Resting State Functional Connectivity as a Pre-clinical Diagnostic Tool for Alzheimer's Disease

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Writer's Comment: *The complexity and plasticity of the brain in human aging has become a large interest of my undergraduate studies as I have gained more research experience in the field of Alzheimer's. I used the literature review assignment from Dr. Amy Clarke's UWP 104F course as an opportunity to challenge myself with investigating the applications of imaging technologies. I had been working at Dr. Charles DeCarli's Imaging for Dementia and Aging Lab and wanted to learn more about other projects at the lab. Right around the time Dr. Clarke assigned the literature review, I attended Dr. Owen Carmichael's Grand Rounds talk on the topic of Imaging Aging Brain Networks. I left the lecture fascinated with the direction that imaging research was headed and had even more questions that I wanted answered. I took an initiative in learning more about brain functional connectivity and associated analytic data used on brain scans by choosing these topics as the focus for my literature review. I hope to see these imaging tools reach their potential to diagnose patients early in the clinical course of Alzheimer's disease during my years as a medical professional. I am humbled to have had the opportunity to work with Dr. Carmichael on this paper and would like to thank him for suggesting excellent literature and providing me with feedback. In addition, I would like to give a special thank you to Dr. Clarke for helping me polish the paper and for advising me throughout the course and editing process.*

Instructor's Comment: *Alzheimer's disease is an already-tragic condition made worse by a lack of early diagnostic tools that can establish whether symptoms like memory loss are the result of normal aging or in fact of a disease progression. In her literature review, Jessica Liu discusses rs-fMRI (resting state functional magnetic resonance imaging) as a diagnostic tool for Alzheimer's, a tool that can discern otherwise hidden biomarkers of the disease. Don't be deceived into thinking this topic fell easily into the logical and straightforward organizational pattern of the version printed here or that the existing literature was easy to summarize and discuss. Jessica poured*

a good deal of well-focused attention into crafting this document, impelled in part by her sense of the topic's importance and her own interest in helping elucidate a disease that is a real scourge of our times. Should you need a neurologist sometime in the future—though I hope you do not—you would do well to find Dr. Liu. You will be in good hands.

—Amy Clarke, University Writing Program

Abstract:

The clinical course of Alzheimer's disease (AD) can be prolonged for decades following the onset of cognitive decline. However, growing research efforts on neural network organization through brain imaging techniques have identified resting state functional magnetic resonance imaging (rs-fMRI) as a potential identifier of biomarkers and therefore as a preclinical diagnostic tool for AD. Rs-fMRI has been proven to detect preclinical stages of AD in individuals with mild cognitive impairments before the onset of clinical symptoms. The exact relationship between the default mode network, a collection of brain structures that are particularly active during rest, and declining functional connectivity is still not fully understood. Even with the associations made between AD and rs-fMRI through emerging neuroimaging technique, further studies are needed to reassess the reliability and validity of statistical measurements derived from the intrinsic neural networks.

Key Words:

Alzheimer's disease, rs-fMRI, mild cognitive impairments, default mode network

Introduction

Figures released in March 2013 by the Alzheimer's Association reported that death from Alzheimer's disease (AD) increased by 68% between 2000 and 2010. Currently, the disease affects 5.2 million Americans[1]. While the scientific community and general public have increased their understanding of AD pathogenesis, researchers have not found a reliable method for tracking biomarkers in the disease's early clinical course. Because of their silent nature, AD symptoms often obscure diagnosis during preclinical stages.

Fortunately, positron emission tomography (PET) scans of amyloid accumulation followed with rs-fMRI have correlated the alterations in

the default mode network (DMN) with mild cognitive impairments (MCI) and AD pathology. Further development with these imaging tools will increase the possibility for early diagnosis, providing affected individuals more time to manage for the future and greater possibilities for intervention. Rs-fMRI presents a promising tool for detecting biomarkers and tracking the clinical course of AD, but factors such as variable resting state, small participant pools, and the questionable function of the DMN contribute to methodological issues that create controversy over its usefulness. This review will present rs-fMRI data from recent studies on MCI and AD, and will report inconsistencies in measuring resting state functional connectivity.

Early clinical course of AD

Disease onset can occur years before the first clinical symptoms manifest. Even patients who report mild complaints about episodic memory decline may be years or decades into the clinical course of AD. Features marking the onset of AD pathology include biochemical markers such as tau protein, a precursor of neurofibrillary tangles (NFTs) found in cerebral spinal fluid (CSF), and amyloid plaques[2]. Tau, however, is non-specific to AD pathogenesis. NFTs, on the other hand, are disease specific and important in diagnosing AD[3]. Because NFTs are typically found during postmortem autopsies, they fail to serve as predictive biomarkers[3]. More often, NFTs confirm AD among other forms of later-life dementia.

The sequence of events leading to characteristic pathology is typically initiated by amyloid plaque deposition[3]. PET scans on individuals with MCI can reveal amyloid plaque accumulation associated with preclinical stages. Studies have established PET scans as a diagnostic tool[12], and so far, this imaging method has been applied to tracking conversion from MCI to AD. Researchers find that amyloid plaque accumulation obstructs neural networks, contributing to declining integrity in functional connectivity. Because studies have correlated two distinct biomarkers present during the disease's early clinical course, researchers have been able to better predict MCI progression to AD[2]. Sheline et al[13] compared cognitively normal older adults with increased amyloid plaque accumulation to a control group of cognitively normal older adults; those with plaque accumulation showed an increased rate of progression to AD in a 3-4 year follow up period based on neural network activity. The

study suggests that tracking both amyloid accumulation and functional connectivity in brain networks provides a better prediction of the disease's clinical course.

Rs-fMRI in MCI and AD

Before rs-fMRI came into practice, task-related fMRI served as the main method for observing network integrity through disease progression. However, task-related fMRI studies lack standardized protocol for administering tasks to participants. In addition, this method can activate networks unique to only certain individuals and networks that were not previously recognized as part of the activated system[10]. Consequently, more researchers are exploring rs-fMRI to measure functional connectivity in the DMN. Measurements of the intrinsic network using rs-fMRI are different from previous methods because rs-fMRI targets a default property present in all brain systems[10].

Recent studies have shown that even when MRI data indicate little to no atrophy in gray matter, fMRI during resting state can produce data showing decreased coherence in the DMN and other neural networks associated with AD progression[5]. Moreover, studies have found that many of the regions within the DMN are most subject to amyloid deposition during the early clinical course of AD[5]. These strong associations between amyloid accumulation and altered neural networks suggest that decline in neural networks precedes brain matter loss[2]. As a result, rs-fMRI is proposed as a strong candidate over other diagnostic tools used in detecting biomarkers during the clinical course of AD.

Measuring neural networks

Functional connectivity within the DMN relies on the presence of statistical dependencies among spatially remote neurophysiologic events[11]. There are two computational methods, goodness-of-fit (GOF)/ independent components analyses (ICA) and region-of-interest (ROI) analyses. Through these computational correlations, measurements made from thousands of time series during a scan are simplified into scientifically relevant data that can potentially be applied in a clinical setting. Measuring the DMN in MCI and AD with these statistical dependencies will reflect activation or deactivation of anatomically distinct regions within the brain and integrity of the neural network as a whole.

Applications of computational methods have indicated that the DMN is most active during resting state. In addition, reduced activity or disrupted functional connectivity in its associated regions suggests AD pathology[2,4]. Hafkemeijer et al[5] found that participants diagnosed with AD displayed decreased resting state activity in the posterior cingulated cortex (PCC) and hippocampus as opposed to decreased functional connectivity of a broader range of DMN brain regions observed in elderly participants undergoing "healthy" aging.

Controversies arise in literature on MCI individuals showing hyperactivity in firing within the hippocampus. Hafkemeijer et al[5] conclude that it is not clear what explains these inconsistent trends when compared with findings mentioned above, where as Carillo et al[2] attribute increased activity to the brain's intrinsic compensatory mechanisms. Further studies are directed toward assessing how compensatory and non-compensatory hyperactivity in the DMN earlier in life relate to onset of AD pathologies later in life[11].

Goodness-of-fit (GOF) and independent components analyses (ICA)

One of the two computational methods is ICA integrated with GOF. GOF provides a quantitative neuroimaging index of DMN connectivity[4]. ICA and GOF combined provide a data-driven technique that decomposes fMRI signals into component functional networks[11]. The method is particularly effective during complex cognitive tasks where multiple operations occur simultaneously[11]. ICA in resting state revealed significant coactivation of the hippocampus in the DMN and, in the earliest stages of AD, indicated abnormal network activity[4]. Supporting Greicius et al[4], Hafkemeijer et al[5] reported decreased resting state activity in the PCC and hippocampus when deriving rs-fMRI data through ICA. The method falls short in distinguishing different nodes within the DMN that are part of multiple overlapping functional networks. While these nodes should be spatially independent among others, they are hard to distinguish as independent when ICA is applied[14].

Region-of-interest-based measurements

The second method of quantitative neuroimaging analysis involves a hypothesis-driven measurement of connectivity based on a-priori region-of-interest (ROI). Just as the name implies, ROI involves specifying a region-of-interest and averaging a time series of all of the voxels from the

fMRI within that region[4]. In AD participants, reduced DMN activity has been observed in the hippocampus and PCC, both major regions of the DMN[15]. ROI-based applications in Prvulovic et al[12] emphasize significant decreases in functional connectivity between core DMN regions in individuals who appear cognitively normal but display significant amyloid plaque deposition in PET imaging.

Because ROI analysis is limited to coactivation of specific regions within the DMN, this method does not reflect functional connectivity of the brain as a whole[15]. Networks that extend throughout the brain are affected by AD pathology. Consequently, a method that can reflect both integrity of specific regions and activity of the entire DMN could provide conclusive data on functional connectivity during the clinical course of AD. Investigators believe that a multivariate approach allows one method to compensate for the other's limitations, and as a result, could produce conclusive data necessary for rs-fMRI to serve as a powerful diagnostic tool[7].

Drawbacks in analytical methods

Variability of brain activity during rest

Rs-fMRI results in less performance-related variability when compared to task-related fMRI analyses[11], but Patrella et al[11] and several other studies identify problems in measuring resting state[6,12]. Common criticism for rs-fMRI techniques involves the variability of rest. Resting state can be difficult to constrain and distinguish due to its involuntary nature, and factors such as perceptual processing can influence cognition during rest[6]. Studies have participants keep their eyes closed or fixated on an object throughout the imaging process to control for perceptual processing, but errors can persist from overlapping stimulation of other domains associated with task performance, sedation, and sleep[6].

Small participant pool

Kelly et al[6] measured the inter-individual variation in intrinsic neural networks by computing correlations between age and function of a particular region in the DMN for sets of randomly sampled subgroups ranging from 100 to 1,090 individuals. The results were largely varied around the mean correlation of .23 when sample sizes were less than 100. On the other hand, sample sizes of over 1000 participants remained close to the mean. Most studies using rs-fMRI to understand the relationship

between DMN and AD progression have employed relatively small sample sizes. The study by Patrella et al[11] concluded that its small sample size of 68 participants resulted in overlap with GOF index values. In ROI-based approaches, Prvulovic et al[12] reported that limited participant pools in various studies contributed to differing results and diagnostic values.

So far, stability, reliability, and diagnostic value of data derived from rs-fMRI have been based on a limited number of studies and need validation from larger trials[12]. To solve this problem, the 1000 Functional Connectomes Project (FCP) and International Neuroimaging Data-sharing Initiative (INDI)/the Human Connectome Project (HCP) have begun providing data to the brain imaging community. This public data will be crucial in validating current understanding of the DMN through AD progression[6].

Unknown biological basis of rest activity

Raichle[9] refers to the intrinsic activity of the DMN as "dark energy," since observations of the DMN are limited to rs-fMRI. Neuronal responses to external stimuli account for a small portion of the brain's total energy consumption with less than 10% of all synapses in the brain involved in external pathways. Scientists hypothesize that the remaining amount of brain metabolic activity is used by the DMN, suggesting that intrinsic networks are crucial in facilitating response to input signals. Another possibility is that the DMN accounts for unconstrained cognition, which is stimulus-independent[9]. Because the network's true biological function continues to be questioned, measurements taken in the DMN are still not entirely known or observable outside of rs-fMRI.

Discussion

Current studies using rs-fMRI to understand clinical course of AD have not yet provided conclusive data to develop a reliable tool for identifying biomarkers in the earliest stages of the disease. While declining integrity and decreased activity of the DMN are often associated with MCI and AD pathology, correlations between DMN functional connectivity and the clinical course of AD remain questionable. Depending on whether ICA/GOF or ROI based-analysis is applied in rs-fMRI, the results may emphasize either coactivation of regions in the DMN or activity in specific regions, but not both. Studies have suggested that multivariate approaches will allow for one method to compensate for the other's limitations and vice versa[7]. However, combining methods may add to the

challenges associated with controlling for overlapping networks. While two national-level projects, the 1000 Functional Connectomes Project (FCP) and International Neuroimaging Data-sharing Initiative (INDI), are solving the issue of limited participant pools, further investigation is needed to address the variability of brain activity during rest and the unknown biological nature of the DMN. As researchers improve their understanding of the function and purpose of intrinsic networks, they will have better control over sources of variability such as interfering domains.

Strong associations between amyloid accumulation and altered neural networks indicate that rs-fMRI can be more powerful than other imaging tools in detecting biomarkers during the early course of AD. Analyses of CSF that include amyloid, tau, and other molecular biomarkers should be taken in conjunction with rs-fMRI data to provide more comprehensive results in future studies. Furthermore, if treatments slowing disease progression become available, rs-fMRI can become even more crucial as a tool in identifying biomarkers through the clinical course of AD[6]. Rs-fMRI's potential for providing early diagnosis in AD patients makes it a promising area for further investigation.

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