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Seed-based Analysis of Functional Connectivity of Hippocampal Network of People Suffering from Clinical Depression

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Preface

Abstract

The absence of biological markers makes it exceptionally difficult for neurologists to diagnose a person with a mental disorder. Currently, diagnosis of mental disorders is based on behavioral observations and patient-reported symptoms and the Diagnostic and Statistical Manual of Mental Disorders (DSM) classification. Although there have been thousands of studies revolving around the implementation of various imaging modalities for deciphering the etiology and the physical cause of several mental disorders, the findings from these studies do not appear amongst the diagnostic criteria. Meaning that the findings from these studies are not used for diagnosis purposes. A critical barrier to the clinical translation of many findings is the reverse inference fallacy as neurological disorders are multifaceted and are influenced by more than one factor and neuroimaging results can be heavily influenced by external factors such as patient movement and instrumental artifacts. However, neuroimaging for diagnosis of mental disorders seems promising in the future and as a matter of fact, a bold (choose correct word here) minority have already started to implement neuroimaging techniques such as fMRI, SPECT, PET for the diagnosis of psychiatric disorders. Nevertheless, there is no solid molecular or imaging basis that is widely accepted for the assessment of mental disorders. Here in the proposed research we plan to evaluate functional network connectivity of the hippocampus in patients with Major Depressive Disorder based on their MR images and investigate the changes in the brain network compared to that of healthy controls matched according to age and gender.

Abbreviations

ACC Anterior Cingulate Cortex

AFNI Analysis of Functional Neuroimages

ASN Anterior Salience network

BDI Beck Depression Inventory

BOLD Blood Oxygen Level Dependent

CA Cornu Ammonis

DG Dentate Gyrus

DMN Default Mode Network

DSM Diagnostic and Statistical Manual of Mental Disorders

ECN Executive Control Network

EEG Electroencephalography

fMRI Functional Magnetic Resonance Imaging

HC Healthy Controls

HPA Hypothalamic Pituitary Adrenal

ICA Independent Components Analysis

ICD International Classification for Diseases

MDD Major Depressive Disorder

MFC Medial Frontal Cortex

MFG Middle Frontal Gyrus

MR Magnetic Resonance

OFC Orbitofrontal Cortex

PET Positron Emission Tomography

PMC Premotor Cortex

rFPDD Recurrent Familial Pure Depressive Disorder

ROI Region of Interest

rs Resting State

rsFC Resting-state Functional Connectivity

SCA Seed-based Correlation Analysis

SPECT Single-Photon Emission Computed Tomography

sMRI Structural Magnetic Resonance Imaging

SNRI Serotonin and Norepinephrine Reuptake Inhibitors

SSRIs Selective Serotonin Reuptake Inhibitors

vPFC Ventrolateral Prefrontal Cortex

Contents

1 Introduction

1.1 Major Depressive Disorder

Major Depressive Disorder, generally abbreviated as MDD, is one of the most common and serious mental disorders. MDD is also referred to as clinical depression, or just depression as well. MDD can be characterized by an array of distinct symptoms; persistent feeling of sadness, feelings of low self-worth and guilt, and overall reduced ability to take pleasure from activities that previously were enjoyable are a few symptoms prevalent in MDD. Although, the exact symptoms of depression may vary from person to person, depending on their upbringing and various socio-demographic variables such as age, sex, religious affiliations, employment, income, etc for an individual to be classified as "suffering from MDD", five out of ten symptoms, one from a set of two and additional symptoms from another set of five, must be present during a span of two weeks [7]. In addition to the symptoms that may be prevalent in a person suffering from depression, there can be morphological differences in several brain regions, including the frontal and temporal lobes. On top of that, individuals suffering from MDD also have abnormal functional connectivity. According to the World Health Organization, more than 264 million people of all ages suffer from depression worldwide [7]. Fortunately, there are effective psychological and pharmacological treatments for moderate to severe depression. The pharmacological treatment includes medications such as, SSRIs and SNRI which are the two most commonly prescribed antidepressants [11]. The psychological treatments include psychotherapy and electroconvulsive therapy depending on the severity of the depression. These treatments can take a few weeks or much longer.

1.2 Brain Networks

A brain network, on a large scale, can be defined as a collection of brain regions working together to produce a specific function. Brain networks can be identified at different resolutions, therefore there is no universal atlas of brain networks that fits all circumstances. However, based on converging evidence from related studies, six large-scale, core brain networks that are most widely accepted due to their stability:

1. Default Mode Network
2. Salience Network
3. Dorsal Attention Network
4. Frontoparietal Network
5. Sensorimotor Network
6. Visual Network

There are more subsets of these six networks such as the limbic, auditory, right/left executive, cerebellar, spatial attention, language, lateral visual, temporal and visual perception/imagery. An emerging paradigm in neuroscience is that cognitive tasks are performed not by individual brain regions working in isolation but rather by brain networks consisting of several discrete brain regions that are said to be "functionally connected". The functional connectivity of brain networks can be acknowledged through (statistical) analysis of images acquired through a variety of techniques such as the fMRI, EEG, PET or SPECT [2].

1.3 Resting State Functional Connectivity

Functional connectivity can be defined as the temporal correlation between spatially remote neurophysiological events, expressed as deviation from statistical independence across these events in distributed neuronal groups and areas. The results of the study connected by Bharat B. Biswal et. al. suggests that while variations in blood flow might contribute to functional connectivity maps, BOLD signals play a dominant role in the mechanism that gives rise to functional connectivity in the human brain [1]. During resting conditions, our brain remains functionally and metabolically active. The fact that brain remains "metabolically active" means there will be consumption of oxygen which results in fluctuations in the BOLD signal. Resting state functional connectivity can be defined as the correlation patterns in the spontaneous fluctuations of BOLD signal in the absence of any stimulus or task. [5].

Resting-state functional connectivity measures the temporal correlation of spontaneous Blood Oxygen Level Dependent (BOLD) signals among spatially distributed brain regions, with the assumption that regions with correlated activity form functional networks.

There are two methods that are most commonly used to examine functional connectivity:

- Seed-based Correlation Analysis (SCA) and
- Independent Components Analysis (ICA)

In seed-based approaches, activity is extracted from a specific region of interest and correlated with the rest of the brain. In contrast, ICA does not begin with pre-defined brain regions. It is a multivariate, data-driven approach that deconstructs fMRI time-series data throughout the brain into separate spatially independent components. The resting-state fMRI study produces reliable and reproducible results, and several features of resting-state fMRI makes it favorable for investigating the functional correlation of various brain regions in psychiatric and neurological disorders. First, compared to the modular representations of traditional fMRI, functional connectivity provides a broader network representation of the functional architecture of the brain. Second, the absence of an explicit task eases the cognitive demand of the fMRI environment, thereby eliminating the problem of whether or not to match groups on task performance and allowing researchers to investigate under-studied populations, including infants and cognitively impaired individuals. Finally, the relatively standard manner in which resting-state fMRI data are acquired makes it ideal for multi-site investigations and data sharing.[11]

1.4 Neuroimaging

Neuroimaging or brain imaging is the use of various imaging modalities to either directly or indirectly image the structure, function, or pharmacology of the nervous system. Current neuroimaging techniques reveal both form and function. They reveal the brain's anatomy, including the integrity of brain structures and their interconnections. Neuroimaging can be divided into two broad categories:

1. **Structural Imaging**, which deals with the structure of the nervous system and the diagnosis of gross (large scale) intracranial disease (such as a tumor) and head injury.
2. **Functional imaging**, which is used to diagnose metabolic diseases and lesions on a finer scale (such as Alzheimer's disease) and also for neurological and cognitive psychology research and building brain-computer interfaces [9].

Functional Magnetic resonance imaging (fMRI) is a modern technique of imaging, which is a powerful non-invasive and safe tool used for the study of the function of the brain based on the measure of the brain neural activation. The fMRI can localize the location of activity in the brain which is caused due to sensory stimulation or cognitive function. In the clinical setting, fMRI allows the researchers to study how healthy brain functions, how different diseases affect the brain functions, how brain functions altered due to disease or injury can be restored, and how how drugs can control the disease's effect on brain activity [8].

2 Objectives

The objectives of the proposed project are as follows:

2.1 Specific Objectives

- Deploy computational tools, and implement image processing strategies for the exploration of MR image datasets of the human brain using AFNI.
- Explore data visualization tools, with emphasis on displaying functional brain networks.
- To perform Seed-based Analysis (SCA) to explore functional connectivity within the brain based on the time series of a seed voxel or Region of Interest (ROI).

2.2 General Objectives

- Perform analysis of the functional connectivity of the hippocampus in patients suffering from Major Depressive Disorder and acquire a comprehensive idea about how it compares to that of normal individuals of the same age group.

3 Problem Statement

3.1 Need For An Imaging Basis

The diagnosis procedures that are the gold standard for the diagnosis of psychiatric disorders are wholly based on behavioral observations and patient reported symptoms. Current diagnostic procedures involved do not have an imaging or a biochemical basis [10] [6]. Two most widely established symptoms are used to classify these manifestations, one is the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the other is International Classification for Diseases (ICD). Despite each being, widely used as the other, both of these diagnosis manuals are more like frameworks that provide a way of classifying a psychiatric disorder depending on patterns of behaviour rather than interpreting the etiology and the physical cause of those disorders. This statement alone raises an argument that "although reliable, current diagnostic procedures in psychiatry are not entirely valid".

Let us take an example of the diagnostic procedure involved in the diagnosis of Major Depressive Disorder. The DSM-V, published in 2013, is the most up-to-date manual and is based upon the work of expert study groups and makes use of large sets of data. According to the DSM-V, for a person to be classified as "suffering from Major Depressive Disorder", he/she must report with either depressed mood or anhedonia (inability to feel pleasure in normally pleasurable activities) along with four out of eight additional symptoms [4]. This makes it possible for two distinct individuals who do not share a single symptom in common and to receive similar treatment (or medication) for MDD.

Furthermore, the current diagnostic procedures such as the DSM-V are not perfect. For example, impulsivity, emotional lability (the property of changing rapidly), and difficulty with concentration each occur in more than one disorder. Now, the fact that different exemplars of the same category can share no symptoms and that the exemplars of two different categories may share common symptoms, raises questions about the validity of the current diagnostic procedures in psychiatry.

In addition to that, some other medical conditions such as thyroid disease, brain tumors, and vitamin deficiency can mimic depression-like symptoms[3]. Therefore, a diagnosis may also have to be conducted in order to rule out some other medical condition that might be causing depressive symptoms. For instance, a blood test can be done to ensure the symptoms are not due to thyroid related issues.

Considering the above mentioned arguments, an imaging basis for the diagnosis of mental disorders seems like the need of the hour.

3.2 Reverse Inference Fallacy

In present day and world, a variety of imaging modalities such as ultrasonography, x-rays, computed tomography, MRI, SPECT, PET, fluoroscopy, etc are being implemented for a large number of purposes, most of them include clinical diagnosis of various diseases and the others include research. Now, while some of these imaging modalities such as MRI, SPECT and PET are indeed being used for research that involve diagnosis of psychiatric disorders, they are yet to be implemented for the actual diagnosis of mental disorders.

There exists thousands of published research studies using functional neuroimaging methods such as SPECT, PET, and fMRI that revolve around diagnosis of mental disorders. However, findings from brain imaging do not appear amongst the diagnostic criteria; aside from its use to identify potential physical injury or tumours, neuroimaging is not used in diagnostic procedure in psychiatry.

Now, at first glance it might seem quite unusual and wrong and foolish that such advanced imaging techniques are not being used for diagnosis of mental disorders especially after so many researchers have done studies on it, there is actually quite a good, and as a matter of fact, quite an important reason behind it.

The reason behind this is the reverse inference fallacy. Most psychiatric imaging studies involve subjects from only two categories- patients from a single diagnostic category and people without any psychiatric diagnosis (healthy individuals), the most that can be learned from such a study is how brain activation in those with a particular disorder differs from brain activation in those without a disorder. This raises a dilemma for the diagnosing clinician, as the question is not "does this person have disorder X or are they healthy?" but rather "does this patient have disorder X,Y,Z or are they healthy?" because the pattern of images that distinguishes patients with disorder X from healthy people may not be unique to X but shared with a other disorders.

In addition to the reverse inference fallacy, standardization is another issue which contributes to neuroimaging not yet finding a place in psychiatric practice. Standardization is relevant in the sense that protocols for imaging studies differ from study to study, particularly amongst functional imaging studies.

Findings on the patterns of activation acquired in studies of psychiatric patients depends strongly on the task being performed by the subjects and the statistical comparisons made by the researcher afterwards. Such findings are pretty much incomplete unless they include the information about what task evoked the activation in question: whether the patient wa resting, processing an emotional stimuli, resisting emotional stimuli or engaged in some other task? Therefore the fact that imaging study's conclusions are relative to the tasks performed adds further complexity to the problem of consistently discriminating patterns of activation of healthy and ill subjects.

Now, in the word of technology that is advancing day in day out, development (more sophisticated) methods of image analysis may hold promise discerning the underlying differences among the many disorders that feature similar regional abnormalities. Nevertheless, the scope of neuroimaging seems promising for the aid in diagnosis, and hopefully treatment of psychiatric disorders.

4 Review of Literature

4.1 Background

Efforts are continuously being made in order to discover reliable biomarkers for the clarification of biological mechanisms that are involved in psychiatric disorders, identification of subjects at risk and provide etiology-based treatments. Imaging modalities such as structural magnetic resonance imaging (sMRI) and functional magnetic resonance imaging (fMRI) are used to outline brain irregularities over Major depressive disorder (MDD).

Multiple modalities have been considered for assessment of functional connectivity of brain networks, but fMRI is the most commonly used amongst the others. This is because (insert reason a valid here).

Most studies that have been referred to, whilst writing this review have utilized fMR-imaging modality to conduct investigations on the core aspects of functional brain alterations in patients suffering from MDD.

The goal of this literature review is to gain a comprehensible knowledge about the associations of various different brain networks with Major Depressive Disorder and also to acquire a brief overview of how the brain networks, especially the hippocampal network gets affected by MDD.

Since this project is mostly concerned with the hippocampal network, most of the literature will be more or less be related to the temporal lobe and its structures.

4.2 Functional Magnetic Resonance Imaging for the Assessment of MDD

People with MDD show distinct functional alterations that differ from those of healthy individuals. Functional brain alterations can be found by detecting the activation of specific brain regions. A brain region become active when there is blood flow in that region, and an elevated level of metabolism. Now, Unlike structural brain imaging that captures the anatomical structures present in the brain, functional brain imaging involves measurement of blood flow and metabolism to visualize the activation of specific brain regions. Therefore, functional imaging techniques such as the fMRI indicates the activation of various different brain regions which makes it quite convenient to identify what parts of brain are active during a condition.

fMRI comes in two flavours, one is the resting-state fMRI and the other is the task-based fMRI. “Resting-state” is when a person is fully awake but isn’t performing any particular task that requires attention and cognition. While many studies are based on the rs-fMRI, researches believe that the rs-fMRI lacks the linearity and stationary signals required for the assessment of MDD.

There have been limited reports of functional alterations in the temporal lobe with the use of pure rs-fMRI. Nonetheless, in one study, treatment resistant patients with MDD showed increased levels of hippocampal activation during loss events.

Yu et al., in their reasearch showed functional alterations in the activity of the right hippocampus, right para-hippocampal gyrus, left amygdala and the entire caudate nucleus, which ultimately suggests that the temporal lobe and various structures in the temporal lobe, such as the hippocampus might have an important pathophysiology of MDD. Therefore, additional studies are needed to determine the relevance of these findings.

In another study, the duration of MDD was directly associated with hippocampal volume loss in women with MDD.

It was also found in some task-based fMRI studies that the presentation of sad faces led to increased activation of left hippocampus, amygdala and para-hippocampal gyrus.

Stoyanov and colleagues found out that there is a weak correlation between medial frontal cortex (MFC) and MDD subjects. In addition, they also made an implication that the pathophysiology of MDD was because of the activation in anterior thalamus, hippocampus and para-hippocampal gyrus areas.

4.3 Resting State Functional Connectivity of Hippocampal Networks

Various studies have focused on the abnormal functional connectivity of several brain networks in the patients with MDD.

Studies have shown that MDD not only shows associations with regional deficits, but also with abnormal functional integration of distributed brain regions. A number of brain regions with abnormal activities in the resting-state have been identified to be associated with MDD, such as para-hippocampal gyrus, prefrontal cortex, cingulate gyrus, fusiform gyrus, and thalamus. Moreover, disruptions in functional connectivity has been observed between specific pairs of regions in MDD through functional connectivity analyses which may or may not include seed-based correlation analysis.

Greicius et al. (2007) used the independent component approach (ICA), selecting a set of regions with shared fMRI signal fluctuations and a high degree of spatial similarity to the DMN, and reported increased connectivity with the thalamus and the subgenual ACC in depression.

Many studies have found that the hippocampus, which is complex structure embedded deep into the temporal lobe, plays an important role in MDD. Hippocampus can be subdivided into 3 sub-structures, and theses structures are enumerated below:

1. Cornu Ammonis (CA)
2. Dentate Gyrus (DG)
3. Subiculum

Various studies have been performed with each of these sub-structures as the seed or the region of interest. The findings from some of the studies that are relevant to this project are listed below:

- Increased connectivity in the left premotor cortex (PMC) and reduced connectivity in the right insula with the CA seed region.
- Increased connectivity was reported in the left orbitofrontal cortex (OFC) and left ventrolateral prefrontal cortex (vPFC) with the DG seed region.
- The subiculum seed region revealed increased connectivity with the left premotor cortex (PMC), the right middle frontal gyrus (MFG), the left ventrolateral prefrontal cortex (vPFC) and reduced connectivity with the right insula.

Furthermore, a region-of-interest based correlation analyses performed in rs-fMRI showed FC with the hippocampus in limbic system, sub cortical areas, temporal lobe, medial and inferior prefrontal cortex, while at the same time, negative FC was in bilateral prefrontal cortex, parietal and occipital cortex and the cerebellum.

In addition to that, many researches have implicated abnormalities in the prefrontal-hippocampus neural circuitry in patients suffering from MDD. fMRI studies have also found abnormal hippocampal activation as well as abnormal functional connectivity of prefrontal-hippocampus circuitry in adults who were suffering from MDD. Moreover, Peng et. al. in one of their recent studies reported decreased rsFC between hippocampus and insula in medication-resistant adult patients.

The hippocampus has been proven to play an important role in memory and emotion processing. Functional abnormalities of the hippocampus in adult MDD have been consistently reported in several fMRI studies. According to an fMRI study, decreased brain activity in the hippocampus was reported in depressive patients.

Similarly, the hippocampus and amygdala of MDD patient's showed an overlapping pattern of reduced FC to the dorsomedial-prefrontal cortex and fronto-insular operculum. Both of these regions are known to regulate the interactions among intrinsic networks (i.e., default mode, central executive, and salience networks) that are disrupted in MDD.

A few postmortem studies have found decreased cellular density in the hippocampus, including one study that showed patients with MDD have fewer anterior dentate gyrus granule cells than control subjects. However, functional imaging studies at this resolution in patients with MDD are lacking.

For several reasons, researchers have focused on the role of the hippocampus in depression. The hippocampus is involved in the regulation of the hypothalamic pituitary adrenal (HPA)-axis, which is responsible for production of stress-related glucocorticoids such as cortisol. In this context, depressed individuals have been found consistently to report high levels of stress, which is reflected biologically in elevated rates of hypercortisolemia and disturbed HPA-axis functioning. Moreover, depressed patients have also been found to be characterized by difficulties in hippocampal-dependent learning and memory.Also, Problems can occur when excessive amounts of cortisol are sent to the brain due to a stressful event or a chemical imbalance in the body.

4.3.1 Overview of Hippocampal Circuitry and its Functions

Hippocampus is a relatively simple one that can be related to the functional requirement of episodic memory and more specifically to the storage and retrieval of memory.

The hippocampus is part of the hippocampal formation which includes the dentate gyrus, Para hippocampal gyrus, and hippocampal gyrus.

The hippocampal gyrus contains areas such as the entorhinal cortex and subiculum, which are both vital in the flow of information through the hippocampus.

The hippocampus is divided into CA1 to CA4 regions which stands for cornu ammonis. The CA1 has an important role in memory due to the high levels of NMDA glutamatergic receptors located in the CA1 Schaffer collateral neurons.

The synaptic plasticity of these neurons heavily relies on long-term potentiation (LTP) induction to allow the strengthening of declarative memory which includes two types of implicit memory such as episodic and semantic memory such as facts and events.

4.4 Important FCs for Diagnosis of MDD

Default mode network (DMN), Anterior salience network (ASN) and Executive control network (ECN) are the brain networks linked with clinical depression. Increased functional connectivity within the DMN is primarily associated with depression. At the same time, it is found that the DMN-ECN and the DMN-ASN pairs have less interactions or connectivity during episodes of depression. Within the ECN, the functional connectivity may be excessive or deficient. Furthermore, the ECN in depressed women is correlated with negative self-directed thoughts and the ECN-DMN functional connectivity is related to rumination. Researches have shown that ASN which includes main emotional areas maybe over, under or normally connected in depression. Depression is also related with the impaired functional connectivity of other brain networks besides the ones mentioned above.

In addition to that the Posterior Cingulate Cortex which is a part of the DMN has shown significant relationship with the hippocampal network, albeit this is not just specific to MDD.

Hindawi Neural Plasticity et. al., on comparing the functional activity within DMN, found that there was decreased functional connectivity within DMN network in depressed people, which contradicted with the most researches that have been conducted. This may be because the patients involved in their study had mild to moderate depression, which showed cognitive similar features as in depression (MDD) like rumination and control deficits, but lacked neural markers present in typical serious condition like MDD.

Significant rs-fMRI differences between groups were identified in multiple clusters in the DMN and ECN. Greater positive connectivity within the ECN and between ECN and DMN regions was associated with poorer episodic memory performance in the group of healthy individuals but better performance in the MDD group. Greater connectivity within the DMN was associated with better episodic and working memory performance in the Non-Depressed group but worse performance in the MDD group.

These results provide evidence that cognitive performance in MDD may be associated with aberrant functional connectivity in cognitive brain networks and suggest patterns of alternate brain function that may support cognitive processes in MDD.

Results also showed that the DMN–left fronto-parietal network is the pair discriminating between healthy and depressed people to the highest degree. According to Davidson and Heller models, left prefrontal activity is related to positive emotions and motivations, while right corresponds to negative emotions and withdrawal of motivation.

Relatively active right prefrontal area and idling left prefrontal cortex together may be a neurophysiological signature of depression. Therefore, coupling of left prefrontal with DMN denotes its passivity and that there's is less approach motivation, less happy mood which is one of the most important depression related signs.

Decreased functional connectivity between left fronto-parietal network and subsystems of the DMN can be seen in fMR images of depressed patient.

Many studies that have been published showed increased functional connectivity within DMN in depression, which was found to be contradiction with one particular research paper which may be due to sample differences like severity of the disorder, age group,and other demographics.

4.5 Structural Changes associated with MDD

The latest research shows that the size of specific brain regions can decrease in people who experience depression. Researchers continue to debate which regions of the brain can shrink due to depression and by how much.

Hippocampus, thalamus, amygdala and the frontal prefrontal cortices are the regions that have the most shrinkage. The amount by which, these areas shrink is linked to the severity and the length of the depressive episodes. In the hippocampus, for example, noticeable changes can occur anywhere from 8 months to a year.

It was found in a study that people experiencing their first depressive episode had a normal hippocampus size but as the number of episodes of depression a person had would increase, the greater the reduction in hippocampus size. It has been widely reported that there is a significant reduction in hippocampal volume in depression patients. This situation was found in both adult and adolescent depressed patients, whether they were in their first or recurrent depressive episodes. A recent study reported that, in female patients with recurrent familial pure depressive disorder (rFPDD), volumetric reductions of the right hippocampal body and tail were significantly larger than those of the left, while the whole brain volume was approximately equal to that of healthy subjects.

There is evidence that stress via the hypothalamic-pituitary-adrenal axis can result in elevated glucocorticoid levels in patients with depression and can act on the glucocorticoid receptors in the hippocampus. Thus, hippocampal atrophy occurs as a result.

Reduced gray matter volume and reduced functional activity in the hippocampus would lead to negative emotion and the inability of cognitive processing in depressive patients. Depression can also decrease neuronal dendrite branching and plasticity in the hippocampus.

In addition, depression can trigger activation of the hypothalamic-pituitary-adrenal axis, increase level of corticosteroids, and down regulate hippocampal neurogenesis. Depression makes changes in hippocampal volumetric changes, hippocampal neurogenesis, and apoptosis of hippocampal neurons.

4.6 Reverse Inference Fallacy in MDD

The diagnosis of MDD relies heavily on patients for symptom recall. Like in many other mental disorders there is no specific physical symptom in MDD, therefore neurologists are unable to deduce MDD based on conventional MRI.

Moreover, different mental disorders can produce similar structural or functional brain alterations which puts the neurologist in a much greater dilemma as they are unable to determine whether a specific alteration in the brain is attributed to MDD-alone. So, the reverse inference is invalid as structural or functional activity patterns from MRI cannot be used to diagnose a patient with a specific neurological disorder.

Researchers, over the past few decades have been attempting to develop a “bridge”, such as novel biomaterial, high resolution and multi-modality imaging technique, artificial intelligence, novel nanomaterials and quantitative electrical signal acquisition technologies to overcome reverse inference fallacy that hinders the study of MDD.

Conclusion of the Literature Review

Evidence shows that major depressive disorder (MDD) patients at resting-state brain connectivities are aberrant compared with healthy controls (HC). Abnormal resting-state functional connectivities of distributed brain networks are believed to contribute to the MDD illness process.

And after a thorough review of literature, it seems as if structural MRI and fMRI look promising for providing excellent and reliable indexes for the aid in the diagnosis and ultimately treatment of MDD.

Once it over-comes the afore mentioned hurdles, MRI may become a clinical decision support tool aimed to reduce unsuccessful treatments and improve treatment efficacy and efficiency.

Reliable, reproducible and valid conclusions must be derived from these types of studies for imaging modalities like fMRI to not only aid in the diagnosis but also to optimize patient care, reduce treatment resistance and shorten the duration of illness.

5 Feasibility Study

The following points addresses the feasibility of the proposed study:

- This project will primarily focus on analysis of the functional connectivity of the hippocampal network of patients suffering from Major Depressive Disorder.
- Although the approach of neurological study is new in Nepal, thousands of research has been conducted worldwide that involves similar approaches for the exploration of functional connectivity.
- Data will be acquired form a public database, which is available online for the sake of this project.
- There are not many materials or components required for the project. We will be using open-source softwares such as Analysis of Functional Neuro Images (AFNI) and the Linux operating system, this adds to the feasibility of this project.
- Furthermore, all the work involved in this project can pretty much be conducted virtually at home, therefore this eliminates the obstacles that may arise due to the on going pandemic.
- Hence, the feasibility study to conduct this proposed project is positive and supportive.

6 Methodology

Based on resting-state functional magnetic resonance imaging data, this project will attempt to investigate the functional connectivity changes in the hippocampal network of 30 MDD patients and just as many well-matched healthy controls.

6.1 Methods and materials

We plan to employ resting-state functional MRI (rs-fMRI) to investigate topological changes of the functional connectome in patients with MDD. Our plan is to collect data from (NUMBER) MDD, and (NUMBER) healthy controls (HC) to study alterations in functional connectivity of hippocampus regions, and to explore their relationship with memory and emotional behaviors.

6.2 Data Acquisition

For the data acquisition part, the *SRPBS Multiorder MRI Dataset* was used. The public dataset that we will be using contains the 3T MRI images data from 1410 participates collected at 11 sites.

Statistical analysis methods such as the T-test and the P-test will be applied on this big data to narrow it down to just 30 participants including (NUMBER) patients with MDD and (NUMBER) demographically matched healthy controls (HC) based on age and sex.

Importantly, we plan to choose (number) right handed patients from each group with MDD and HC. Here, we engaged MDD patients with BDI (Beck depression Inventory) index more than 30.

Since we will be acquiring the data from large scale public dataset, diagnosed by neurologist, this assures our research to be tilted more to accuracy and efficiency. All the participants, extracted from the public data set, have underwent a standardized clinical evaluation protocol, which included a general and neurological examination, which will make our research more feasible.

6.3 Image Pre-processing

Before statistical analysis, it is necessary to convert the raw fMRI data to a form that is understandable by the software and also to improve the signal quality of the data obtained from the MRI scanner, which includes artifact detection, baseline correction, realignment, movement correction, co-registration, normalization, and smoothing.

The fMRI data will be preprocessed using AFNI. AFNI is an open source software created an maintained by Robert W. Cox at NIH.

Pre-processing involves spatial or temporal filtering of the fMRI data and improving the image resolution. Seed based resting-state functional connectivity (rsFC) analysis of hippocampal network will be performed such that for each seed region, rsFC will be calculated as the correlation between its *mean time* course and the time course of every voxel in the brain. Then we will submit the rsFC results for each seed region to a 2 x 3 (hemisphere x group) mixed-design analysis of variance with age and head motion included as covariates. The final rsFC results, between the MDD patients and HC will be compared using statistical approach.

6.4 Functional connectivity analysis

Once the rs-fMR images from the public data set has been pre-processed, Seed- based rsFC analyses will be performed by implementing statistical methods.

Specifically, we plan to assess functional connectivity between various regions of hippocampal area using fMRI. To assess functional connectivity in the brain region, Resting-state analyses, that is, time-series correlations in BOLD fMRI data acquired in a task-free state will be used.

A statistical approach to image analysis makes it possible to discover, spatial and temporal patterns that correspond to performance of specific tasks and specific diagnoses. Such statistical methods have only been begun to be applied to clinical disorders but show promise for increasing the "specificity" of brain imaging markers for mental illness.

7 Cost Estimations

8 Time Frame & Proposed Work Flow

9 Conclusion

Previous studies indicated discrepant functional connectivities between MDD patients and HC. However, it is unknown whether these connectivities can be used as diagnostic biomarkers of MDD.18 Indeed, whether the future diagnostic models built on the functional connectivity values can improve treatment prediction and clinical outcome depend on its accuracy performance.

While clearly not sufficient to provide a detailed understanding of the complex and changing functional connectivity of the brain which can make actual diagnosis of MDD, this project will lay the foundations for further research and development.

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