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

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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 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.

Reverse inference is a kind of reasoning that is applied to infer the involvement of a specific cognitive process from observed brain activation during a task. It attempts to uncover specific cognitive processes or behaviours that may be associated with specific structural or functional brain alterations. However, reasoning backwards from brain activity is problematic because neurological disorders are multifaceted and are influenced by several factors such as concurrent diseases, disease history and artifacts.

For this reason alone, neuroimaging is not "widely accepted" in the process of psychiatric diagnosis. Despite, the reverse inference fallacy, 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 psychiatric disorders. Nevertheless, there are no solid molecular or imaging basis that are widely accepted for the assessment of mental disorders.

Here in the proposed research we will be *assessing* MR images of 35 subjects who, are suffering or have suffered, from one major depressive disorder and *making an attempt* at arriving to a comprehensive conclusion about how the "limbic brain network" of patients suffering from Major Depressive Disorder compare to that of healthy individuals who share similar socio-demographic parameters as the subjects.

1 Introduction

1.1 Major Depressive Disorder

Major Depressive Disorder, generally abbreviated as MDD, is one of the most common and a serious mental disorder. MDD is also referred to as clinical depression, or just depression as well.

MDD can be characterized by an array of distinct symptoms; persistent felling of sadness, feelings of low self-worth and guilt, and an 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 5, must have to present as a bare minimum during span of 2 weeks. reference here

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 also have abnormal functional connectivity.

According to the World Health Organization, more than 264 million people of all ages suffer from depression worldwide. Fortunately, there are effective psychological and pharmacological treatments for moderate to severe depression. The pharmacological treatment includes medications, SSRIs and SNRI are two antidepressants that are most commonly prescribed. The psychological treatments include psychotherapy and electroconvulsive therapy depending on the severity of the depression, treatment 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 various different resolutions, therefore there is no universal atlas of brain networks that fits all circumstances. However, on the basis of converging evidences from related studies, there are 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 Cortex

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.

1.3 Resting State Functional Connectivity

Resting-state functional connectivity can be defined as a significant correlated signal between functionally connected brain regions in the absence of any stimulus or task. Resting-state functional connectivity measures **temporal correlation** of spontaneous Blood Oxygen Level Dependent (BOLD) signal 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 produces reliable and reproducible results, and in addition to that, there are several features of resting-state fMRI that it makes it favorable for investigating the correlation of 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.

1.4 Neuroimaging

Neuroimaging or brain imaging is the use of various techniques 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 falls 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 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.

Functional Magnetic resonance imaging (fMRI), a modern technique of imaging, is a powerful non-invasive and safe tool which is used for the study of the function of the brain based on measure of the brain neural activation (Farah, 2002). The fMRI can localize the lo-cation of activity in the brain which is caused due to sensory stimulation or cognitive function (Gabral, Sil-veira, & Figueredo, 2011). In clinical field, fMRI allows the researchers to study how are the healthy brain func-tions, how different diseases affect the brain functions, how healthy brain function is recovered after damage and how drugs can control the diseases effect on the brain activity (Daliri & Behroozi, 2012). near-term and long-term prospects of neuroimaging? and what obstacles block the use of such methods? Answer to the 2nd: The nature of imaging studies and of psychiatric diagnosis.

2 Objectives

The objectives of the proposed project are as follows:

2.1 General Objectives

- Deploy computational tools , and develop image processing strategies for the exploration of MR image datasets of 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 Specific Objectives

- Perform analysis of the functional and structural connectivity of the hippocampal network of patients suffering from Major Depressive Disorder and acquire a comprehensive idea about how it compares to that of normal individuals from the same socio-demographic background.

3 Problem Statement

3.1 Need For An Imaging Basis

The diagnosis procedures that are the gold standard for diagnosis of psychiatric disorders are wholly based on behavioral observations and patient reported symptoms. There are two most widely established symptoms that 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 as widely used as the other, both of these diagnosis manuals are more like frameworks 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.*

This makes it totally possible for 2 distinct individuals who do not share a single symptom in common and yet receive 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 occurs 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, vitamin deficiency can mimic depression like symptoms. Therefore, a may also have to be conducted in order to rule out some other medical condition that may be causing depressive symptoms. For instance, a blood test might be done to ensure the symptoms are not due to thyroid related issues.

Taking the above mentioned arguments into consideration it is crystal clear that there is a need for an imaging basis for the diagnosis of mental disorders.

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.

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.

Now, in the word of technology that is advancing day in day out, the scope seems promising.

- development (more sophisticated) methods of image analysis may hold promise discerning the underlying differences among the many disorders that feature similar regional abnormalities

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 positive FC (positive in what sense?) 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.

4.4 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.

On comparing the functional activity within DMN, it was 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 this particular 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.

Increased 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. But current studies have shown that the following parts of the brain can be affected:

hippocampus thalamus amygdala frontal prefrontal cortices

The amount these areas shrink is linked to the severity and length the depressive episode lasts. In the hippocampus, for example, noticeable changes can occur anywhere from 8 months to a year.

People in the study experiencing their first depressive episode had a normal hippocampus size. But the more episodes of depression a person had, 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.

A recent meta-analysis covering (different markers) found neuroimaging to overall be most successful in predicting treatment response in depressed patients.

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.

Past work seems like structural MRI and fMRI look promising for providing excellent and reliable indexes for the aid in the diagnosis and ultimately treatment of MDD.

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.

5 Feasibility Study

- This project will focus in analysis of the functional and structural connectivity of the hippocampal network of patients suffering from Major Depressive Disorder.
- Although the approach of neurological study is new in Nepal, various research has been conducted worldwide, so we can use the public data/information present in internet for our project.
- There isn't many components required for the project and can be carried out in given time frame with low budget.
- The research and study can be done pretty much virtually at home, which is much more favorable during pandemic moment.
- 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 30 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: Public Data Set

We will recruit (TOTAL NUMBER) participants, including (NUMBER) patients with MDD and (NUMBER) demographically matched healthy control (HC) subjects from public dataset which will be matched according to age and sex. Importantly, we plan to choose (number) righthanded 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 Functional connectivity analysis

Resting functional magnetic resonance imaging data will be collected and processed with standard procedures. We tend to perform Seed- based rsFC analyses.

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.

6.4 Pre-processing

6.5 Statistical Analysis

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.

10 Bibliography & References