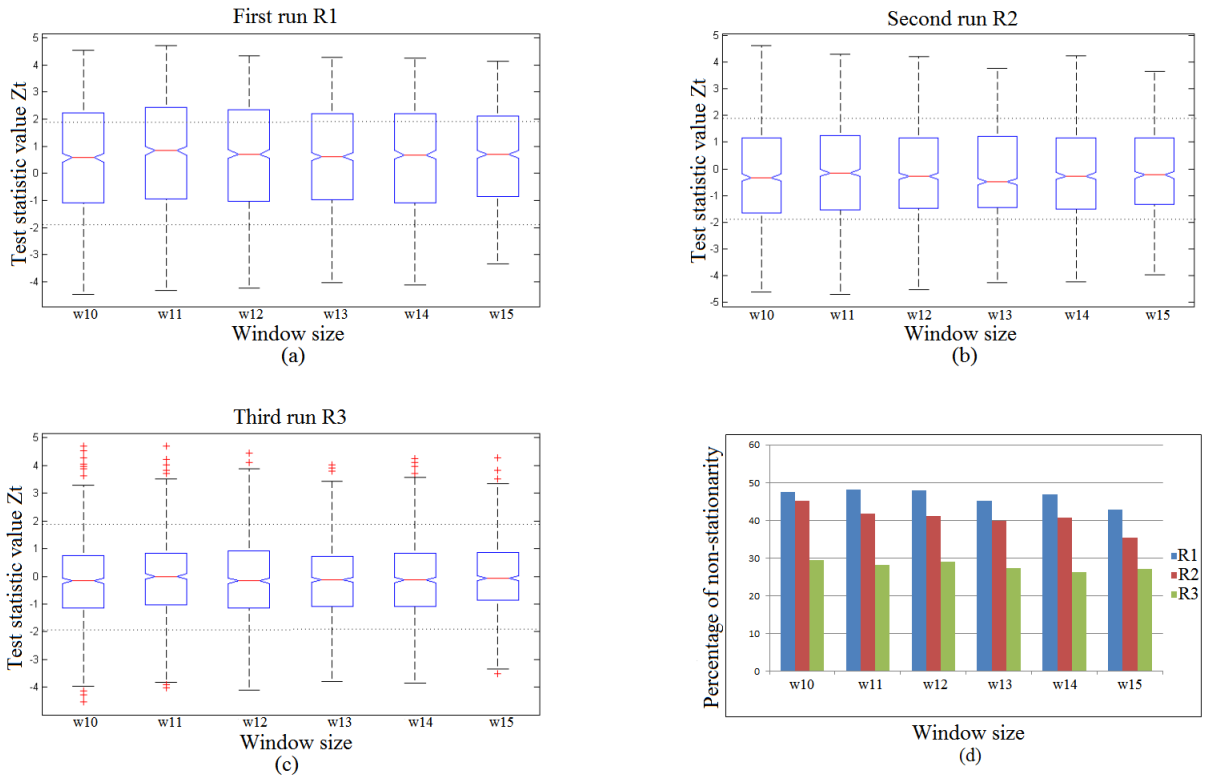

Figure 4.1: The effect of window size on the stationarity test statistic, Z_T, during the foot tapping task: first run R1 (a), second run R2 (b), and third run R3 (c); and the effect of window size on the percentage of non-stationary time series identified for each of the three runs (R1 = run-1, R2 = run-2, R3 = run-3) respectively (d). R1 and R3 are motor learning set runs; R2 is a control set run.

- It can be also noticed from the first and last runs R1 and R3, which have the same task sequence, that only in the last run R3 the 25% and 75% of the Z_T values fell within that range. For the first run R1, only the 25 percentile fell within the range. In each run (R1,R2 and R3) as shown in Figure 4.1, the number of stationary time series tended to increase with increasing window size.

- With increasing window size, the variation in the stationary statistic remains relatively constant as shown in Figure 4.1. Therefore, an intermediate value of 13 points is utilized for further analysis.

4.2.2 Sources of non-stationarity

As defined at the beginning of this study, a time series is said to be strictly stationary if its statistical properties are time-invariant. We investigated the sources of non-stationarity using the intermediate window size 13. It can be noticed that the last time course will be trimmed from every time series because of the indivisibility of time series lengths on the window size. We then calculated the mean and variance for each segment and tested for a significant linear regression relationship. What we observed from the extracted fMRI signals as shown in Figure 4.2 is that the non-stationarities can be mostly attributed to a change in the mean value over time. Furthermore, very few signals experiences time-dependent variance alone, and fewer signals demonstrated both non-stationary means and variances.

Based on our observation, non-stationarity was found in different brain regions rather than in specific brain regions. However, the regions that were seen stationarity among all participants are listed in Table 4.1.

These regions are illustrated in Figure 4.3. Intuitively; since those regions have shown stationarity behavior among all participants, this imply that those regions were not involved during the learning task. There no signal statistic change which means blood oxygenation within those regions is not changing. This has been proved in the second part of the study where we found only the thalmus, middle frontal gyrus and left pre-central gyrus were the most interacting regions during the learning task.

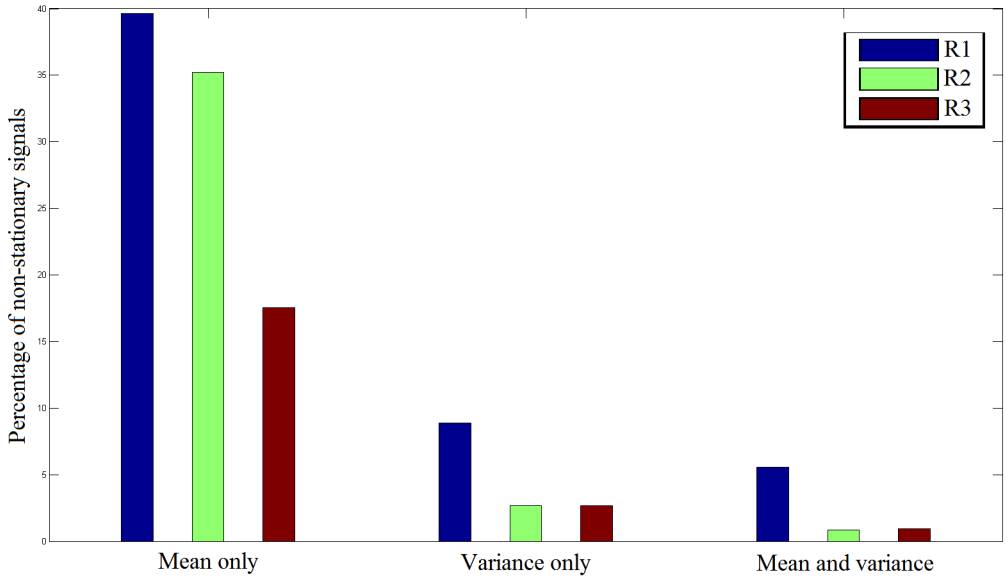

Figure 4.2: Sources contributing to non-stationarity time series as a percentage of non-stationary time series identified within each foot tapping task run: R1 = run 1, R2 = run 2, R3 = run 3.

Interestingly, the intensity of colors in the image does not reflect the amount or the percentage of stationarity/non-stationarity but rather reflects depth of the region in the brain. So the regions that are deep in the brain have low intensities, whereas the regions that are closer to the cortex have a higher intensity.

Table 4.1: Stationary regions among all participants.

Region Name	**Location on Hemisphere**
Amygdala	left hemisphere
Caudate	left hemisphere
Caudate	right hemisphere
Medial Orbitofrontal Gyrus	left hemisphere
Insula	right hemisphere
Olfactory	left hemisphere
Inferior Parietal Gyrus	right hemisphere
Superior Parietal Gyrus	left hemisphere
Precuneus	left hemisphere
Supramarginal Gyrus	left hemisphere
Middle Temporal Gyrus	left hemisphere
Superior Temporal Pole	left hemisphere
Superior Temporal Gyrus	left hemisphere

4.3 STATIONARITY DISCUSSION

The human brain has been viewed as one of the most complicated physiological networks [112]. Researchers try to understand how brain networks respond to and interact with different stimuli using neuroimaging techniques. Our investigation informed us about the suitability of potential signal processing tools to be used to evaluate and interpret brain interaction during learning task. People have initiated different tools and applied them to fMRI time series [113], as a way to identify functional clusters of activated brain regions during a finger tapping task. Previous studies utilized cross-correlation [114], cross-coherence [115], and mutual information [13] among others. How-

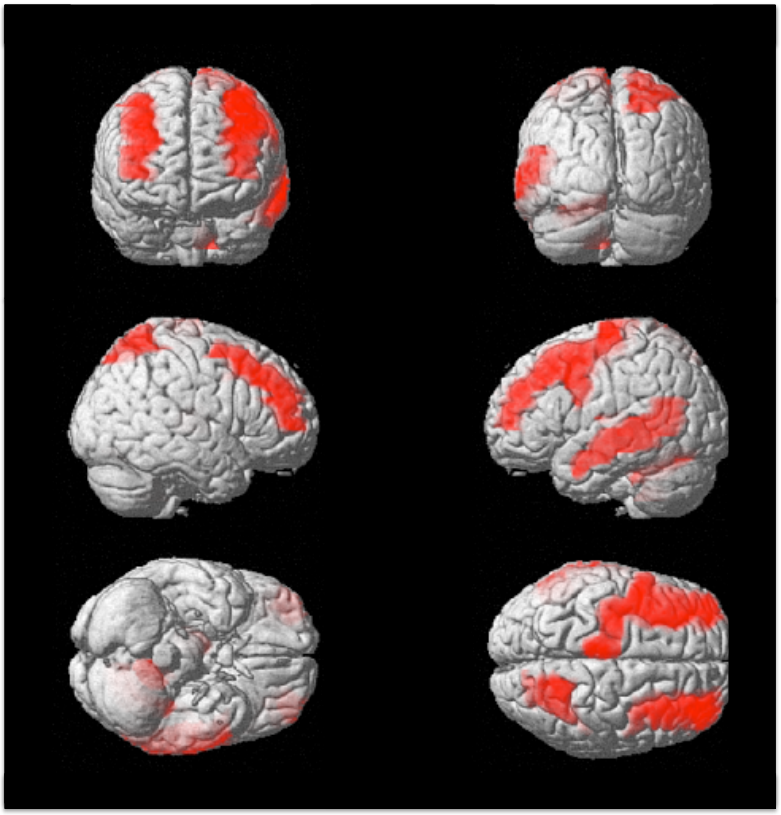

Figure 4.3: Brain regions found stationary in all participants. Brain images are shown in the sequence: Front-Back, Right-Left, Bottom-Top.

ever, given that some fMRI time series are non-stationary, approaches resistant to non-stationarities should be considered (e.g., wavelets [116], [117], [118]) if no manipulation, such as whitening, to stationarize the siganls has been done to the series. In our case, we chose to apply PPI to the processed data and extract the active regions and analyze the interactions. In general, applying RAT we observed fewer non-stationarities in the third run R3 compared to first run R1, even-though the signals were acquired under the same stimuli and the same experimental procedure. This could be interpreted as a result of ”priming” a phenomenon defined as ”a change in the speed, bias or accuracy of the processing of a stimulus, following prior experience with the same, or a related,

stimulus" [119]. The implicit memory phenomenon, known as direct or repetition priming, has been considered as one of the three different categories of priming [120]. From the brain activation point of view, implicit memory captures the effect of previous experience on the current experiment, even in the absence of conscious awareness of the past [119], [121], [122], [123], [124]. Moreover, repetition can also be another main reason of decreased brain activation and blood flow level in the repeated task R3. Neural activity usually decreases for repeating stimuli [125]. In particular, Gruber and Muller have discussed the repetition priming task using electroencephalogram technology [126] by analyzing the induced gamma band activity during the repetition of familiar and unfamiliar line drawings. Penhune and Doyon have also discussed such a phenomenon and revealed a dynamic network of motor structures that have different activation during different phases of learning and repetition. They have shown that the recall of motor sequences in humans is mediated predominantly by cortical networks, which suggests the involvement of cerebellar mechanisms in the early learning procedures. These cerebellar mechanisms are no longer recalled or involved in the repeated tasks [127]. Repetition suppression has also been observed using fMRI and PET technologies; referred to as the "response suppression phenomenon" [128] or "decremental responses" [129]. Processing a stimulus more than once will produce what is called the "sharpening phenomenon" of the stimuli's cortical representation. This can be explained as some of the neurons that processed and coded the stimuli at the beginning exhibiting a lower response in the repeated task showing "a response suppression phenomenon." The lower response from the previous neurons decreases the mean firing rate of a neuron population, resulting in a decrease in the captured fMRI signal [119].

4.4 STATIONARITY SUMMARY

In this part, we have successfully investigated the stationarity of fMRI time series in 12 healthy participants while they performed motor sequence learning foot tapping tasks in three different runs. We found that stationarity and non-stationarity were not concentrated or found in specific brain regions so that further analysis and interpretation can be introduced. We have also showed that some of the extracted time series are non-stationary, primarily in the form of time-varying mean. These findings provide a new insight into what approach should be considered prior to establishing the connectivity matrices, which lead us to the second part of the study ”Graph theory analysis”.

5.0 CH2- PSYCHO-PHYSIOLOGICAL ANALYSIS (PPI)

5.1 GLM AND PPI ANALYSIS

It has been well known that statistical analysis of fMRI data uses mass-univariate approaches which are based on *General Linear Models* or (GLMs) [130]. In this work, we have divided the analysis into two separate steps. The first analysis is to extract the region/regions or cluster within the brain, on a group level, where learning was greater than the control. In other words, we are interested in region/ regions that learning has greater impact onto than control. We performed a two-step analysis on the foot-tapping data. We first took the approach of a conventional general linear model (GLM) using SPM12 [130]. To do so, for each subject we performed a linear regression between the BOLD signal and the learning and control tasks. The learning and control tasks were 60 seconds long and these blocks were convolved with a Canonical Hemodynamic Response Function (HRF) for the GLM. We also used motion as a covariate. We took the contrast learning greater than control to the group level, where a one-sample t-test was performed. This analysis informed us of areas where the learning task elicits a greater BOLD activation than the control task. We extracted these clusters as masks. For the second step of this analysis, we performed a *psycho-physiological interactions* (PPI) analysis. This was handled using the PPI toolbox in SPM12. We took the extracted masks from the group level analysis and calculated the principal time-series using principal component analysis (PCA). From this, an interaction term can be constructed; specifically, the in-

teraction between learning greater than control task blocks and the region of interest (ROI/mask). Figure 5.1 below shows an example of one subject's interaction term. Basically, you take the ROI perform a de-convolution (to get the timings of the neural activation) and you multiply that by the canonical response and then re-convolve the new interaction. Now a GLM analysis is performed again (the same one described above) except now three new terms are included: the learning greater than control canonical response, the ROI time-series, and the interaction signal. We are mostly interested in whether there is a significant interaction term in our regression. The interaction contrast is then taken to the group level.

The excratcted cluster (Thalamus) was then taken to the next level of the analysis which is the PPI anaysis. We chose to use the PPI for analysis of hypothesized changes in connectivity between the Thalamus and the rest regions of the brain during motor learning foot tapping task. We did the analysis of psycho-physiological interaction PPI associated with fMRI foot tapping task. As we described above, spheres of radius 5 mm around each subject contrast maxima within activation regions in the Thalamus were defined as seed regions for extracting the first eigenvariate of the signal and creating the psycho-physiological interaction term for the respective delay-period contrast of interest (learning $>$ control). We then take those terms and use them as regressors in the individual subject GLM that we mentioned above in this section. This process will generate new PPI contrast images which will be used in the in the group level analysis using one sample t-tests. This process we call the PPI second level analysis.

Brain responses and interactions during the learning task we referred to as *psycho physiological interactions* as we mentioned before. We defined *psycho-physiological interactions* as functional integration by observing that the percentage to which activity in one brain region can be predicted on the basis of activity in another corresponds to the contribution of the second to the first [131], [132]. It is important here to distinguish between brain interactions that occur among BOLD signals and those that occur at the neural level [131]. These interactions are not necessarily the same. Previous studies have demonstrated a need for deconvolving the region of interest eigenvariate,

generating an interaction term between that signal and the expected response, and then reconvolving with the hemodynamic response function (HRF). This process is explained in greater detail

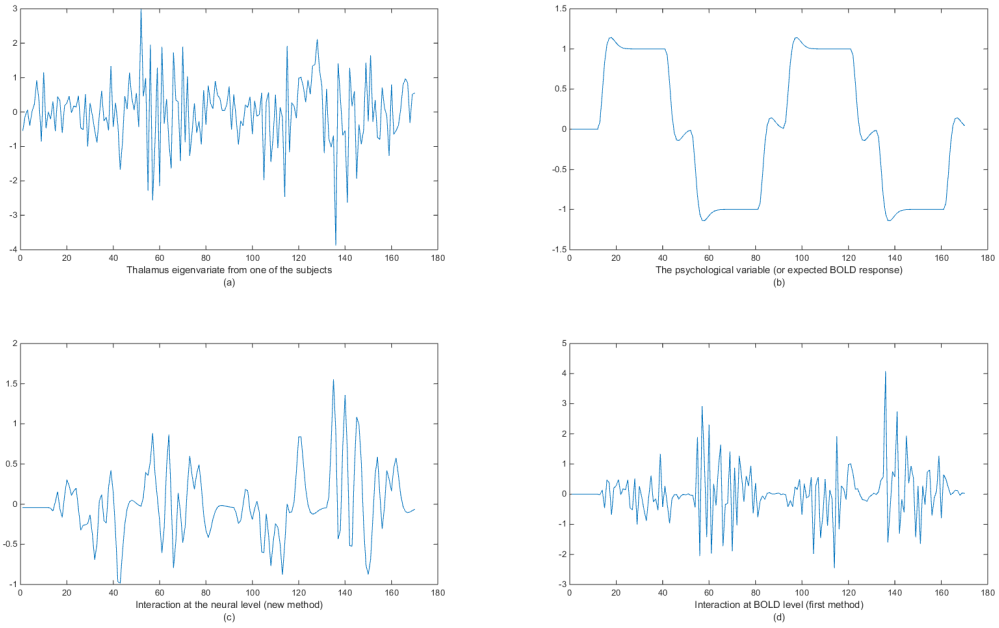

Figure 5.1: (a) An example eigenvariate from one of the subjects in the thalamus, (b)The psychological variable (or expected BOLD response), (c) Interaction at the neural level (new method), (d) Interaction at BOLD level (first method)

.

in [131].This new signal is used as the interaction that opposed to calculating the interaction term as the element wise multiplication of the ROI eigenvariate and the expected response (convolved with the HRF). It has been found that this is more important in event-related designs versus block-design studies. In figure 5.1, an example eigenvariate from one of the subjects in the thalamus is extracted and shown in figure 5.1 (a). The psychological variable (or expected BOLD response) is shown in figure 5.1 (b). It is shown as learning minus control. Figure 5.1 (c) and (d) show the method of interaction at the neural level vs. the BOLD level, respectively.

In reality, brain interaction are actually represented at neural level not at the level of hemodynamic response [131]. So, the good models of neural interactions need to have the real neural signal or, at minimum, a good approximation of it [131], [132]. Since the fMRI will provide us with blood oxygen level dependent (BOLD) signal, the best way to get an approximation of the neural signal is by de-convolving it with an assumed hemodynamic response. This de-convolution is important to be at neural level because we are mathematically modeling interactions at hemodynamic level, whereas brain interaction occur at neural level [132], [131], [133]. People have witnessed the importance of de-convolution when we need to analyze fMRI data. For more information regarding de-convolution importance we refer to [131].

5.2 RESULTS

In this part (the Psycho-physiological interactions PPI), we have chosen to apply the PPI analysis technique to probe the function of cognitive network using inter-subject learning task-related variations in BOLD fMRI signals. From the first level analysis, we have found that the Thalamus was mostly involved during the learning task. Along with the thalmus, we have also found that it has interacted with other regions which we have found to be the ”the right middle frontal gyrus” and ”the left pre-central gyrus” as can be seen from figures 5.3, and 5.2 below. We have also introduced a 3D figure showing those regions on the whole brain, see figure 5.4

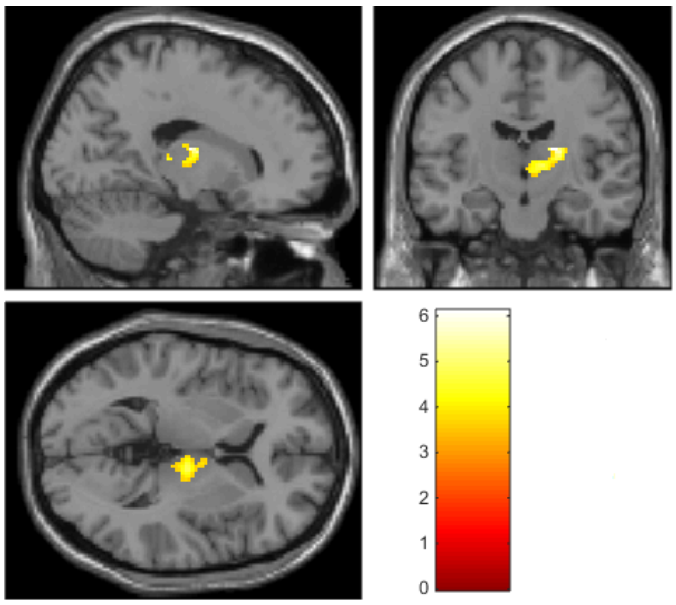

Figure 5.2: Region of interest ”Thalamus” that was mostly modulated and activated during the learning task

.

5.3 PPI DISCUSSION

Researchers try to understand how brain networks respond and interact to different stimuli using neuro-imaging techniques. Our investigation informed us that the PPI analysis is one good nominee approach and one of the most suitable and potential signal processing tool to be used while investigating brain activation during stimulus task such as foot tapping learning. PPI analysis technique has been applied to our data in order to probe the function of cognitive network using inter-subject learning task-related variations in BOLD fMRI signals. In this work, we have introduced the idea of experimenting the interaction between learning task parameters and brain responses using fMRI neuroimaging [131]. We have found that the Thalamus was mostly involved

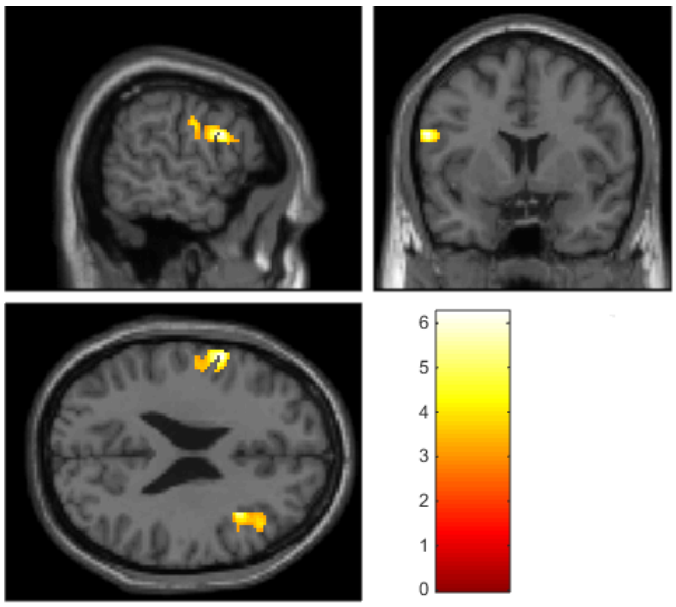

Figure 5.3: Right middle frontal gyrus and left preventral Gyrus that were mostly interacting with 'Thalamus' during the learning task

during the learning task and has interacted with other regions. The regions we have found were the Ventrolateral which is part of the "left precentral gyrus" and "light Middle Frontal Gyrus/inferior frontal gyrus" as can be seen from figures 5.3, and 5.4.

In the first level: Thalamus is certainly involved in learning and motor learning, the ventral lateral thalamus would also be a key area as it is central in communications between the cerebellum and cerebral cortex in adjusting timing, amplitude, speed and switching between agonist and antagonist [eg foot tap: up = dorsiflexion and down = plantarflexion] as well as side to side; VL is also thalamic nucleus involved in motor sequencing and fronto-parietal cortex to striatal connections [eg putamen] for creating well-learned motor sequences.

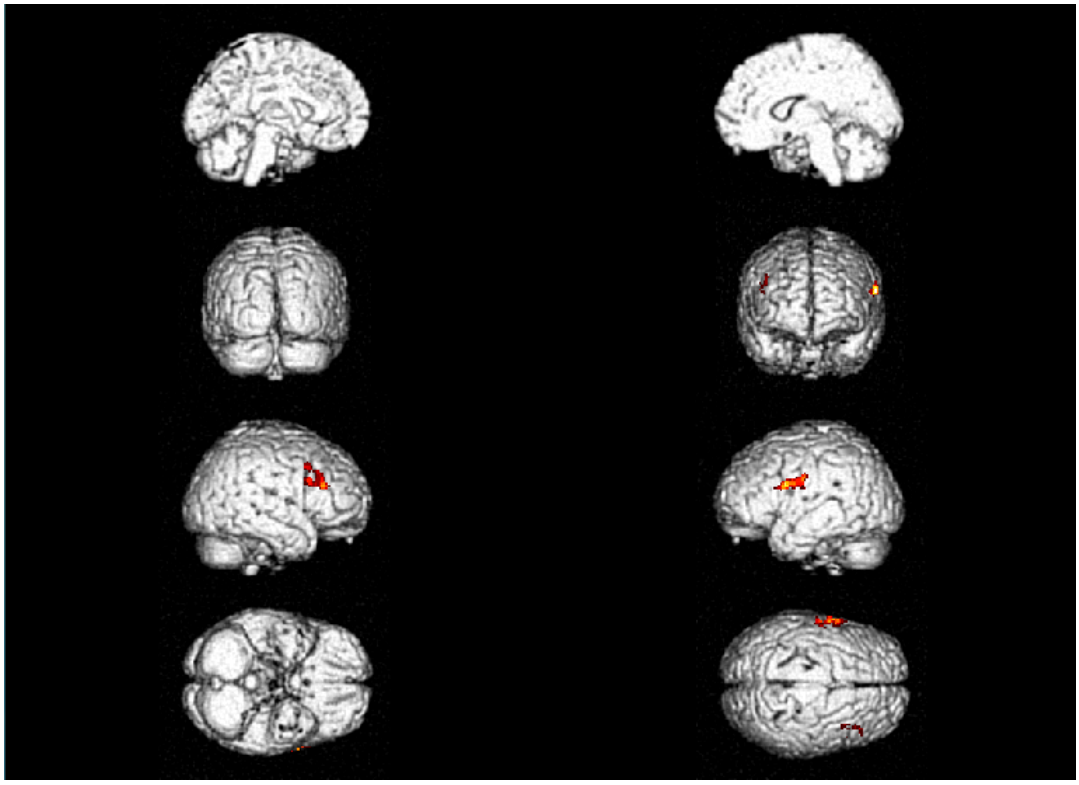

Figure 5.4: Whole 3d brain image showing region of interest that was mostly interacting with 'Thalamus' during the learning task

Precentral is primary motor medial which can be the foot control; but ventrolateral, more likely that the person might be repeating the foot tapping pattern viewed. On the other hand, the middle frontal gyrus likely dorsolateral prefrontal cortex which is like cognitive control of actions and part of lateral premotor region which is involved in the cortico striatal- thalamic back to cortex closed loop of motor skill acquisition. Those regions are interacting more in learning than control which take us to the next level whether the precuneus connections with the Thalamus might be reduced in learning compared to control. Using the concept of contribution, this means that attention to the designed visual motion has significantly modulated the contribution of "left precentral gyrus" and "Right Middle Frontal Gyrus/inferior frontal gyrus".

In the second level: left ventrolateral precentral/postcentral and extending into the inferior frontal gyrus: ventrolateral prefrontal cortex which would be in inferior frontal gyrus has roles in cognitive control of task with recognition as in recognize an object and plan what to do with it —[communication is extensive with a ventral stream that may extend into the postcentral gyrus and further posterior portions of the parietal lobe]. This ventrolateral inferior frontal regions, as well as the middle frontal gyrus, have been shown to be involved in the early stage of motor sequence learning [particularly visuo-motor sequence learning, which this task was]. With increasing learning later stage, the increases in the cortex shift to more dorsolateral prefrontal cortex, premotor and medial premotor regions. Some have related this to the ease of chunking or learning and carrying over a chunk [motor sequence] to the next set of learning. Interestingly, the carryover to future sets seems to be easier for larger sequences. Thus, for the foot tapping short sequence, the increases in the ventrolateral prefrontal/ inferior middle frontal gyri may be related to the early stage of motor sequence learning. The short sequence and relatively short trial did not lead to the intermediate stage of learning.

Psycho-physiological interaction can be seen from two different prospectives: either from the functionally specific change in the contribution of one area to another point of view; or, from the modulation of responses in one area to the psychological or experimental variable by the contribution from another area point of view. In our case, this can be interpreted as the attention to visual motion significantly modulated the contribution of 'Left Precentral Gyrus' and 'Right Middle Frontal Gyrus/inferior frontal gyrus'.

6.0 CONCLUSION

In this work, we have successfully investigated the stationarity of fMRI time series in 12 healthy participants while they performed motor sequence learning foot tapping tasks in three different runs. We found that stationarity and non-stationarity were not concentrated or found in specific brain regions so that further analysis and interpretation can be introduced. We showed that some of the extracted time series are non-stationary, primarily in the form of time-varying mean. Since these regions have shown stationarity behavior among all participants, this imply that those regions were not involved during the learning task. There were no statistical changes within those regions which means blood oxygenation level is not changing. This has been proved in the second part of the study where we found only the thalmus, middle frontal gyrus and left pre-central Gyrus were the most interacting regions during the learning task. By applying the PPI approach to our data, we were able to identify regions within the brain that were mostly involved and active during our pre-designed motor sequence foot tapping task. Our results add a new dimension to our understanding of the relation between motor learning and brain activity and potentially provide a powerful new technique to examine the neuronal machinery. Enabling more definitive classification and diagnostic application, and thereby ultimately contributing to the thorough characterization of the human neural functional architecture.

6.1 FUTURE WORKS AND CHALLENGES

Many challenges facing network approaches to cognitive neuro-science have already been discussed including data acquisition and network definition. One main important issue needs to be covered is task complexity which is an important determinant of how staged or segregated the process is. Complex motor tasks require several training sessions interspersed with periods of rest and sleep, so we highly encourage to increase both rest and task periods. Interactions directionality should also be taken into consideration since it is still inapplicable to see the exact detailed interactions between the mentioned regions in this study. Methodological and interpretational limitations also exist as a result of uncertainties in data recording and network definition. Bearing in mind these limitations, a major appeal of network models is that they establish a firm link from neuro-science to a rapidly expanding theoretical framework for understanding complex networked systems. Overcoming these limitation, more sophisticated multi-scale methods for extracting network modules have been also proposed [134] , and such methods are beginning to be applied in brain network studies [135],[136].

The selection of the appropriate approach to analyze the data also needs to be considered. This will probably be a key focus of future work that might be combined with further studies of clinical disorders or cohorts at different stages of normal development. More work can be done regarding data analysis where one can use different analysis tools other than regular correlation such as Wavelet.

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