EEG analysis:
Brain connectivity in stroke

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The declaration

I certify that this work does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Printed name	**Signature**
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ABSTRACT

Today in the modernization world everything has become so simple in one click of button, but this fast living life and changes in way of living has led to some major problems. Brain stroke is one of the leading problems in today's middle or elder age people. Science has progressed a lot and looks for many network analysis to deal with such problems. But still it's a field in which many unfolds still exist which creates a hinder to successfully unturned the issue. Brain consists of 100 billion neurons and one trillion gila. This network of brain stores experiences and houses consciousness. Focal brain lesions affect multiple network properties simultaneously and how changes on smaller scales influence those on larger scales.

Although understanding of the brain was enhanced by the stroke, stroke is one of the biggest killers and a leading cause of disability. Stroke describes damage to the neuraxis (the brain and spinal cord), resulting from an abnormality in cerebral blood supply. It is a neurological disorder characterized by interrupted or insufficient blood supply to certain parts of the brain. It is a significant cause of mortality and morbidity. The main causes of ischemic stroke in large blood vessels are building up of abnormal fatty lumps on the inner lining of arteries supplying blood to the brain, infections such as valvular diseases, ischemic heart disease and diabetes that narrow cerebral blood vessels or abnormal heart rhythms. In small cerebral blood vessels, fatty lumps on the inner walls of the arteries could break off and transported by the bloodstream to lodge in the narrower blood vessels in the brain causing embolic occlusion.

The main causes of leaking or rapturing of weak blood vessels in hemorrhagic stroke are aneurysm and arteriovenous malformations. Aneurysm results from a weakened part of a blood vessel ballooning. If unattended, the region continues to balloon and weaken until it raptures and releases blood into the brain. Arteriovenous malformations refer to a group of abnormally formed blood vessels. Any of these blood vessel can rapture and release blood into the brain cavity. Other causes of rapturing of weak cerebral blood vessels are cranial (head) trauma, an abnormal accumulation of blood in the cranial cavity, disorders such as hypertension and cerebral amyloid angiopathy tumors in the brain, the use of therapeutic anticoagulation (blood-thinning medication) or bleeding disorders that cause a considerable reduction in platelets.

The motivation for this work includes an electroencephalogram (EEG)-based experiment on the performance of several mental tasks including reading, auditory, subtraction and finger tapping among others in 9 patients with multilateral stroke, the main challenge was to analyze that the anatomic lesion affects the functional brain network on multiple levels.

In the past few years a large number of studies in the specific field have been developed. A broad range of detecting follows the morphological based methods. However, many of the methods, proposed previously failed to give good performance at the output. Sahil Bajaj [2015] [35] proposed a method which attracts the field in new limelight. In the paper, the author's aims at primary motor area during motor imagination (MI) task and how this differs during motor execution (ME) task are still questions of interest.

A new scheme to make some improvement on this is to explore the application of Normalised Transfer Entropy (NTE) measure to construct EEG based directed brain network. Along with this, the bedrock is to quantify and plot the network for statistically important connections for both stroke and healthy subjects and to determine information flow patterns during different tasks.

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TIA	Transient ischemic Stroke
TPA	Intravenous injection of tissue plasminogen activator
FFT	Fast Fourier Transform
NTE	Normalised transfer entropy
AM	Adjacency matrices
3-D	Three – Dimensional
RRMSE	root mean squared error
DCM	Dynamic causal modelling
GC	Granger Causality
VAR	Vector autoregressive
DTF	Directed transfer function
ME	Motor execution
MI	Motor imagination

CHAPTER I: INTRODUCTION

1.1 Overview

Admiring all the wonders created in this world of medicine and awareness in the field dedicated to cerebral networks working for the pathophysiology of strokes in last 25 years have been devoted to the study of Brain Network and many strategies came in limelight to avoid it in the person’s body. Research shows that in present time brain strokes remain the leading cause of trouble of speaking, paralysis, blurred vision, headache and loss of balance in the body [1]. Widespread presence of brain stroke is found in working age people who are ordeal with the problem from a long period of time. Stroke is defined as a stage when contribution of blood towards the brain remains undernourished and brain does not get appropriate amount of oxygen, hence leads to fully damage of brain cells [2].

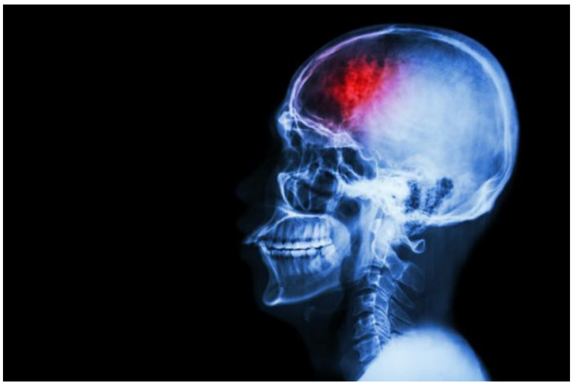

Figure 1.1 “Strokes occur due to problems with the blood supply to the brain; either the blood supply is blocked or a blood vessel within the brain ruptures” [2].

According to the statistics of World Health Organization, 15 million people undergo through the pain of stroke either in low level or high level stage. Approximately 5 million are die or suffer with the complete or partial damage of the body. In the United States, it has shown that Stroke is the third leading cause of death in the United States. “More than 140,000 people die each year from stroke in the United States.” [3]. Research shows that ratio of strokes in females are more than as compared to males. 40 % males are being affected with the brain strokes, while 60% females are in the impact of brain strokes further,” American Heart Association (AHA)”, after analysing dark skinned people with white skinned shows that dark skinned people suffered with twice the percentage with the risk of stroke in a danger level. Although it does not cause permanent disability, 30% of people experiencing transient ischemic attack have a greater likelihood to suffer from ischemic stroke within a year.

1.2 Incitement and contingency of Brain Strokes

Brain network also known as default mode network, is a network which is always active and can interact with inner, outside and surrounding network. Basically it is a loop or mesh of very tiny wires called nerves connected to each other. "Anatomical studies of the brain's cytoarchitecture, cellular circuits, and long-range fibre systems have yielded an extraordinary amount of detailed information about the brain's structural organization" [4]. Examination of topology of brain is only possible after the existence of image acquisition methods and their further developments in the area. Brain stroke is one of the biggest problem to the today's man health issues. People in the middle age suffers a lot with the above mentioned problems. Treatment to the brain stroke is only possible if one has a proper diagnosis about the type of their stroke. Usually brain stroke is divided into following stages:

1. **Ischemic Stroke:** A very common type of stroke, caused due to the jamming and contraction in arteries, which is primary responsible for providing blood to the brain. This blockage reduce the supply of blood and hence leads to the blood clots which can appear anywhere in brain most significantly in the areas near to connecting arteries to brain or in the blood vessels. These clots are the deposition of the blood in one area called the plaque which drastically reduces the flow of blood in brain [2]. Ischemic stroke is further classified as of following types: Thrombotic stroke and Embolic Stroke which will be analysed in detail.

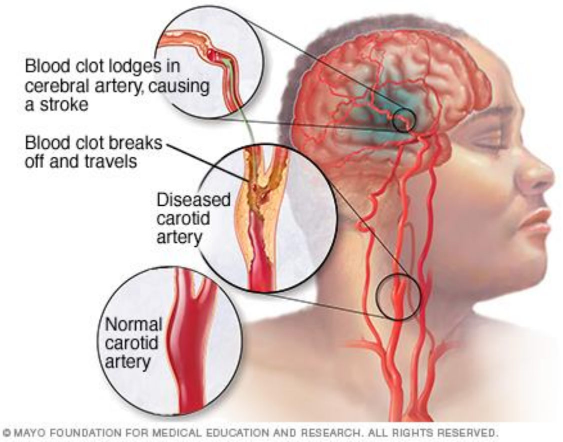

Figure 1.2 Ischemic stroke [1]

- Thrombotic stroke**.** This type is caused due to occurrence of plaque in the brain. The name thrombotic is given due to the blood clot deposition (thromb). The formation of plaque in arteries shapes to the atherosclerosis or other worse artery states [1].

- Embolic stroke**.** The situation of Embolic stroke occurs when lumps being formed away from the areas of the brain. This takes place usually in heart and is "swept through your bloodstream to lodge in narrower brain arteries. This type of blood clot is called an embolus' [1].

2. Transient ischemic Stroke: Transient ischemic Stroke (TIA) is also abbreviated as Mini stroke. This happens when there is a temporary stage of decrease of blood supply in the brain. The maximum duration lasts for this stroke is up to five minutes. This stroke is being temporary, but is more harmful as it can cause serious affect as loss of balance to body and paralysis etc. If a person is having TIA, it is because of partially blocked or narrowed artery. Research shows that "up to half of people whose symptoms appear to go away actually have had a stroke causing brain damage" [2].

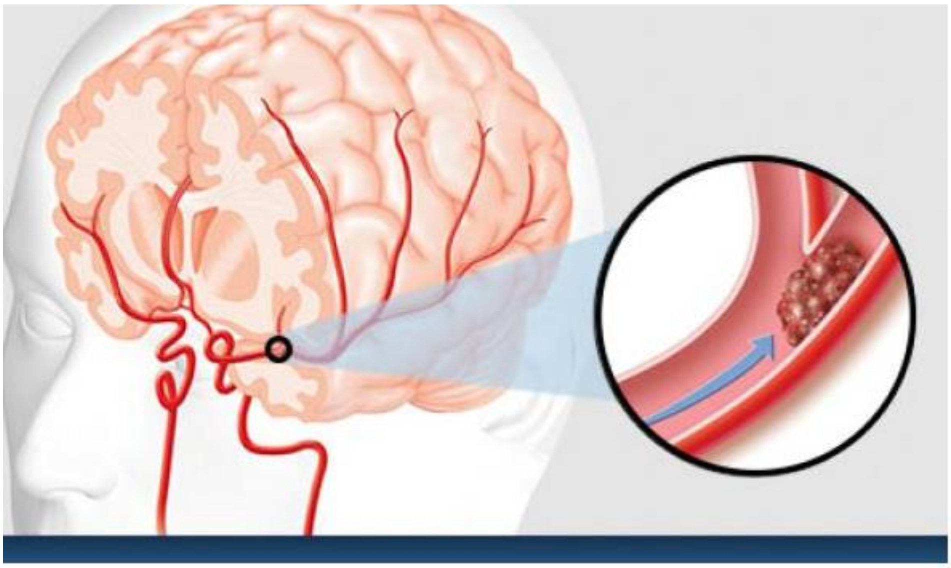

Figure 1.3 Transient ischemic Stroke [5]

3. Hemorrhagic Stroke: Hemorrhagic Stroke happens when there is either a leaking or bursting open blood in the brain, which applies pressure on the brain cells and hurt it. The spill blood is then spread in the areas of brain and skull. The main cause of the stroke is over-stress and weakness in blood vessel walls. The types of hemorrhagic stroke are intracerebral hemorrhagic and subarachnoid hemorrhagic.

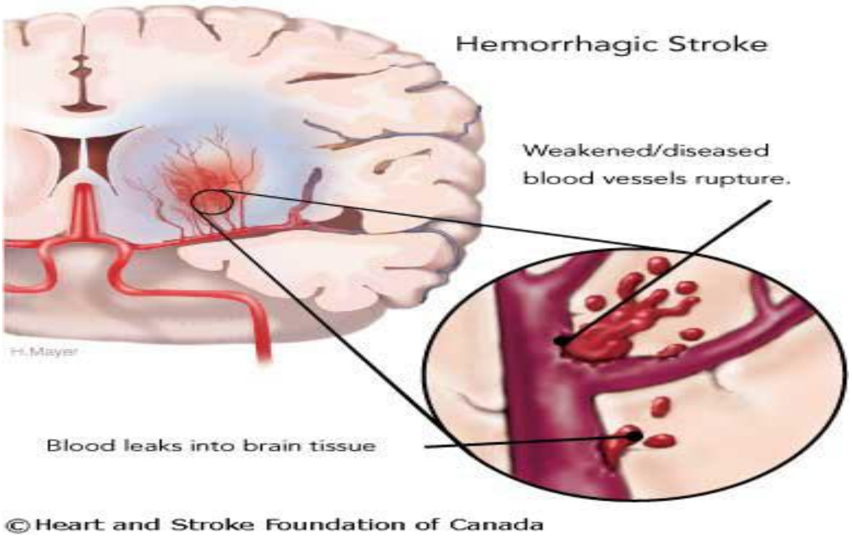

Figure 1.4 Hemorrhagic Stroke [6].

Intracerebral hemorrhagic: In this type, a blood vessel when spurt out and spills in the surrounding area damage the brain cells and those area which are beyond to this limit are damaged due to lack of blood in the particular area. The major cause of this type is due to high blood pressure, and over stress [2].

Subarachnoid hemorrhage: It causes due to the small but effective leakage in the brain. This leakage is small as compared to the intracerebral hemorrhagic but quiet prominent and can cause serious after affects in the body. The blood vessels may either widen or narrow down causing visible damage to the brain cells. The symptoms lead to severe and sudden headache [2].

1.3 Symptoms and Detection

There are no early or later stage symptoms of a stroke. It does occur very sudden and in the way that person do not realize or think about the stroke. Headache, dizziness, feeling sick and look pale are some of the symptoms of the stroke. The basic symptoms, which should not be ignored, are as follows:

- **Dealing with the problems of Aphasia**: when a person is experiencing a problem in speaking or slur in speaking the words, it could cause due to damage or injury in the language parts of brain [7].

- **Bell's palsy:** Bell's palsy is due to the sudden numbness, shaky feeling in the body or the paralysis in any particular part of the body. This is due to the result of harm to the facial nerve that controls muscles on the face [7].

- **Eye disorders:** sudden dim vision or totally black out in front of the eyes could be the one of the symptoms of the brain strokes [7].

- **Headache and walking abnormalities:** A sudden, severe headache leads to giddiness or mind alteration is the prominent significance of stroke. Advanced stages of stroke leads to the loss of balance and coordination with the whole body [7]. A very simple way of detection is performed by following the three easy steps:

  - Smile test: this test can help in finding if there is one side facial disorder developing in the patient. "Just try to smile by stretching the cheeks".
  - Stretch your arms to the fullest: usually a person suffering from the stroke is unable to fully extend his both hands on the same height.
  - Speak some complicate sentences: speaking of some common sentences with difficult in speaking can help to detect the slurring language, which could be an indication of the stroke. As an example "Don't cry if milk is spilled".

1.3.1 Scientific Diagnosis of Brain Strokes

The motor activity in a man's body is a composition of neurological in concert placed in particular cortex areas primary responsible for communicating each other in any state of period. The cooperation among the various parts of the motor system is quiet essential and influence that modulate motor behavior, attention and sensory perception [8]. Stroke affects the functional connectivity of the brain by depriving of oxygen and nutrients to tissues in the affected region causing them damage (formation of lesions) or death. In most cases, stroke compromises electrical activity (connectivity and communication) in the brain by damaging the white axonal tracts that connect and facilitate communication between spatially distributed cortical and subcortical regions [8]. The motor system in the human brain is composed of neuronal ensembles located in distinct cortical and subcortical regions that interact with each other temporally and spatially. The interaction is a complex functional balance caused by excitatory and inhibitory influences that modulate motor behavior, attention and sensory perception [8]. Stroke causes a structural lesion that disturbs the complex balance within the motor system and the functional network of neuronal ensembles in cortical regions in both the left and the right cerebral hemispheres including neuronal ensembles distant from the structural lesion [8].

If a structural lesion resulting from stroke affects critical cortical or subcortical regions or white matter connecting the critical regions, it disturbs brain balance and connectivity leading to functional impairment of sensory, attention or motor behavior [8]. Hemorrhage of the brain stem and the thalamus that maintain arousal leads to impairment of consciousness and damages to white matter in the corticospinal tract causes impaired dexterity.

1.4 Significance of the Study

If the risk is identified in preliminary stage, it could be detected and proper care and diagnosis can help in avoiding 98 % of risk to and devastation to human structure [7]. Intravenous injection of tissue plasminogen activator (TPA**)** is a term defined as a well-known access in finding out the world-wide community which is in danger. But in many cases related to stroke, the method has find out as not so much effective for the treatment. Today's ultra-modern world, continuous research has been carried out and giving a new outlook to dealing with the detection and managing the brain strokes [8]. As its quiet obvious fact that preliminary stage detection of the problem could reduce the risk of strokes in effective manner. EEG analysis of brain stroke can be diagnosed and can be treated if the symptoms persists are deal carefully. Despite the discovery of these advanced treatments, complete solution to get rid of stroke is still under cover. Hence considering the first stage detection to be very important in order to reduce the risk to human body and affecting various body-parts in a dangerous level [8], this study will primary focus to the following points:

- Explore the application of normalized transfer entropy measure on raw EEG data of stroke
- Construct EEG based directed brain network
- Quantify and plot the network of statistically important brain connections

1.4 Research Objectives

- Explore the application of NTE measure to construct EEG based directed brain network
- To quantify and plot the network for statistically important connections for both stroke and healthy subjects
- To determine information flow patterns during different tasks

1.5 Layout of Research work

Chapter 2 reviews of literature on encephalography EEG and brain connectivity in stroke.

Chapter 3 is a methodology section which explores the ways towards the design and implementation of the proposed detection method. In this chapter, the focus is towards the tools used for the utilization of the proposed idea. Use of the different figures will help in giving the better idea of the proposed idea and their usage.

Chapter 4 debates on outcomes of the implemented idea for EEG analysis in brain connectivity using different mental tasks. The screen shots will justify the results and explanations being done for them will give better prospective of the scheme

In conclusively, chapter five is titled as discussions and conclusion of the thesis. The final outcome for the whole work contributed to the research has been laid out by discussing the important facts. Further future research directions and guidance to new research had been mentioned.

Chapter 2

Background and Literature Review

2.1. Overview

This chapter discusses the utmost main features by deep investigation of related literature which builds up a strong platform to carry out the importance of the area of research. The chapter instigates with the necessary points of review of literature on EEG and brain connectivity in stroke and further examines the literature.

2.2 Review of existing EEG and brain connectivity in stroke detection schemes

Electroencephalography is a brain imaging method that measures electrical activity generated by neural activity in the brain. It is the measurement of electrical activity from the scalp using multichannel electrodes; the neurophysiological activity is caused by the firing of neurons in the brain [9]. EEG signals thus refer to a series of electrical impulses measured from systematic neural activities in the brain [10]. Active neuronal cells in the brain produce current flows. EEG records current flow resulting from synaptic excitation of the dendrites of neurons in the cerebral cortex [11]. Measurement uses sensors (electrodes) placed on the scalp in a pattern consistent with the international 10/20 standard electrode placement [12]. Recording of EEG signals can be bipolar (between two active electrodes) or mono-polar (between an active and a reference electrode) [10]. The recorded EEG signals are then plotted on a graph as voltage magnitude against time. The voltage of the EEG signals range between 10μV and 100μV. It provides a measure of the degree of synchrony between localized neural ensembles within the range of the electrodes placed on the scalp [13]. The frequency of EEG signals ranges between 0.1Hz and 100Hz but only the following four frequency bands (a-d) ranging between 0.5Hz and 30Hz are clinically relevant [10].

- Delta waves (δ): ultraslow waves having a frequency range of between 0.5Hz and 4Hz and varying amplitude. They are dominant in infants below one year and in adults during deep sleep.

- Theta waves (θ): slow waves having a frequency range of between 4Hz and 7.5Hz and amplitude of about 20μV. They are common in young children and young adults and indicate creative inspiration and deep meditation.
- Alpha waves (α): normal waveform having a frequency range of between 8Hz and 13Hz, and amplitude varying between 30μV and 50μV. They appear as a rhythmic activity on occipital cortex region of the brain. They are common in adults and are associated with relaxation state (closing eyes) but reduced or disappear during opening eyes (stress state).
- Beta waves (β): fast waves having a frequency ranging between 14Hz and 26Hz, and amplitude varying between 5μV to 30μV. They are symmetrically distributed and most evident in the frontal and central regions of the brain. They appear in all ages and are associated with active thinking and attention, and panic state.
- Other observed frequency bands that are less relevant in clinical use are gamma (γ) and Mu (μ).

- The Gamma waves are ultrafast and have a frequency range greater than 30Hz. They indicate movement of the right and left index finger, right toes and tongue movement. Mu waves have the same frequency range as Alpha waves (8Hz and 13Hz) but they appear on the motor cortex region of the brain. Mu waves indicate spontaneous (motor) activities in the brain. The normal frequency in adults for ultraslow signals range between 0.3Hz and 7Hz and for ultrafast signals the range is above 30Hz. However, the predominant frequency range is between 8Hz and 13Hz (alpha) and 14Hz and 30Hz (Beta) [12].

In the 1920s, Hans Berger recorded the first human EEG signals and discovered a correlation between changes in EEG signals and mental activities. Since then advancements in recording, measuring and analysis techniques have demonstrated the clinical significance of EEG signals in studying anatomic and functional architecture of the brain [10]. EEG has been since extensively used to investigate mental diseases such as Alzheimer and Epilepsy in addition to carrying out academic based research such as in understanding cortical rhythms in cognition, cognitive analysis and effects of meditation on the brain. Despite of its poor spatial resolution EEG is suitable in different circumstances when other techniques cannot be used. For example, unlike fMRI, EEG does not expose participants to strong magnetic fields. Also, radioactive material is not required for using EEG. High temporal resolution is one of its greatest advantages.

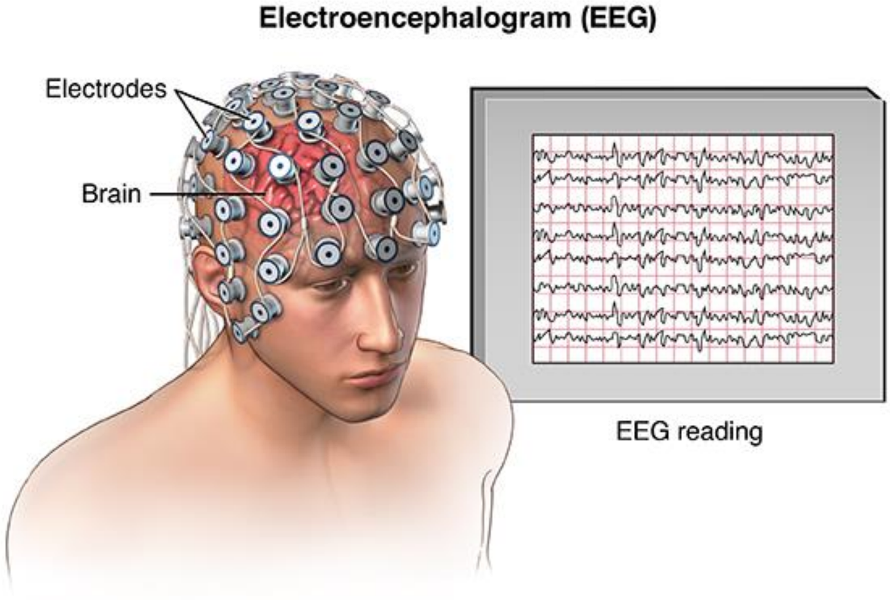

Figure 2.1 Electroencephalogram (EEG) [9]

Furthermore, EEG equipment is both light-weight and inexpensive thus is available to a wider range of research situations. More importantly, although EEG can be distorted by gross bodily movements by participants, smaller movements (such as eye blinks) can be easily removed from the data; this thus allows the design and implementation of a broad range of research paradigms, including language-based paradigms. It was in part because of the design flexibility, and in part the temporal resolution, that EEG was chosen for the research outlined in this thesis. EEG signals have made significant contributions to the contemporary understanding of the structural and functional connectivity of the human brain. They have underpinned theoretical and mathematical models used to describe electrical connectivity in the brain. The models have enabled non-invasive and in vivo characterization of functional connectivity of spatially distributed regions of the brain during both normal and pathological conditions. Different mental tasks produce different values of voltage and amplitude recorded as different EEG signals. The differences in EEG signals provide an approximation of electrical activities in the brain during normal task and rest states as well as in pathologic conditions. Statistical analysis (correlation, coherence function and synchronization methods) of the EEG signals thus enables the diagnosis of brain disorders such as stroke that alter functional connectivity. Stroke interrupts or reduces blood supply to the brain causing changes in the Blood Oxygen-Level Dependent (BOLD) signal associated with functional connectivity between related cortical regions of the brain. For instance, stroke causes statistical differences in the Amplitude of Low Frequency Fluctuation (ALFF) BOLD signal during resting state [14]. In the case of structural lesion resulting from thrombotic or hemorrhagic stroke, the cortical regions generate lower frequency EEG signals. Other indications of distorted EEG signals indicating stroke or other neurological disorders are a considerable reduction in amplitude, a notable decrease of the dominant frequencies beyond the normal limit and presence of spikes or abnormal patterns in the computed EEG graphs [11]. Besides clinical diagnosis of neurological disorders, EEG signals have been applied in monitoring alertness, coma and brain death; detect damaged areas in the brain after head trauma, control the use of anesthesia, locate seizure origin in epilepsy, monitor brain development, investigate sleep disorders and test drugs for convulsive effects [11]. EEG signals also contributed to the development and advancements in Brain Computer Interface applications. These applications assist disabled people to use their brain to control external devices such as wheelchair and prosthesis [10].

2.6 Brain connectivity

EEG signals measure brain connectivity. Brain connectivity refers to the approaches of characterizing how different neuronal ensembles in spatially distributed regions of the brain connect with one another to form networks, and how they interact with one other in these networks during normal task and rest or during pathological conditions. The two main categories of brain connectivity are functional and effective connectivity [13]. Together, functional and effective connectivity techniques help to characterize the neurophysiological nature of the brain as a set of interconnected elements embedded in a larger unit [15].

Functional connectivity in the brain measures temporal correlation in the activity of different neuronal assemblies in spatially distributed regions of the brain regardless of direct structural anatomic links [16]. The main assumption behind functional connectivity is that parts of the brain play specialized roles in perceptual or motor processing and the specialization is anatomically segregated within these parts. The specialized regions have functional integration with many other specialized areas during brain activities. The assumption of localized functional connectivity was based in early findings that associated structural lesions resulting from stroke in specific part of the brain caused cognitive deficits. Functional connectivity thus measures the statistical dependency of remote neurophysiological events [13]. Functional connectivity applies to changes in both task-dependent and resting state (in the lack of overt task). Task-dependent functional connectivity measures changes in functional connection between neural elements as the demand of task changes whereas resting state functional connectivity measures the pattern of functional connections and relates them to the anatomic structure. The assumption is that in resting state anatomic connections between neural elements mediates functional connectivity. Correlations of resting state connectivity provide measures of the integrity of functional networks and connectivity in the brain [16].

Effective connectivity in the brain conceptualizes the influence of one neural assembly on another at synaptic or assembly levels underpinned by the assumption that a simple neural circuit would produce the same temporal relations as experimentally observed between two neurons in a neuronal ensemble [17]. Unlike functional connectivity, which measures pairwise interaction between neuronal ensembles using correlation or covariance, effective connectivity studies the systematic variations in the activities of neuronal ensembles [13]. Effective connectivity incorporates structural (anatomic) connections and simultaneous interactions of several neuronal ensembles to measure the effect of one neuronal ensemble on another. The underlying assumption is that a change in one neural element causes a change in the influences of another connected neural element. Thus, looking at the activity of one neural element in isolation fails to factor in the afferent affluent of another connected neural element [16]. Effective connectivity differentiates top-down and bottom-up effects in interactions between neuronal ensembles. Effective connectivity can measure category specific responses in the ventral occipitotemporal lobe considered a top-down effect. In estimating effective connectivity using Dynamic Causal Modelling (DCM), [18] observe category specific sensory areas change their effects in relation to stimuli but higher-order association areas do not change their effects suggesting a bottom-up effect in category specific connections. Effective connectivity shows reciprocal connections between neural elements underlie category specific connections, suggesting besides hierarchical representations of neural elements and their connections, the nature of neural connections is also dynamic and interactive [16].

2.4 Literature Survey

The literature survey has been reported in detail thereafter:

Nagata, [1988]; Faught [1993] et al. [19, 20, 21] presented an EEG data obtained from ischemia patients contains predictable changes such as reduction of fast activity and increased amplitude in the slow-wave band. Repeatable changes can be observed in EEG for stroke patients as cerebral blood flow (CBF) falls to low from normal. Changes in amount of cerebral blood flow creates abnormal changes in EEG, these changes are categorised into four categories. Decrease in amplitude of faster frequencies may be observed in EEG at CBF 25-35 ml/100g/min. Theta frequencies may get affected in EEG as the CBF lowers to 18-25 ml/100g/min.

Phan Luu, [2001] et al. [21] EEG is sensitive to metabolic and ionic disturbances caused by ischemia, therefore it can be a useful tool for detecting stroke and monitoring affected area (lesions). In this study Fast Fourier Transformation was performed on average reference data by focusing on theta and delta frequencies. Results of the study demonstrated that spectral analysis of five of six stroke patients, correspondence between ischemic-related EEG changes and patient symptoms and CT, MRI investigations.

Honey and Sporns [2008] et al. [23] in this regard, studied how the focal brain lesions affect the synchronization of cortical networks. For this study, they have used connectivity profiles of 47 areas with different oscillator models. They found that lesions to ‘connector hubs’ affected larger areas of the brain networks than lesions to provincial hubs. Connector hubs are the regions like parietal areas 5, 7a and frontal eye fields with long-range connections linking to nodes in different clusters whereas provincial hubs are regions such visual are V4 or somatosensory are SII that mainly connect to adjacent areas or areas within the same functional cluster. Therefore, according to the authors networks stroke which affects parietal and pre-frontal areas will affect the integration process all over the system for the rapid re and desynchronization of the functional brain networks.

Alstott [2009] et al. [23] have studied effects of focal lesions on functional brain networks across the scalp using structural connectivity data and graph theoretical measures based on a neural mass model. They have published similar results after this investigation. They have used diffusion tensor imaging data to study connectivity between distant regions and found that the subjects affected by lesions due to stroke have reduced communication among the brain regions.

De Vico Fallani [2009] et al. [24] used graph theoretical measures using EEG data to study the functional connectivity during preparation and execution of a finger tapping task, and reported results conformed to results discussed above. The results indicate that the subjects affected by stroke showed reduced capacity to integrated information between distant brain regions, this phenomenon was observed due to lower global-efficiency index. They also showed that significant number of nodes was disconnected and increase within other nodes. Therefore, the authors inferred that the regions affected by lesion have decreased connectivity, which the brain tries to compensate by increasing the connectivity in other regions but this does not overall connectivity of the brain due to drastic reduction in integration of the information. Coherence analyses of EEG data obtained from recovered stroke patients also showed reduced functional connectivity in the cortico-cortical region of the lesioned hemisphere and higher number of connections in contralesional hemisphere.

Van Meer [2010] et al. [25] authors compared the performance of above-mentioned subjects and results are further supported by functional MRI studies which investigated the impact of stroke on functional connectivity. For example, functional brain networks of rats recovering from experimentally induced stroke were investigated for connectivity in sensorimotor systems while functional connectivity within the hemisphere was not disturbed in animals although they showed behavioral changes, contralesional functional brain connectivity was increased with larger lesions extending onto the cortical surface. Furthermore, as the connectivity between sensorimotor regions of the two hemispheres increased, sensorimotor functions showed improvement.

Carter [2010] et al. [26] came out with the advanced version and showed that their results are confirmed by functional MRI study with human patients using resting state data. This study revealed that the loss of coherence in inter-hemispheric blood oxygen level-dependent fluctuations between homologous motor regions predicted behavioral deficits, while changes in intra-hemispheric coupling were not correlated with motor performance of the patients. Unaffected inter-hemispheric connectivity indicates that language tasks are not affected much due to aphasic stroke. Functional connectivity between left and right dorsal parietal cortex were compensated which results in recovery from visuospatial neglect. Stroke induces changes in functional regions which are not directly connected to the lesion are affected although they seem to be dependent on lesion localization.

Nomura [2010] et al. [27] studied the Impact of stroke lesions on functional networks obtained from resting state data while engaged in cognitive control. They found that brain connectivity within the local clusters distant from the lesion was reduced when compared with other networks which are not affected by the lesion. This implies that lesion damages go beyond the area, however they are limited to the borders of existing network connections.

Grefkes, Fink [2011] et al. [28] rightly reviewed about Stroke disrupts the connectivity between cortex and spinal cord, and may also cause disruptions in brain networks among different cortical areas distant from the lesion. The concept of ‘diastasis’ introduced by Russian-Swiss neurologist Constantin von observed reduced activity in the adjacent regions of damaged site. Therefore, as by network simulation studies have indicated that the extent of functional brain networks strongly depends on location of the lesion within the network. However, an ischemic lesion may also affect functional connectivity of cortical areas in the regions distant from the lesion. “Taken together, resting-state functional MRI data sampled across different functional systems and species strongly suggest that functional outcome after stroke can be predicted by how both hemispheres are coupled in the absence of any active task.”
Forman and Claassen [2012] et al. [29] proposed other morphological method of considerable suppression of frequencies might appear with further reduction of flow to 12-18 ml/100g/min. All frequencies would be suppressed when the CBF drops below 8-10 ml/100g/min.

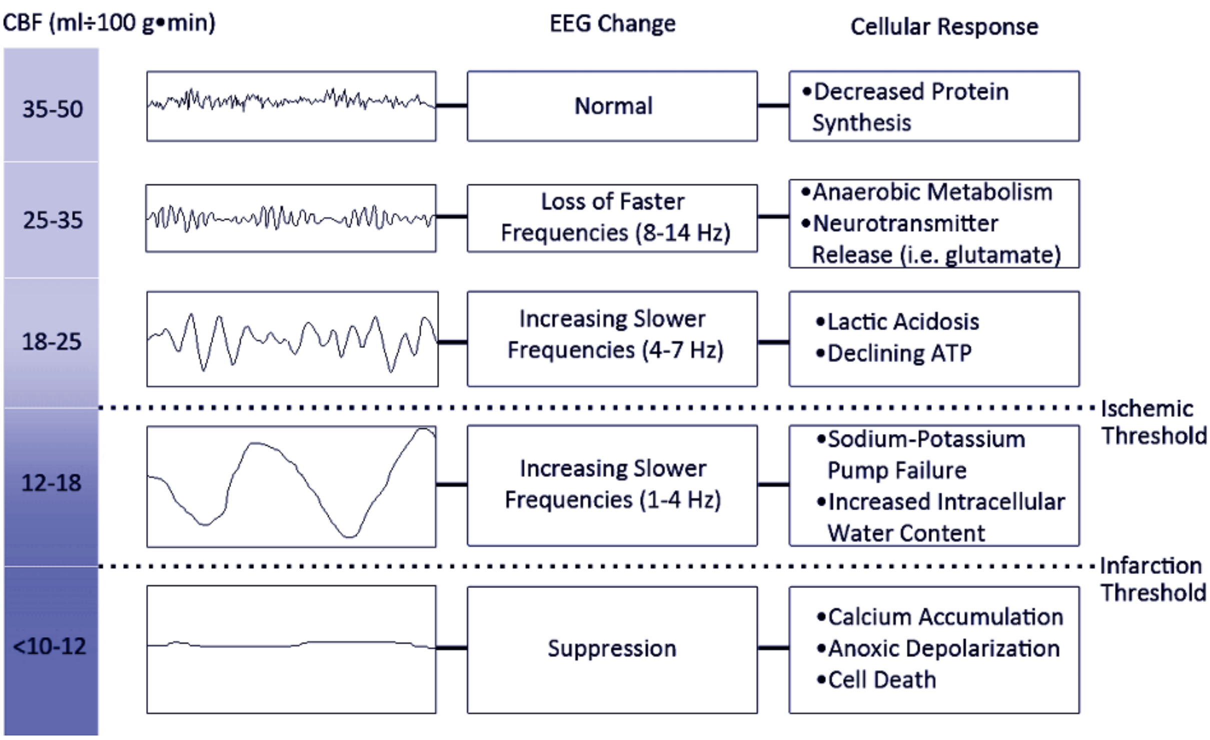

Figure 2.2: Relationship between cerebral blood flow and EEG (Forman and Claassen, 2012)

2.5 Effective connectivity after Stroke

As discussed before, effective connectivity can estimate the causal effects of one area over the other, unlike the functional connectivity, which only shows correlations between the regions without directional component. Knowing about the region causing the influence allows the researchers to further investigate the specific role of the region for a given task. For example, analyzing effective connectivity in healthy subjects performing rhythmic fist closures with the left or right hand showed that neural coupling among key motor areas is symmetrically organized [27]. Furthermore, [29] carried out analysis using dynamic causal modelling which revealed that motor areas such as SMA, M1 and premotor cortex showed increased connectivity with each other. Whereas, stroke patients have showed several changes in this pattern of normal connectivity intra and inter hemispheres. Especially, the connectivity which does not depend on movement between ipsilesional SMA and isilesional M1 drastically reduced compared to healthy controls. Performing a motor imagery task, and found no difference in regional blood oxygen level-dependent activity compared with healthy controls. In contrast, effective connectivity analyses by means of structural equation modelling revealed that neural coupling within an extended motor network was abnormal in the patients' group.

2.6 Summary

The paper by Bajaj [2015] [35] provides a modern and evolved method for demonstrate that "therapeutic interventions, such as repetitive transcranial magnetic stimulation, which aims to interfere with abnormal cortical activity, may correct pathological connectivity not only at the stimulation site but also among distant brain regions". The brain is a combination of cortical and subcortical areas which enough intelligent to communicate via excitatory and inhibitory circuits, and hence controls the whole motor activities. This whole complex system is get disturbed even with a slight stroke and hence capable of damaging the whole or partial body. A stroke can be either temporary or permanent harms the motor system, thus can make numerous of problems to the outside of the body. The author focussed on network analysis of effective connectivity on neuroimaging data and shows that how strongly it disturbs the motor system and interaction between motor areas are effected and how changes in connectivity relate to impaired motor behaviour and functional recovery. In summary, analyses of connectivity driven treatment strategies to promote recovery of motor function in patients.

CHAPTER 3

METHODOLOGY

3.1 Data

Detection of risk of stroke in its early stage represents one of the major problems recently facing the current medical industry for an effective design of high performance stroke stoppage algorithm. On the other hand, they provide a comparison of results, which is useful for the verification of performance metrics. The chapter presents important details about the methodology being used in the thesis. The evaluation criteria known from literature analysis are introduced and described. The presented strategy is used for examining the following chapters of this research work.

Before discussing the performance evaluation criteria we have to define NTE-Normalized Transfer Entropy. "An information theoretic measure is derived that quantifies the statistical coherence between systems evolving in time. The standard time delayed mutual information fails to distinguish information that is actually exchanged from shared information due to common history and input signals. In our new approach, these influences are excluded by appropriate conditioning of transition probabilities. The resulting transfer entropy is able to distinguish effectively driving and responding elements and to detect asymmetry in the interaction of subsystems" [33].

3.1.1 Ground Truth

Several approaches are available to measure the effective connectivity. Dynamic causal modelling (DCM), Granger Causality, Directed Coherence and phase-slope index are some of the extensively used in research. DCM aims at inferring the causal architecture of the coupled or distributed dynamical systems and are modelled on ordinary differential equations. DCM was mainly developed for measuring the coupling among brain regions [30]. Physiological and biophysical sequence of events would produce observable functional measurements, which can be measured by using state-space continuous-time models in DCM. If two neural connections have effective connection between them, then current value of one of the networks can be predicted using the past value of the other network. This methodology is known as Granger Causality (GC), which was proposed by Wiener and consolidated by Granger [31]. Original invention of GC was linear which was extended to nonlinear models later. Directed coherence (DC) is one more method to measure effective connectivity, which is closely related linear GC introduced by Saito and Harshima [33]. DC relies on vector autoregressive (VAR) models for computing causal relationships between two systems defined as time series. Two most prominent DC-based connectivity measure is directed transfer function (DTF).

3.1.2 Transfer Entropy

Transfer entropy is the amount of information transferred from one random variable to another random variable. Transfer entropy from X to Y is not same as from Y to X. Suppose that the two random variables $X = x_t$ and $Y = y_t$ can be approximated by Markov process, as proposed by Schreiber, Transfer Entropy is represented from X to Y is represented as

$$TE_{X\to Y} = \sum_{y_{t+1}, y_t^n, x_t^m} p(y_{t+1}, y_t^n, x_t^m) \log\left(\frac{p(y_{t+1}|y_t^n, x_t^m)}{p(y_{t+1}|y_t^n)}\right) \quad \ldots 3.1$$

Transfer entropy consists of both directional and dynamical information. Transfer entropy can be rewritten as a conditional mutual information [32]. $TE_{X\to Y}$ Can be considered as the information about future observations y_{t+1} obtained from the past observations of y_t^n and x_t^m minus the information about future observations y_{t+1} gained from past observations of y_t^n only. TE ranges from $0\ to\ \infty$.

3.1.2.1 Advantages of Transfer Entropy:

1. Transfer entropy does not require the definition of type of interaction beforehand, therefore it allows exploratory investigations [31].

2. Interactions in the brain are nonlinear in nature; transfer entropy is very useful in measuring nonlinear interactions.

3. There could be interaction delays between different regions of the brain. Transfer entropy can be used to measure effective connectivity in spite of such delays between the two signals.

4. Transfer entropy is suitable for the applications involving electro- or magnetoencephalography signals since this measure immune to linear cross-talk between two signals.

3.2 Processing Steps

This research used an existing data collected previously by a research team [36] in the Brain Signals Laboratory at Flinders Medical Centre. For the purpose of this study, only 9 stroke subjects were used and compared with 9 control subjects.

3.2.1 Subject Selection

Data has been collected from both normal controls and stroke patients after obtaining ethical approval from the Flinders Clinical Research Ethics Committee. Written informed consent was obtained from all the participants before proceeding with data collection. Subjects indicated their approval to participate in the study without individual approach, in other words no one was convinced or forced to participate in the study [36].

Healthy controls were individual volunteers or matched controls for individuals. Matched controls were taking part in a study to analyse the impact of disease on gamma range (i.e. 30-100Hz). Written, informed consent was obtained from all the subjects. Verbally based estimation of intelligence was measured by conducting National Adult Reading Test (NART), which was used to derive Wechsler Adult intelligence scale WAIS-R.

3.2.2 Preparation and EEG collection

EEG recording from healthy controls was undertaken with standard scalp preparation using bilateral ear referencing, 200 Hz sampling rate and 500 Hz low-pass filter. Digital EEG recording was employed with 128 channel EEG system (Comp medics, Victoria, Australia). Recorded data was referenced using a common average head reference offline. Faraday cage was used to minimize the interference from electrical equipment where subjects were seated. The subjects took eight cognitive tasks and two baseline tasks eyes-open and eyes-closed which were presented in a standardized fashion (using Presentation software version 9.2 (NBS http://www.neurobs.cm)) on a computer screen, while instruction were presented auditory and visually [36].
A simple push button panel was used to respond to the questions and was recorded to calculate the accuracy of responses. Subjective fatigue was noted down from the subjects throughout the test.

3.2.3 Mental tasks

All subjects have undertaken 9 tasks with 30 min per subject. Tasks were presented in 3 blocks and task presentation was randomized within those three blocks.

3.2.3.1 Block 1:

Baseline eyes-open task: subjects were instructed to watch the computer screen for one minute by sitting in front of it.

Baseline eyes-closed task: subjects were instructed to face the screen of the computer in eyes closed state for one minute by sitting in front of it.

Visual discrimination task: an object is displayed in shape with the subject being required to find it amongst the four choice shapes shown below it. Visual-Perceptual Skills (M. Gardner, Psychological and Educational Publications) have been modified for this purpose.

Auditory discrimination task: twenty word pairs are presented to the subjects who are instructed to identify whether each pair of words are same or similar. Auditory Discrimination Test (ADT) was modified for this purpose.

Finger tapping task: a sensitive touch pad was utilized for this task. Subjects were required to tap this pad as far as possible for 10 seconds with the index finger. This test was repeated three times with each hand.

3.2.3.2 Block 2:

Reading task: subjects are instructed to read from a passage of text from “Danny Champion of the World” by Roald Dahl. Subjects are ensured to read the entire period of 30 seconds of time by choosing a passage lengthier enough. The subjects were required to answer three questions related to the passage to ensure that they have really read the passage.

Verbal working memory task: The subjects are presented with a list of unrelated words and are asked to repeat the words after all words are presented. Subjects are required to remember the list of 12 words presented to them and had to recall immediately. In each of the four times the list presented, the subjects have to recall immediately. If the subject cannot recall, then the subjects are presented words visually along with distractor words. This test was modified from the Auditory Verbal Learning Test (AVLT).

3.2.3.3 Block 3:

Subtraction task: the subjects are given two numbers. Instructions are given beforehand to subtract one from the other in the head, i.e. they are not given pen/paper or calculator for the task. For example, the subjects were given two numbers 500 and 7. The subject is asked to subtract 7 from 500 and continue to subtract 7 from the answer. The experimenter may interrupt the subject to know what number is currently subtracting from. Then the subject needs to speak out the number and continue with the subtraction until the number reduces below 7.

Maze task: a maze is presented on a computer screen which contains a hidden pathway. Subjects are instructed to learn and remember the hidden pathway. Manual key-press-initiated cursor movements are utilized to discover the path. Then the subject was required to make efforts to complete the path accurately two times in a row. This needs to be completed in six minutes.

Visual rotation task: two shapes are presented on the computer screen, one of which could have been rotated and/or mirror-imaged. The subjects were required identify whether the shapes were mirror-images or not, irrespective of the rotation. This task contains four trials.

The overall methodology can be simply explained by the following block diagrams. Figure 3.1 and 3.2 show how the process is working in a flow in order to identify the brain strokes.

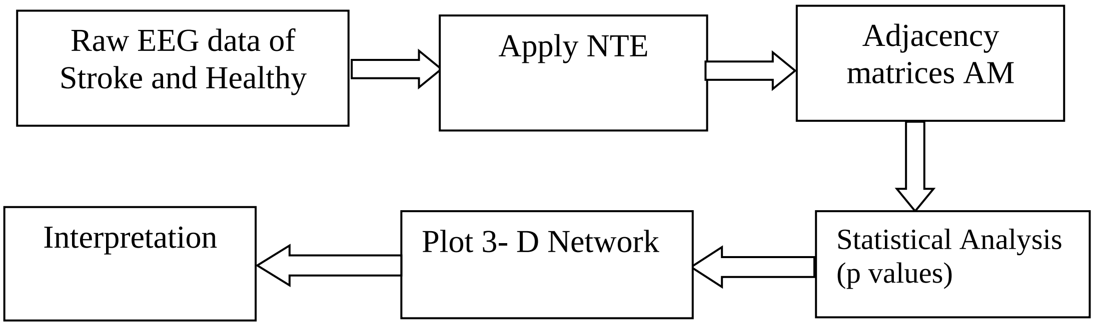

Figure 3.1 Basic block diagram of the methodology

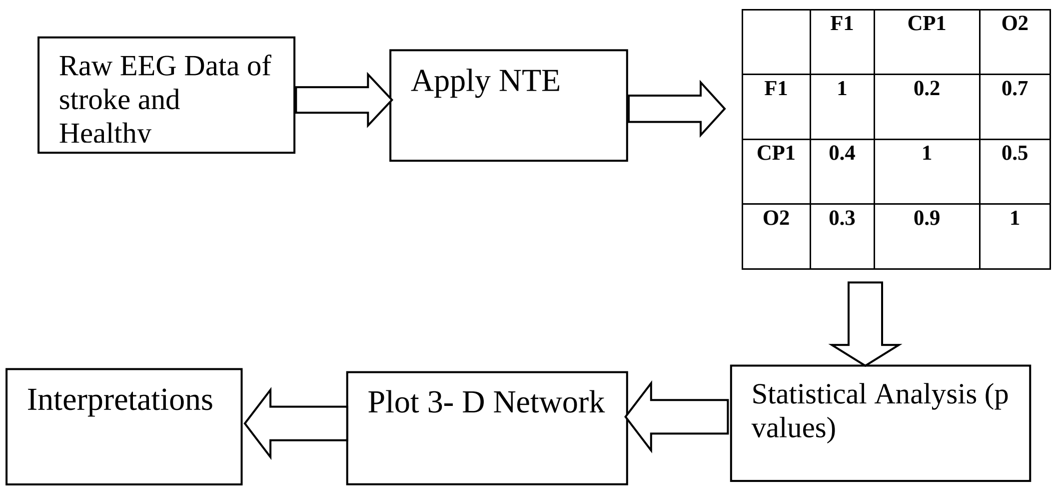

Figure 3.2 processing steps of methodology

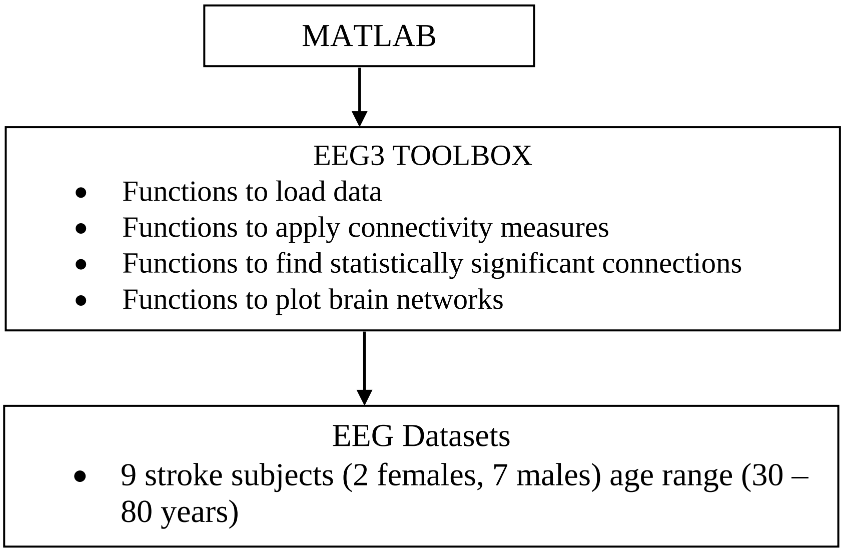

Figure 3.3 Matlab functioning for EEG Analysis: Brain Strokes

3.4 Summary

This chapter identifies the various procedures, which we follow for strokes detection. The whole process methodology is crushed in one simple diagram as shown in figure 3.4.

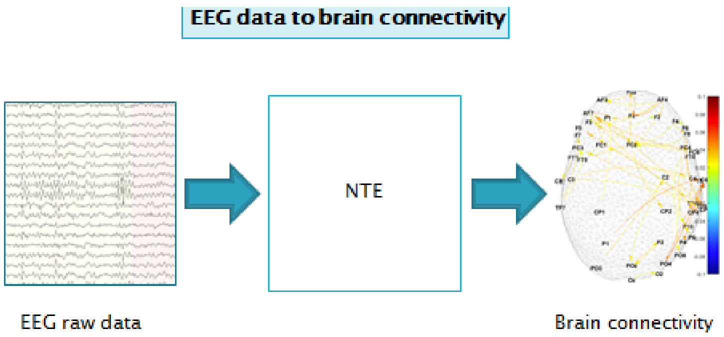

Figure 3.4 EEG data to brain connectivity

Finally, the chapter lists following principle steps that have been used in this research.

- Pre-processing of image is executed from the data set obtained as explained above.
- Extract the NTE with the mathematical morphological methods.
- We propose to use the AM for the matrices solving and making the system bit simple.
- Re-examination is done by statistical analysis and then data is handed by the next step for the 3-D plot of the image.

CHAPTER - 4

RESULTS & DISCUSSIONS

The chapter details the results collected after implementing the idea on MATLAB. The benchmark for the performance evaluation shows the rigidness of the model. The results have been collected out by several mental tasks including reading, auditory, subtraction and finger tapping among others in 9 patients with multilateral stroke, the main challenge was to analyze that the anatomic lesion affects the functional brain network on multiple levels.

4.1 Results

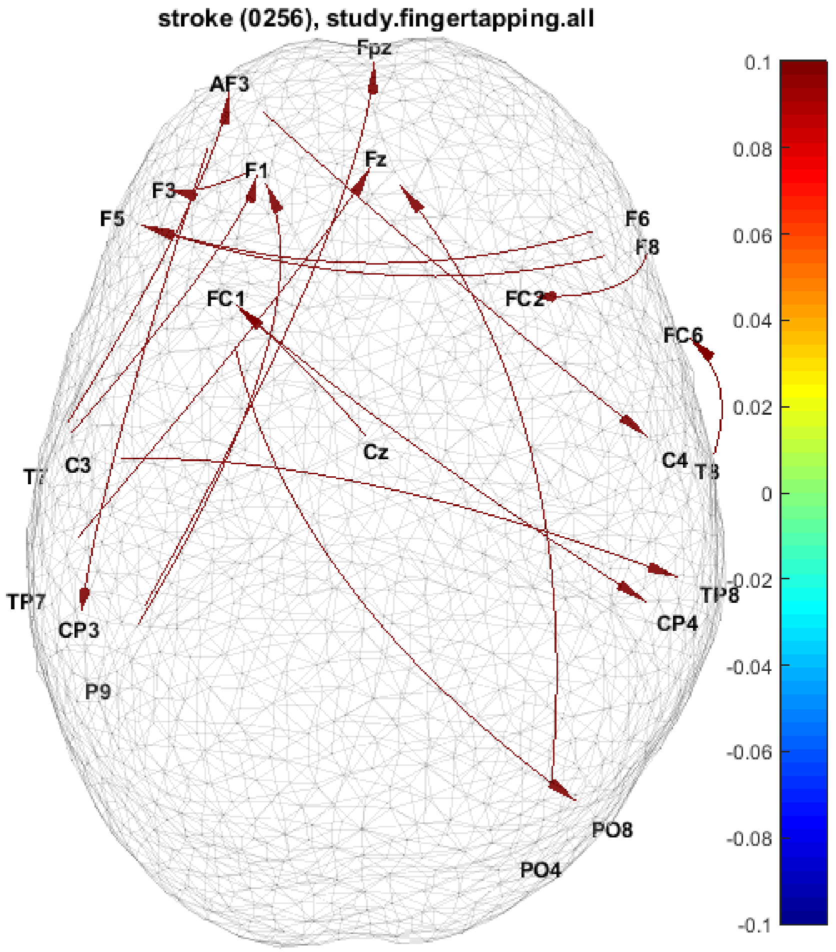

Figure 4.1 brain network for stroke subject finger tapping

Figure 4.1 shows the statistically significant connection between different brain regions (channels labels). Each arrow represents the direction of information flow between one brain area to another. The magnitude of the information flow is represented by the color of the arrow; the blue reflects low magnitude and the red reflects high magnitude. This figure shows the application of the methodology used in this study on the EEG signal of a stroke subject (ID 0256) while preforming a finger tapping task.

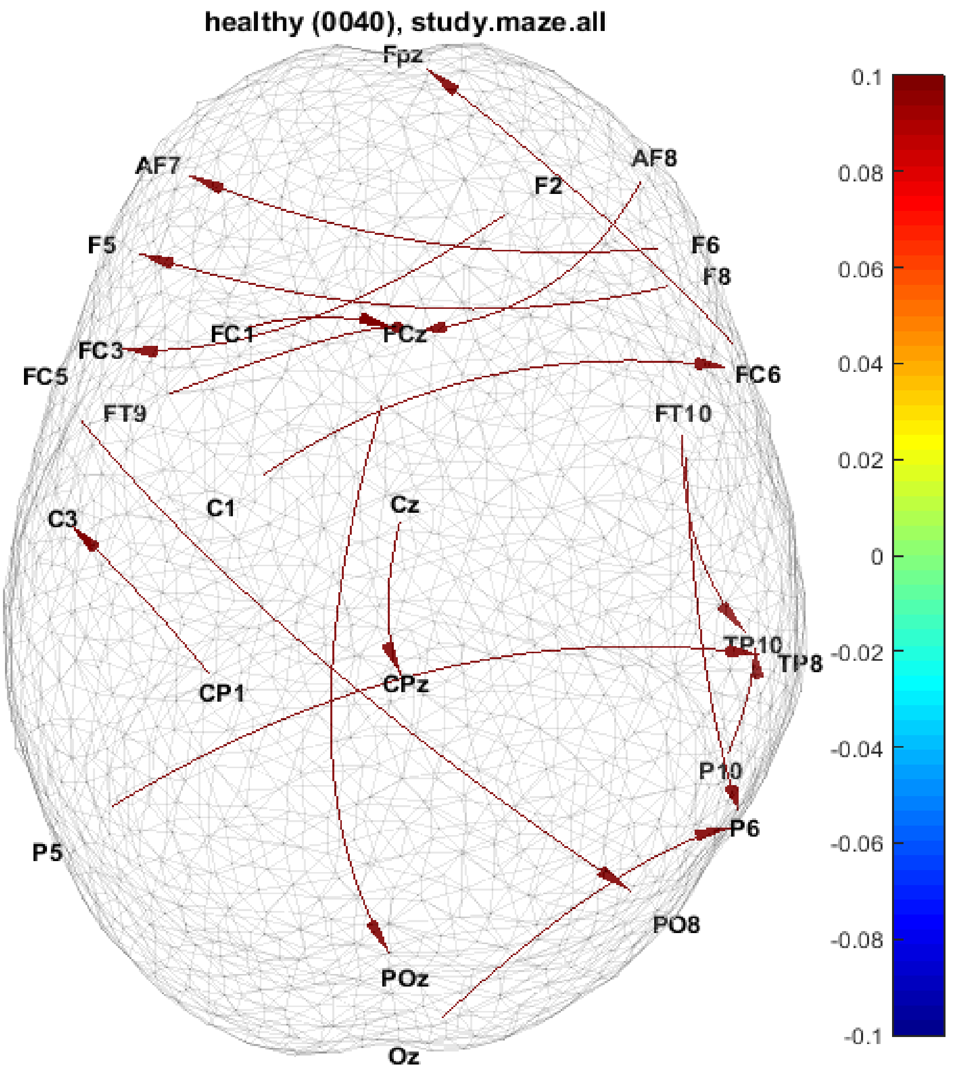

Figure 4.2 Brain network for healthy subject maze

In Figure 4.2 the figure revels the outcome of the used methodology on a healthy patient with the identification number of (ID 0040). The task was performed during the recoding of this data is maze. By maze the data means that it will solve the problems in its own intelligent way. The color code used here is to represent the movement of signals in the brain from one end to other. If the channel flow of signals is being reoriented by the blue shows the low magnitude while the red colour shows the high magnitude which is desirable and in our healthy subject the flow of signals from one end to other is laid down by high magnitude

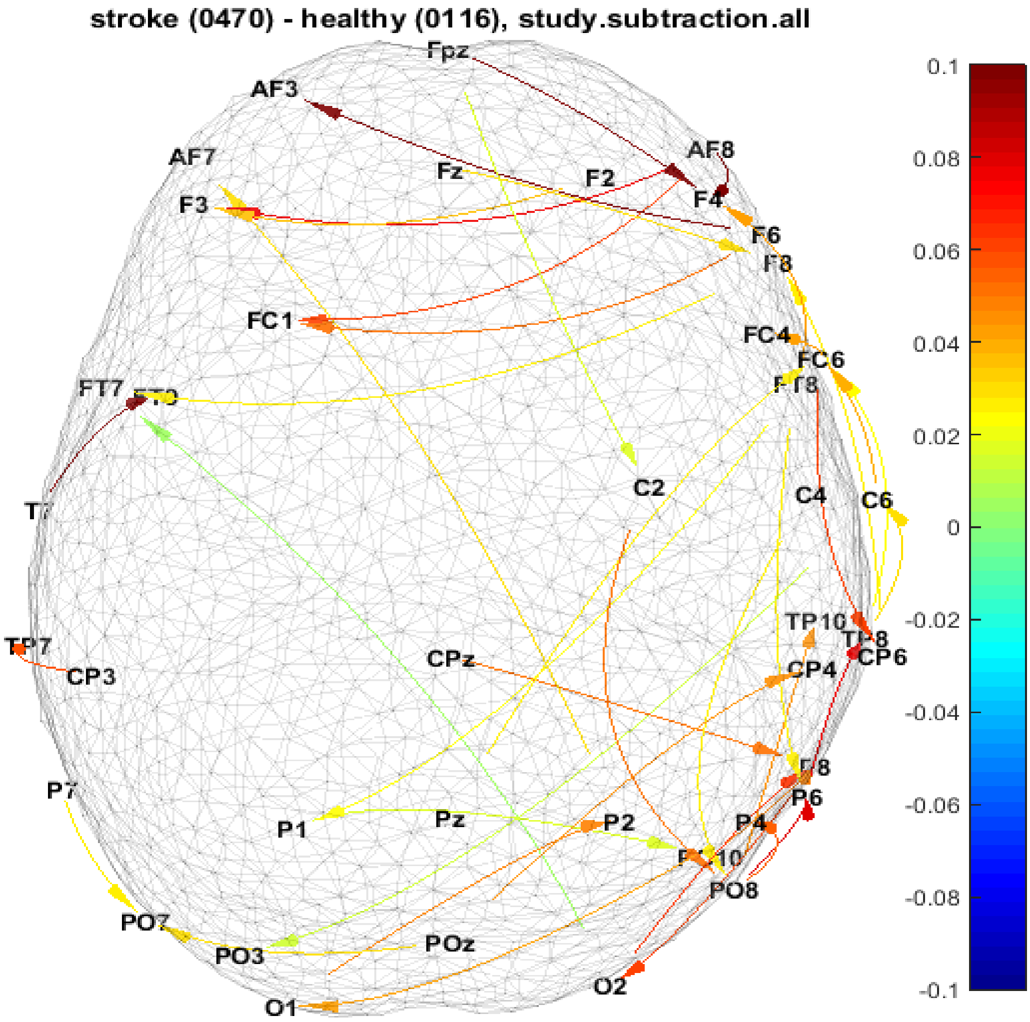

Figure 4.3 Difference between two brain networks

In figure 4.3, the plot is for the differences in adjacencies matrices outcome from the application of NTE on a stroke subject (ID 0470) and a healthy subject (ID 0116). Here the subjects are subtracting the two numbers in the way being mentioned in the methodology subtraction task. The outcomes shows that after all interruptions the task is being performed and the subject has made the calculations till the desired value is achieved

4.2 Conclusion

The chapter is summarized by the following points:

- The differences in connections of two brain networks are plotted using the methodology described
- This methodology identifies statistically significant differences in connections in both stroke and control subjects

CHAPTER-5

SUMMARY AND FUTURE SCOPE

5.1 Summary

Although stroke has helped us understand the brain, stroke is one of the biggest killers and leading cause of disability. It is a neurological disorder characterized by interrupted or insufficient blood supply to certain parts of the brain. There are an estimated 750,000 incidents per year. Of these, 15% die while 80% recover with persistent disability. Stroke and many other neurological disorders have been examined with many techniques and methods, one of which is brain connectivity measured from EEG data. EEG data obtained from stroke contains predictable changes such as the reduction of fast activity and increased amplitude in the slow-wave band. Repeatable changes can be observed in EEG for stroke data as cerebral blood flow (CBF) falls to low from normal Brain connectivity is classified into structural, functional and effective connectivity. Anatomical links define the structural connectivity, whereas functional connectivity is more logical in nature with the existence of temporal correlations between the elements of the brain. Effective connectivity, on the other hand, is the causal relationship between them. Stroke disrupts the connectivity between cortex and spinal cord, and may also cause disruptions in brain networks among different cortical areas distant from the lesion.

The methods were successfully applied on real EEG data. For all subjects and tasks, there were no statistically significant differences found in connectivity patterns consistently related to the lesions' locations.

The results show statistically significant connections in different regions of the brain for individual subjects and tasks. However, it is difficult to conclude whether these connections are due to brain activity or due to other sources (e.g. ocular, muscular, etc.). Also, the methods depend on the comparison between individual stroke subjects with their matched control, and this could be biased by the individual variation in both subjects. This is best addressed by increasing the number of subjects available for the study.

5.2 Future Scope

Today there is much interest in detection of brain strokes so as to stop the decay of person's health in early stages especially in women. Currently, the algorithm for identifying strokes from real raw EEG data is not accurate due to the possibility of interference of signals from several sources rather than brains origin. Probably, cleaning the EEG data is a primary step in order to achieve the desired outcome. Therefore, more research will be needed in the future. The study may be carried on in future with following direction:

- Increase the number of disease participants to increase averaging and improve accuracy.
- Better prune or clean the EEG data of artefacts to avoid contaminating effects.
- Create an average model for the control samples to reduce the effect of individual variation.

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