Resting state brain networks and their implications in neurodegenerative disease

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ABSTRACT

Neurons are the basic units of the brain, and form network by connecting via synapses. So far, there have been limited ways to measure the brain networks. Recently, various imaging modalities are widely used for this purpose. In this paper, brain network mapping using resting state fMRI will be introduced with several applications including neurodegenerative disease such as Alzheimer’s disease, frontotemporal lobar degeneration and Parkinson’s disease. The resting functional connectivity using intrinsic functional connectivity in mouse is useful since we can take advantage of perturbation or stimulation of certain nodes of the network. The study of brain connectivity will open a new era in understanding of brain and diseases thus will be an essential foundation for future research.

Keywords: Neurodegenerative disease, Alzheimer’s disease, Frontotemporal lobar disorder, Parkinson’s Disease, resting-state networks, fMRI, OIS imaging, two-photon microscopy

1. INTRODUCTION

Traditionally, activation and response in the brain to a stimulus or task has been used to map and generate functional organization within the brain. However recent studies have shown that correlations spontaneous neuronal activity can be used to map functional brain networks within the brain. This means that even in the absence of task or stimulus (hence the term “resting state”), regions of the brain which share task or cognitive functions, show a high degree of correlated spontaneous activity. This phenomenon was first observed using resting state functional magnetic
resonance imaging (rs-fMRI). Biswal et al.\textsuperscript{[1]} observed that slow wave or low-frequency (<0.1 Hz) fluctuations (LFFs) in blood oxygen level dependent (BOLD) signal show high correlation in regions which activate in response to a bilateral finger tapping task. These studies have been replicated extensively to map other functional network in the brain\textsuperscript{[2-7]}. Additional studies have shown that these LFFs are not a result of noise or random physiological process, but are a result of organized neuronal activity\textsuperscript{[8-13]}.

These functional networks generated from correlations in spontaneous BOLD signal have come be referred to as resting state networks (RSN) (Figure 1). These networks can be generated by seeding target regions and performing region on interest (ROI) analysis\textsuperscript{[1, 6, 14, 15]} or by using data driven methods such as independent component analysis (ICA)\textsuperscript{[16-18]}. More task specific networks can also be analyzed using ROI analysis or by using high order or a modified version of ICA\textsuperscript{[19-22]}.

![Figure 1. Commonly Visualized Resting State Networks (RSNs). Networks are generated using ICA from 23 healthy subjects. Each RSN represents a large scale functional network which shows high correlation in BOLD LFFs.](http://proceedings.spiedigitallibrary.org/)

The consistency in which these RSNs can be reproduced along with the high degree of spatial agreement with known cognitive networks and the discovery of a neural basis behind these LFFs allows for a variety of research applications. The lack of an experiment paradigm is especially advantageous as it allows for analysis of networks which cannot be visualized due to technical constraints in addition to analysis of subjects who are unable to perform a given task due to physical or mental constraints (i.e. patients with neurological or pathological disorders). In addition, studies have shown that these spontaneous fluctuations persist even in different levels of anesthesia and sleep making it possible to image sedated subjects or patients\textsuperscript{[23-25]}. While most research analyzing resting state fluctuations have predominately dealt with fMRI, electroencephalography (EEG) and magnetoencephalography (MEG), recently studies have utilized optical methods such
as functional near diffuse optical tomography (DOT) \cite{26}, infrared spectroscopy (fNIRS) \cite{27-29} and optical intrinsic signal (OIS) imaging\cite{30, 31}. Techniques such as DOT, fNIRS and OIS are promising in that they offer a high sampling rate than fMRI and offer more spatial resolution than MEG/EEG. OIS imaging offers addition benefits in that they can be used to image mouse animal models as fMRI techniques are difficult due to the small size of the mouse brain \cite{32}. This is essential as research using animal models allows comparison between molecular manipulations and functional connectivity maps.

This paper will investigate the applications of RSNs in the study of neurodegenerative disease such as Alzheimer’s disease (AD), frontotemporal lobar degeneration (FTLD) and Parkinson’s disease (PD).

2. APPLICATIONS TO NEURODEGENERATIVE DISORDERS

Neurodegenerative diseases are progressive disorders which cause a steady decline in brain function. Interestingly many neurodegenerative disorders share identical pathological features however show different symptoms based on the affected brain region \cite{33, 34}. In addition, evidence suggests that the pathology of these diseases does not begin in one region and expand to neighboring regions, but rather spreads through neural networks \cite{35-38}. Cortical atrophy patterns concur with these results as specific neurodegenerative diseases shows significant atrophy in specific brain functional networks rather than anatomical regions. As a result the pervading hypothesis is that neurodegenerative diseases target larger scale functional networks rather than specific regions of the brain \cite{39}.

2.1. Alzheimer’s disease:

Possibly the most extensively researched neurodegenerative disease is AD. This is largely due to the fact that it is the most common form of dementia. Pathologically AD is characterized by excessive buildup of β-amyloid peptide (Aβ) and neurofibrillary tangles or tau proteins \cite{40, 41}. Aβ is a nature product of metabolism, and is non-toxic in its most prevalent form (Aβ40). This type of Aβ is soluble and is easily cleared from the body. However cleavage of the amyloid precursor protein (APP) by the beta-site amyloid precursor protein-cleavage enzyme (BACE-1) and subsequent cleavage by γ-secretase, results in the toxic aggregation-prone form (Aβ42) \cite{42}. The “amyloid hypothesis” postulates that the accumulation of Aβ is a result of an imbalance between the clearance and aggregation and that this buildup causes onset of AD \cite{43, 44}. In the case of tau proteins, hyperphosphorylation causes tau to detach from microtubules and aggregate into neurofibrillary tangles \cite{45-47}. Since tau functions in assembly and stability of microtubules, detachment of tau destabilizes microtubules inhibiting axonal transport \cite{40}.

While AD is not directly caused by ageing, the chances of being diagnosed with it increase rapidly after 65 years of age. This is critical because as the average lifespan continues to increase in modern societies and developed countries so will the prevalence of AD. As of yet there is no cure for AD as current treatments only reduce the symptoms and may slow disease progression. Therefore early detection of the disease is paramount for optimal treatment.

The noninvasive and task free nature of rs-fMRI makes it an ideal method for early detection and disease characterization and to assess brain connectivity and function. Structural MRI shows atrophy beginning in the hippocampus and expanding to the rest of the entorhinal cortex and the posterior cingulate cortex (PCC). Other studies also show spread and aggregation of Aβ proceeding in a similar fashion \cite{48-53}. These regions show strong spatial correlation with the RSN known as the default mode network (DMN) \cite{44, 54, 55}. This is in line with the idea mentioned earlier that neurodegenerative diseases target specific large-scale networks. In the case of AD, the target network is the
DMN. Indeed various rs-fMRI studies confirm this by showing decrease resting connectivity in the DMN when comparing age-matched healthy controls with AD patients [56]. Figure 2 shows significant decreased DMN connectivity with healthy controls and late stage AD subjects. Other studies report decreased connectivity with regions of the PCC and the hippocampus [57, 58] in addition to decreased connectivity with other regions of the brain [59, 60]. They also report increased connectivity during the early stages of AD and amnestic mild impairment (aMCI) which suggest compensatory mechanisms which recruit addition neuronal resources to make up for cognitive deficits. These dynamic changes in resting state connectivity have prompted additional studies using machine learning algorithms, such as support vector machines (SVM), to classify an individual’s rs-fMRI scan based on the connectivity between different brain regions [61]. These studies have yielded promising results with some cases able to classify subjects with over 86.5 percent accuracy.

While analysis of rs-fMRI have proved critical in understanding and characterizing the patterns of AD progression, the actual relationship between pathology (Aβ and tau proteins), and functional connectivity remains unclear. For this purpose mouse models are necessary. Technical issues such as the size of the mouse brain make fMRI techniques difficult as it requires high signal-to-noise and spatial resolution [32]. OIS imaging offers a simple and effective alternative (Figure 3). In a study which used functional connectivity OIS (fcOIS), the researchers demonstrated that Aβ deposition was associated with reduced bilateral functional connectivity in AD mouse models [62]. In addition, optical imaging techniques such as two-photon microscopy allow for in vivo imaging of Aβ and the vascular response in capillaries and arteries in regions of Aβ deposition (Figure 4).

2.2. Frontotemporal Lobar Degeneration (FTLD):

Pathologically, FTLD is heterogeneous however the majority of syndromes are associated with tau-positive or TAR DNA-binding protein 43 (TDP-43)-positive inclusion bodies. Clinically FTLD can be divided into three main
groups based on their exhibited symptoms. Those are: behavioral-variant frontotemporal dementia (bvFTD), semantic dementia (SD), and finally progressive nonfluent aphasia (PNFA).

Clinical symptoms of bvFTD include changes in personality and behavior. Patients often show apathy or loss of interest in addition to disinhibition[63]. Structural imaging shows significant atrophy in the anterior cingulate, frontoinsular, striatal and frontopolar regions[37, 55, 64, 65]. These regions together make up a functional network known as the salience network. This network is known to be active during responses to emotionally significant stimulus[55]. Resting intrinsic connectivity analysis shows degeneration of this network in patients with bvFTD[37, 55]. Patients with SD show a progressive loss of knowledge about word and objects[63]. With SD atrophy occurs primarily in the left anterior temporal pole and the subgenual cingulate and again these regions show remarkable colocalization with an identified resting intrinsic connectivity network[55]. PNFA is another language disorder but is different from SD in that subjects exhibit loss of grammar and have difficulty speaking[63]. Comparison of functional connectivity networks and cortical atrophy show spatial correlation in regions of the left frontal operculum or inferior frontal gyrus[55].

![Figure 3. OIS imaging of mouse brain.](image1)

Figure 3. OIS imaging of mouse brain. Use of OIS imaging allows to view the regional changes in oxygenated hemoglobin (HbO), deoxyhemoglobin (HbR) and blood volume (HbT). Figure shows blood response to hindpaw stimulation beginning at 3 seconds after stimulation.

![Figure 4. Two-photon imageing of AD mouse model.](image2)

Figure 4. Two-photon imageing of AD mouse model. Arrows indicate regions of Aβ deposition in vessel walls and parenchyma.
2.3. Parkinson’s disease:

After AD, Parkinson’s disease is the second most common disorder. Pathologically it is characterized by the loss of neurons in the dopaminergic neurons in the substantia nigra (SN) along with the buildup of Lewy bodies and neuritis. These dopaminergic neurons in the SN extend primarily to the striatum, thus the loss of these neurons results in a deficit of striatal dopamine. This in turn causes a net increase of inhibition from the globus pallidus to the thalamus which represses the initiation of movements leading to the clinical symptoms of PD which consist primarily of motor symptoms such as tremors, rigidity and difficulties in balance and movement.

Contrary to previously discussed neurodegenerative disease, PD does not target and degrade a specific functional network. Structural MRI has revealed no significant changes in atrophy which are consistent across studies. Rather the loss of dopaminergic neurons results in the disruption of cortical-striatal networks. As a result, resting state connectivity analysis focused mainly on the dynamic changes in functional connectivity between these regions. In addition, since motor impairment is the primary symptom of the disease, resting state connectivity with the motor, premotor, and their related networks have been studied. In these studies, there is no specific decline in connectivity but rather they report that this disruption due to dopamine depletion leads to a remapping of cerebral connectivity. Figure 5 shows decreased resting state connectivity within the primary motor cortex in PD patients.

![Figure 5. Decreased resting state connectivity in the primary motor somatosensory cortex in PD.](image)

3. CONCLUSION AND SUMMARY

Since the discovery of correlations in LFFs of resting state fMRI, numerous studies have emerged which have provided insight into the functional organization of the brain and how they change with various neurodegenerative diseases. Indeed, the mapping and construction of RSN have revealed a remarkable likeness in pathology, cortical atrophy, and dysfunctional RSNs. These studies have also yielded numerous useful applications of these resting state correlations such as a potential noninvasive means for a biomarker for early detection and classification or a method for modeling disease progression. While functional connectivity may not give a full accurate picture of disease progression, it can easily be combined with other imaging modalities. With fMRI it is simple to combine results of diffusion tensor imaging (DTI) or cortical atrophy to examine the changes in structural connectivity along with functional connectivity. Finally optical techniques allow a more in-depth analysis allowing for imaging of disease animal models which can provide a direct relationship with molecular pathology and correlated blood flow.
4. ACKNOWLEDGMENTS

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