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A Survey on applications and Analysis Methods of Functional Magnetic Resonance Imaging for Alzheimer's Disease

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Abstract

Background: Functional magnetic resonance imaging (fMRI) is an MRI-based neuroimaging technique that measures brain activity basis of blood oxygenation level. This study reviews the main fMRI methods reported in the literature and their related applications in clinical and preclinical studies, focusing on relating functional brain networks in the prodromal stages of AD, with a focus on mild cognitive impairment (MCI) to AD.

New method:The purpose of this article is to present and compare different approaches of supervised and unsupervised fMRI analyses and to highlight the different applications of fMRI in the diagnosis of MCI and AD.

Results: survey article asserts that brain network disruptions of a given dysfunction or in relation to disease prone areas of the brain in neurodegenerative dementias could be extremely useful in ascertaining the extent of cognitive deficits at the different stages of the disease. Identifying the earliest changes in these activity patterns is essential for the early planning of treatment and therapeutic protocols.

Comparison with existing methods: Analysis methods such as independent component analysis (ICA) and graph theory-based approaches are strong analytical techniques most suitable for functional connectivity investigations. However, graph theory-based approaches have received more attention due to the higher performance they achieve in both functional and effective connectivity studies.

Conclusion: This article shows that disruption of brain connectivity patterns of MCI and AD could be associated to the cognitive decline and interesting finding that could augment the prospects for early diagnosis. Multimodal neuroimaging will provide more clinical insight of brain functional and structural mapping.

Keywords: Alzheimer's Disease, Mild Cognitive Impairment, fMRI, Resting State fMRI, Task-based fMRI, Functional Connectivity, Multimodal Neuroimaging.

Contents

1. Introduction

Alzheimer's disease (AD) is one of the most common progressive neurodegenerative dementias where neurofibrillary tangles and amyloid plaques(amyloid $\beta - peptide$ (Aβ) accumulation) in the brain tissue trigger damages in neurons and synapses in the cortex [1, 2]. The disease is characterized by memory loss, neuronal atrophy, cell death and decline in cognition and language, resulting in cognitive and behavioral impairments that affect and limit normal daily activities. [3, 4]. In 2018, almost 5.7 million Americans have AD which is predicted to 13.8 million people in 2050 in the United States [5]. According to data reported

in the 2017 report by the Alzheimer's Association, Alzheimer's disease is affecting 10% of the population over the age of 65 and the growing costs in managing the disease are estimated to be $259 billion. With population growth and rise in life expectancy.

The pathogenic mechanisms of this neurological disorder can be investigated using different imaging modalities that include: magnetic resonance imaging (MRI) to assess structural changes; functional magnetic resonance imaging (fMRI) to gauge the functional patterns of neuronal activities; electro and magnetoencephalography (EEG/MEG) to to study the high-resolution temporal brain dynamics; positron emission tomography (PET) to assess functional and metabolic changes through radioactive tracers in order to delineate healthy brain regions from diseased or affected ones; diffusion tensor imaging (DTI), which is essential for determining the white matter fiber tracks and for elucidating any disruption in these tracks due to disease; and Computed Tomography (CT), although it exposes the subject to a moderate level of radiation (X-ray based technology), it is the fastest image acquisition modality that provides added information on density and texture of body organs and is less prone to subject movement during image acquisition [6]. Of course, the most effective approach to diagnosis, although costly, will be the multimodal neuroimaging approach that combines the individual strengths of these modalities, and consolidate structural measurements to functional and metabolic measurements. In the recent decades, fMRI has been introduced as a non-invasive, radiation-free, and useful imaging analysis technique to diagnosis, predict and classify different stages of a disease, cross-sectionally or through longitudinal studies. The fMRI modality is a reliable tool to investigate functional connectivity, study the spatiotemporal correlations between the different brain regions, and to assess brain dysfunction in terms of its neural connectivity networks [7].

Resting state fMRI (rs-fMRI) is a major field of study that embodies the low-frequency fluctuations of the fMRI signal [8]. The correlations among these low frequency fluctuations is what defines functional connectivity (FC) of the brain [9, 10]. Rest state defines a distinct brain network referred to as the default mode network (DMN). The DMN is presumed to be active during wakeful moments of day dreaming, moments of contemplation or thinking about the past as well as the future, and any other moment in time that is void of external stimulation.

Task-based fMRI (t-fMRI), on the other hand, are advanced techniques for evaluating functional activity alternations and for brain mapping given a specific assigned task (motor, visual, language test, neuropsychological test, etc.). These types of studies investigate functional changes during a particular activity such as memory encoding [11, 12], visual [13], language [14], and auditory encoding [15, 16]. These studies provide evidence of specific functional connectivity patterns in regions of the brain associated with the targeted areas of the task and observe the related disruptions that could occur due to diseased areas or to specific presumed dysfunctions [17, 18].

When contrasting rs-fMRI with t-fMRI, task-based fMRI is more complex to acquire, needs added cooperation from the subjects while performing the task, and often yields a lower signal to noise ratio; while rs-fMRI is easier to acquire as it voids the need for a task to be performed, and is more amenable for use

when involving impaired patients who are unable to participate in performing a given task fMRI. Moreover, with the last assertion in mind, while gauging progression of the disease, rs-fMRI could be very useful in identifying the subtle changes in functional connectivity at the different stages of the disease, and most importantly at detecting the early signs of the disease for the planning of early treatment and therapeutic protocols [8]. Nonetheless, in order to investigate specific brain networks such as visual, motor or auditory, using t-fMRI is necessary. Moreover, empirical evaluations have shown that rs-fMRI and t-fMRI are uncorrelated, and if both are appropriately administered, the assumption of uncorrelatedness supports the notion that the DMN can be thought of as a linear additive model, unless the assumed DMN is affected by the subject's excitation or tiredness during the recording session [19].

In AD studies, many researchers reported gray matter atrophy in some brain regions such as the temporal lobe and hippocampus [20, 21], and some reported white matter volume reduction due to myelin and axon loss [22, 23, 24]. However, recent studies suggested that AD is not only associated with the gray and white matter atrophy but also with changes in the brain region's connectivity that are detectable before structural atrophy due to amyloid deposition [25, 26, 27, 28, 29, 30, 31, 32, 33, 34]. Some studies reported BOLD fMRI signal changes in sensorimotor cortex under resting state condition [35, 36, 37], similar studies explored fMRI signal changes in visual and auditory related cortices [38, 39, 40] [16]. Liu et al. found that strength of disruption in functional connectivity of parahippocampal gyrus is correlated to the disease severity which becomes more pronounced as a subject transitions from the early stage of mild cognitive impairment (EMCI) to the late stage of AD [41]. Another study indicated that low episodic memory is associated with anterior-posterior dynamic alternation in the brain connectivity [42]. Bero et al. corroborated the bidirectional relationship between amyloid aggregation and reduction of resting-state functional connectivity in the brain [43], while at the same time showing an increase in functional connectivity in some other regions [44, 45]. This last finding could suggest the causality that one affected region of the brain could have on other distant regions of the brain as mentioned earlier.

There are valuable review articles that studied AD based on fMRI data [46, 47, 48, 49, 50, 51, 52, 53]. Guo et al. reviewed the effect of medicines on AD by understanding the role of fMRI technology in Alzheimer therapies [46] Friston reviewed the mathematical modeling of effective connectivity [48], while dividing the modeling procedures into two categories of dynamic causal modeling (DCM) and Granger causality modeling (GCM). Xie Teng et al. reviewed AD studies mainly focusing on graph theory applications in brain connectivity [47]. In their review, structural MRI (sMRI), fMRI, and EEG based studies in AD patients are reviewed briefly and some future perspective in AD studies are suggested. Fox et al. reviewed the rs-fMRI and transcranial magnetic stimulation (TMS) techniques in brain connectivity modeling and the combination of TMS and rs-fMRI techniques. However, they didnt focus on a given disease, e.g., AD, and they briefly reviewed studies related to the diagnosis and treatment of neurological disease [49]. However, they didn't focus on a special disease, e.g., AD, and they briefly reviewed studies related to the diagnosis and treatment of neurological disease. Smitha et al. aimed to study the importance of rs-fMRI and its advantages

to the task-based fMRI [18]. Van et al. reviewed the functional connectivity patterns in disease like AD, and schizophrenia using rs-fMRI [53]. Sheline et al. reviewed some studies that cover preclinical AD to clinical AD using rs-fMRI [50]. It was shown that changes in resting-state functional connectivity are detectable from rs-fMRI before any changes that can be identified by PET detection of amyloid accumulation. In [54], three major approaches to study functional connectivity using the fMRI signal were considered, including graph theory, region of interest or seed-based and independent component analysis (ICA). They compared the functional connectivity disruption in normal aging subjects and AD patients and proved that FC was disrupted in normal aging but not uniformly across the brain. However, the accelerated decline in AD subjects considerably affected some particular regions in the brain like default mode network (DMN).

In this survey article, we focus on the most recent functional brain mapping studies and related methods of analysis on AD and MCI using resting-state and taskbased fMRI. In addition, we reviewed the preclinical as well as clinical applications of fMRI. Studies using fMRI have proven the merits of this modlaity as it detects subtle changes in the functional activities prior to any observable changes in the structural (MRI) or in the metabolic/functional (PET) modalities. The rest of paper is organized as follows: Section 2 reviews the most prominent methods for preprocessing and analyzing fMRI data. Section 3 illustrates the brain connectivity fundamentals. Section 4 reviews recent exploration of effective and functional connectivity in clinical AD studies, then, Section 5 studies the preclinical application of fMRI data which represents the functional connectivity alternation along with PET scanning and Apolipoprotein (APOE) $\varepsilon 4$ allel. Finally, in section 6, we discuss the existing limitations and challenges that remain to be addressed and future perspective of fMRI studies. Section 7 provides the concluding remarks.

2. Methods

2.1. Preprocessing

Prior to processing the fMRI data, there is need for minimizing data artifacts, and attenuating the effects of noise and offsetting any potential image degradation during image acquisition [55]. Empirically, the signal of fMRI could be affected by three major sources of artifacts, which include thermal noise of MR imaging, system noise of the MR hardware, and subject-related noise resulting mostly from head motion [56]. Preprocessing is also important to facilitate registration of different imaging modalities (e.g. T1 MRI with PET). In addition, in group analysis it is assumed that every voxel for each subject is located in the same area as for other participants. Consequently, steps for preprocessing fMRI data are slice time correction, co-registration, motion correction and smoothing as illustrated in Figure 1.

Slice time correction shifts the time series of voxels to validate the assumption that data points are collected simultaneously. Motion correction estimates the amount of motion by calculating the translational and rotational parameters of the input and target images. However, motion correction and whole brain regression analyses are controversial since some believe that insufficient motion correction or whole brain

regression produce fake correlations [57]. Co-registration and normalization realigned the functional and anatomical images to provide standard anatomy for each subject. Since every subject has a specific brain shape, size, and features, the data needs to be normalized to be comparable to a large population. Finally, smoothing the signal which is usually defined by Gaussian filter improves the signal to noise ratio to acquire normal data for analysis.

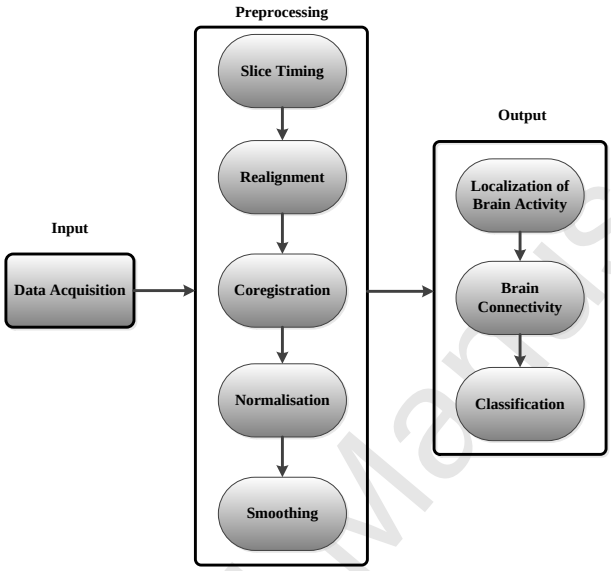

Figure 1: fMRI data processing pipeline from data acquisition to classification.

2.2. Data Processing

Recently, many approaches have been proposed for fMRI data analysis, each with its advantages and limitations. Graph theory remains the most reliable approach that can be used to construct and analyze brain connectivity. Graph theory methodology is able to illustrate the functional and effective connectivity of the brain. In other words, graph theory not only demonstrates the functionally connected regions but also shows how they influence each other [58]. In this section, the main approaches for fMRI analysis are briefly explained.

The model-based approaches including coherence, SPM, and correlation are based on prior knowledge about the region of interest or seed. The region of interest (ROI) was proposed for the first time by Biswal in 1995 in which a region is selected as a reference region and the correlation of the time series with other regions are calculated [9]. In the ROI or seed-based approach, a region is selected as a reference region and the time series of that region are obtained. Then, the correlation of time series of the fMRI signal in seed voxel and time series of all other voxels of the brain regions are calculated. The regions with a high positive value of correlation are functionally connected, and regions with a negative value of correlations are presumed disconnected. A threshold is usually used to determine strong correlations which lead to strong connectivity between the seed and other brain regions. The results of the ROI method are easier to compare

since there is a reference region in this method. Therefore, fewer variations of components and the simplicity of extracting the same networks for the same seed in different subjects makes it preferable to the other methods. However, preselecting ROI in all brain regions is an issue in functional connectivity investigation since it remains unclear how different choices of seed selection would affect the functional connectivity [59]. Seed-based methods need consideration of a seed and find the connectivity map based on prior information about the seed region, requiring significant clinical experience and expert intervention. On the other hand, different seed selections will result in different connectivity patterns, which cause some concerns about these techniques.

On the other hand, data-driven techniques are totally different from prior information-based techniques and can be classified into transformational based and clustering based. The main advantage of data-driven methods is that they do not need prior information of the brain activity. Transformational-based techniques map fMRI signal into the high-dimensional space in order to separate different components of the data. It is also possible to separate the noise from the original data using this approach, which is mainly performed by principal component analysis (PCA) and independent component analysis (ICA). Sometimes, PCA is applied as a preprocessing method before ICA by data decomposition and temporal dimension reduction. On the other hand, clustering based methods classify the time course signal into similar patterns using the correlation between neighboring voxels [60]. Gaussian mixture model, viewed as a general version of the clustering-based method outperformed the ICA for task-based studies when extracting a small number of components; however, they are almost similar when 10 or more components are involved [61].

2.2.1. Cross-Correlation Analysis

Cao et al. introduced cross-correlation analysis (CCA) for the first time in 1999 [62]. The cross-correlation method is based on the required correlation between signal time courses of the seed and another region if they were to be functionally connected. The correlation can be computed as follows:

$$C_{m,n} = \frac{CV_{m,n}(\tau)}{\sqrt{v(m) \times v(n)}} \tag{1}$$

where C defines the cross-correlation at lag τ, $V(m)$ and $V(n)$ are the variances of time courses of $T_m(i)$ and $T_n(i)$ as a seed in lag τ, respectively. $CV(\tau)$ is the cross variance of those time courses that can be defined as follows

$$CV_{m,n}(\tau) = E\{((T_m(i) - E(T_m)) \times (T_n(i) - E(T_n)))\} \tag{2}$$

where E is the mean or expected value and we can determine if $T_m(i)$ and $T_n(i)$ are functionally connected considering a threshold. The computation time for complete calculation would be heavy for all lags. Therefore, there is a need to calculate the correlation with a dozen time points in a time window that limits the application of this method. In addition, cross correlation analysis depends on the hemodynamic response function (HRF) which is different among different subjects or even different regions of the brain in one subject with limited duration time.

2.2.2. Coherence Analysis

Although the cross-correlation analysis is a useful method for both type of fMRI analysis of rs/task-fMRI, the connectivity measurement at zero lag would be argumentative [59]. On the other hand, sensitivity to HRF which is different among subjects and also high correlation caused by cardiac activity noise between regions with no fluctuations in blood flow are disadvantages of CCA method which lead to use coherence analysis (CA) [63]. The coherence measures the correlation of two time series of $T_m(i)$, and $T_n(i)$ at the frequency, f, which can be defined as

$$C(f) = \frac{\mid F_{m,n}(f) \mid^2}{F_{n,n}(f)F_{m,m}(f)} \tag{3}$$

Where C represents the coherence, $F_{m,n}(f)$ defines the cross spectrum in the frequency domain, $F_{m,m}$ and $F_{n,n}$ are the power spectrum determined by Fourier transform as equation 4

$$\begin{aligned} F_{m,n}(f) &= \sum_k CV_{m,n}(k)e^{-jfk} \\ F_{n,n}(f) &= \sum_k CV_{n,n}(k)e^{-jfk} \\ F_{m,m}(f) &= \sum_k CV_{m,m}(k)e^{-jfk} \end{aligned} \tag{4}$$

This coherence method does not depend on neural activity or HRF which can be considered as the advantage over the correlation method [63]. Analysis, the correlation in frequency domain, provides valuable and easier way to get functional connectivity. For example, the frequency below 0.1 Hz is associated with FC while the frequency above 1.2 Hz is contributed to the cardiac activity since the flow fluctuations of the blood have 10-second period [59].

2.2.3. Statistical parametric mapping

Statistical parametric mapping is an approach based on the general linear model (GLM) which includes some useful algorithms such as subtraction, correlation coefficient, t-tests, and ANCOVA [64]. The results of SPM are illustrated usually by the voxels with P-value lower than the threshold in color. In order to estimate the parameters of the data, GLM uses the Gaussian random field to solve the comparison problems. The application of SPM is in preprocessing of the data for motion correction and spatial smoothing. In addition, SPM can be used in the statistical analysis of the data on each voxel for functional mapping and functional connectivity investigations [65]. In this approach, the model is set up and fitted to the data. The GLM for a variable matrix of T which represents the time course of voxels can be defined as

$$T = G\eta + E \tag{5}$$

where G is the column of the coefficients consists of the variables associated with the experimental conditions and E is the vector of errors that are independent and normally distributed. The parameter η is the vector

of unknown parameters at each voxel that can be estimated using the least square method. The Magnitude of the least square, l, demonstrates the activation presence or absence and can be calculated by

$$l = (G^t G)^{-1} G^t T \tag{6}$$

where t denotes the matrix transpose. The variance-covariance matrix, V, can be defined as

$$V = Var(E)(G^t G)^{-1} \tag{7}$$

By defining error term, $E\{l\} = \eta$, the statistical inference can be created. The SPM toolbox provides all statistical analysis which is one of the most popular toolboxes in fMRI studies. The validity and application of statistical GLM have been confirmed in the vast majority of studies in recent decades. However, there are some limitations and assumptions for the application of this method. The error term should be considered normally distributed and observations should have a Gaussian distribution. In addition, this method relies on smoothed images that may decrease the fMRI spatial resolution.

2.2.4. Graph Theory

Functional brain network is a complicated system with properties like small-world characteristic, hub distribution and connection, hierarchy, centrality and modularity, among others. Graph theory is a mathematical method to represent a complicated network as a rather simplified graph characterizing the choreography in terms of activation between brain regions. Using graph theory, the functional network can be investigated in four essential steps [66]. First, the nodes and associations among these nodes need to be determined. The fMRI signal is spatially segregated, and the correlations between pairs of brain regions are stored in a matrix. These correlations of time series of the different brain regions represent the relationship or connectivity of those regions. In the end, the network features of the graph including shortest path length, betweenness, clustering, small-word, and modularity that can be measured mathematically, are calculated. An overall view of graph theory analysis is displayed in Figure 2. Most graph theory based studies use symmetrical calculations like correlation and coherence or partial coherence to find the association between nodes.

A graph consists of N nodes which are shown by dots and K links that are drawn by lines can be represented as $G(N, K)$. It is important to know which pairs of nodes create a link [67]. Node degree that is the most fundamental parameter can be described by the number of connections of a node with the other nodes in the network. Shortest path length, a criterion to show the integrity of a network, provides the optimal pathway and characterization of the internal graph structure as well. This can be represented as a matrix of L which includes all shortest path lengths as follows:

$$L = \left(\frac{1}{N(N-1)}\right) \sum d_{ij} \tag{8}$$

where d_{ij} is the length of the link between node i and node j.

Node betweenness property that provides node centrality is used to detect the individual in a network, and it is determined as:

$$b_k = \sum \frac{n_{ij}(k)}{n_{ij}} \tag{9}$$

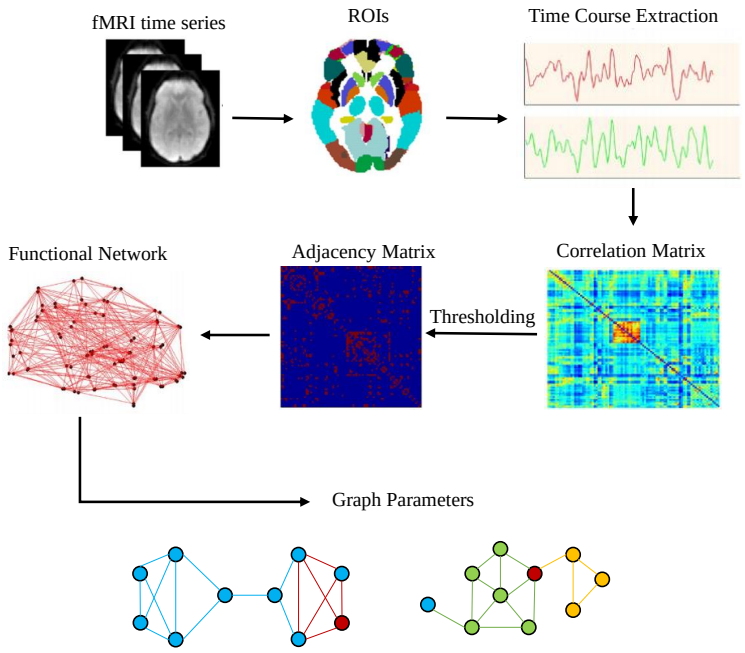

Figure 2: Procedure to obtain the functional network and graph theory parameters

where b_k is betweenness node network property, n_{ij} is the number of shortest path lengths connecting the i and j, and $n_{ij}(k)$ is the number of shortest path lengths connecting the i and j while passing node k. The edge betweenness can be described in the same way as the number of shortest path lengths between a pairs of nodes passing an edge.

Clustering coefficient which is defined by the segregation of a network is related to the neighboring communication. It can be calculated by the ratio between the number of connections of the nearest neighbors and the maximum number of connections or edges that can exist [68, 66]

$$C = \frac{1}{N} \sum g_i \tag{10}$$

where g_i can be defined as

$$g_i = \frac{number\ of\ edges}{maximum\ possible\ number\ of\ edges} \tag{11}$$

The centrality of a node defines the number of shortest paths between node pairs which pass through that specific node in the network. Modularity exhibits how graphs are unified within subnetworks or separated between modules.

Small-world, S, that is mathematically calculated by the the ratio of normalized clustering coefficient to the normalized path length, is a property that determines the global efficiency of a network. A network with a small value of shortest path length and high value of clustering coefficient corresponds to a network with a high value of efficiency. Small-world topology can be obtained through the brain hubs that provide every node the ability to have a low number of connections while remaining linked to the other nodes [57].

Brain hubs can be described as brain regions that strongly connected to many other regions of the brain or nodes with high centrality [69]. Normalization is defined by comparing the value of C and S of the random networks [70].

$$S = \frac{\gamma}{\lambda} \tag{12}$$

where $\gamma = \frac{C}{C_{rand}}$ and $\lambda = \frac{L}{L_{rand}}$

Recently, some toolboxes have been introduced to provide graph theory analysis for the researchers such as GraphVar [71], conn [72], GAT [73], and brain connectivity toolbox [66].

2.2.5. Principal Component Analysis

PCA decomposes the fMRI signal into some variations through an orthogonal transformation which separates important features from those with fewer importance [74]. The data is transferred into a set of eigenvectors by mapping the highest variance on the first principal component, the next greatest variance into the second principal component, etc. In order to apply PCA on fMRI signal, the data needs to be set up in a two-dimensional matrix of voxels and time series which provides components at each time point [75]. The projection can be defined by

$$Y = WX \tag{13}$$

where W is the transformation matrix formed from eigenvectors of the autocorrelation matrix and X is the centered two-dimensional matrix of fMRI data while the mean of distribution was subtracted from the data. The eigenvector matrix, E, is obtained by the following equation

$$X_C E = \lambda E \tag{14}$$

where X_C is the covariance matrix of the fMRI signal and λ is the matrix of eigenvalues. Using PCA for fMRI analysis has been reported by some studies [76, 77, 78]; however, there are some limitations in using PCA for fMRI analysis. For example, the orthogonality of the transformation causes loss of some important data if the main signal and noise are non-orthogonal. In addition, it may cause loss of some functionality patterns or small changes in fMRI signal due to capturing the greatest variabilities [79].

2.2.6. Independent Component Analysis

Independent component analysis known as blind signal separation is a method for source separating components and whose application involves many fields of research. The hypothesis of using ICA is the linearity in data recording from independent non-Gaussian sources which is the key factor for estimating the sources [80]. In fMRI investigation, ICA ICA is an effective method for parsing the two dimensional signal of temporal and spatial data into the spatially independent components that each associated with a time

course. Each spatial distribution determines a spatial map that is uniquely specified [81, 82]. Decomposing the fMRI signal into the map voxel and time courses can be expressed as:

$$X_{ij} = \sum_{k=1}^{N} A_{jk} S_{ki} \tag{15}$$

where X is the matrix of the data which is the fMRI signal, A is the matrix of mixing coefficient, and S is the matrix of map's components. S can be calculated by summing the product of matrix of the fMRI signal, X, and the unmixing matrix, W, for the N points of the fMRI input

$$S_{ij} = \sum_{k=1}^{N} W_{ik} X_{kj} \tag{16}$$

The index of ij describes the j^{th} voxel in the i^{th} component map and the index of ik is the i^{th} time point of the k^{th} voxel.

The advantages of ICA methods are obtaining the time course of the brain activation instead of determining a priori in ROI [83], and separating noise and motion artifacts from fMRI signal [84]. However, there are some challenges in using ICA including the number of independent components, the lack of a predefined model to apply to the data, differentiation of physiological network component from noise component, and the complexity in the group comparison due to a large number of variations in reconstructing the signal [54].

Clustering analysis

Clustering approach which is widely used in functional connectivity studies consists of 3 steps: 1) Calculating the correlation of neighbors for each voxel, 2) Finding the maximally correlated neighbor for each voxel, and 3) Clustering the data according to the voxels and maximally correlated neighbor. Self-organizing maps [85], hierarchical clustering [86], fuzzy C-mean [87], and k-mean clustering [88] are main approaches in clustering analysis that the fuzzy C-mean and K-mean clustering are most beneficial as detailed next.

2.2.7. K-mean clustering

K-mean clustering is a method to find groups in the data defined as x_i observations or time courses that have been set as vectors. In this approach, the data is classified according to the feature of similarity that uses minimization of squared error with an objective function, J, for clustering the data.

$$Jmn = \sum_{m=1}^{K} \sum_{n=1}^{T} (x_m - C_n)^2 \tag{17}$$

where K is the number of clusters, C_n is the number of time courses at n^{th} cluster, and $(x_m - C_n)^2$ is the distance between time courses and the centroid. The centroid can be calculated by

$$Cn = \frac{1}{T} \sum_{n=1}^{T} x_m \tag{18}$$

Therefore, the algorithm is: First, the value of centroid is initialized. Second, the distance between each data point and centroid is obtained, and third, each data point is assigned to the associated centroid

according to the obtained minimum distance. This process is repeated using the new centroid from equation (18) until no data points need to be reassigned. In this approach, the number of clusters is needed to be predefined, which is a disadvantage for the K-mean algorithm. There is no algorithm or general solution to find the initial value; however, it can be estimated using the mean distance to the centroid of each cluster, while the number of clusters in the hierarchical method can be defined in the final stage.

2.2.8. Fuzzy C-mean clustering

The main idea of the fuzzy C-mean method is the minimization of the least square error of objective function that is usually total distances between patterns [87]. Fuzzy partition of the data set is defined by

$$J_n = \sum_{i=1}^{k} \sum_{j=1}^{m} u_{ij}^n s_{ij}^2(x_j, y_i) \tag{19}$$

where m is the number of voxels in fMRI, u_{ij} is fuzzy membership, y_i is centroids, and s is the distance between voxel i and a centroid j. The fuzzy index, $n > 1$, and the number of clusters, $k > 2$, and n is the number of features. Minimization of J_n can be obtained under the following conditions

$$u_{ij} = \frac{1}{\sum_{c=1}^{k} \left(\frac{s(x_j, y_i)}{s(x_j, y_i)} \right)^{\frac{2}{n-1}}} \tag{20}$$

$$y_{ij} = \frac{\sum_{d=1}^{m} u_{id}^n x_{jd}}{\sum_{d=1}^{m} u_{id}^n} \tag{21}$$

where the initial value for u is calculated by

$$U_0 = (1 - \frac{\sqrt{2}}{2})U_a + (\frac{\sqrt{2}}{2})U_b \tag{22}$$

where $U_a = \frac{1}{k}$ and U_b is random partition of fMRI signal. The fuzzy C-mean is less likely to converge unsatisfactory which is one of the advantages of this approach; however, it is based on the threshold value and depends on the number of clusters which makes some difficulties in biological applications.

Table 1 and Table 2 provide the advantages and disadvantages of the discussed methods along with the purposes of the analyses.

As mentioned above, there are various kinds of available methods to analyze fMRI which all follow linearity assumption of connectivity. In general, none of the methods outperformed the others and application depends on the aims of the study. However, graph theory attracts more interests due to the ability to show the complex network analysis visually and providing both functional and effective connectivity information. In addition, there are some nonlinear statistical methods such as synchronization likelihood (SL) based on generalized synchronization [89], maximum likelihood [90], and approximate entropy (ApEn) [91], that can be used to overcome the limitations of linear analyses. However, due to the heavy computational load and probability of not overcoming linear approach limitations, these methods are not popular to use. For example, Deneux et al. developed a technique based on the maximum likelihood to analyze the fMRI signal

Table 1: Comparisons among different model-based methods for fMRI analysis

Method	Purpose	Strength	Limitations
Model-Based	-Measuring the correlation of the seed and other regions	-Easy to implement -Robust in results	-Prior knowledge is required
CCA	-Finding the correlation of the time courses of functionally connected regions	-Easy to implement	-Computing the correlation with a time window of a dozen time points -Sensitivity to the HRF -High correlation caused by cardiac activity noise between regions with no fluctuations in blood flow
CA	-Finding the correlation of two time series in a frequency domain	-It does not depend on the HRF	-Predefining the seed
SPM	-Presenting the variables associated with the voxels signal time course	-Having application in preprocessing of the data for motion correction and spatial smoothing -Having application in the statistical analysis of the data on each voxel for functional mapping -Availability as a software package	-The error term should be considered normally distributed -Observations should have a Gaussian distribution which may decrease the fMRI spatial resolution
Graph Theory	-Finding the functional and effective connectivity using the nodes as voxels and edges as connections -Finding the parameters of the different networks of the brain	-Representing the complex network as a visual graph -Making easier way to distinguish the relationship between brain regions using topological parameters	-Having complexity for implementation

Table 2: Comparisons among different data-driven methods for fMRI analysis

Method	Purpose	Strength	Limitations
Data-Driven	-Separating the different components of the data	-Prior knowledge is not required	-Lower accuracy -Missing data
ICA	-Finding and separating temporal and spatial independent components	-Obtaining the time course of the brain activation instead of determining a priori in ROI -Separating noise and motion artifacts signals	-Defining the number of independent components -Having lack of a predefined model to apply to the data -Having difficulty in differentiation of physiological network components from noise components -Having complexity in the group comparison
PCA	-Finding the most important temporal and spatial components	-Capturing the most important variables	-Orthogonality of the transformation may cause loss of some important data -Loss of some functionality patterns or small changes in fMRI signal Considering orthogonality and linearity assumptions of the data
K-mean Clustering	-Clustering the data according to the feature of similarity	-Easy to implement -Ability of changing the clusters by instances -Being fast	-Predefining the number of clusters -Probability of being influenced by the initial seed -Sensitivity to scaling -failing for nonlinear datasets
C-mean Clustering	-Clustering the data by minimization of the least square error	-Less likely to diverge -Having the best performance for overlapped data	-Depending on the threshold value -Depending on the number of the prior clusters -Having high computational time in comparison to other clustering methods

using the dynamical model which needs great computational procedures [90]. However, they found similar results with linear model ones indicating that linear models are probably sufficient for detecting activation regions in the brain.

3. Brian connectivity fundamentals

Neuroimaging studies, specifically brain connectivity investigation is an approach to examine the brain networks including default mode network (DMN), control network (CON), sensorimotor network (SMN), dorsal attention network (DAN), visual and auditory networks, and salience network (SAN) as shown in Figure 3 [92, 50]. This mapping can be defined as a set of nodes and edges which are arranged based on correlation of time courses contributed to the nodes [93]. The directionality of the connections defines the flow of the information through the brain networks which refers to effective connectivity. Therefore, three major of brain connectivity investigations can be identified: 1) structural connectivity which provides physical connection, 2) effective connectivity, and 3) functional connectivity [48].

The term "functional connectivity" contributes to functional integration that can be described as an interaction between different brain regions while functional segregation is defined as localization of the function in the brain. Segregation shows the distinction of functional activity of cortex that is separated within the cortex. On the other hand, functional integration can be demonstrated as functional connectivity using statistical associations between time series such as coherence and correlation, and effective connectivity using parameters of a model-based approach. Indeed, functional connectivity discovers the statistical patterns of the brain regions while effective connectivity shows how brain regions affect each other. Some approaches use the direction of the connections to illustrate information through brain networks [52]. The most basic visualization of the brain connectivity is a two-dimensional $N \times N$ matrix or using graph theory. Figure 4 shows different modes of brain connectivity using the graph model [94].

Functional connectivity can be investigated through the methods described in previous sections. On the other hand, Friston proposed mathematical modeling of the effective connectivity in two main categories of DCM and GCM [95]. DCM can be expressed as a state-space model that represents the differential equations which govern the activity of the hidden neurophysiological states. DCM using the model of effective connectivity, models the influence of the brain regions activity. On the other hand, in the brain connectivity literature, GCM is an autoregressive based modeling approach for fMRI data that looks for the correlations of that regions. This method tries to test the effects of the regions on each other using models of functional connectivity. Structural equation modeling (SEM) which assumes the neural activity has reached its steady states and is useful in modeling non-time-series data. Friston found out that among these modeling approaches, DCM is a new approach to overcome the limitations of GCM and received the most attention. Here, structural connectivity that uses sMRI or diffusion tensor imaging (DTI) is not discussed since it is out of this research scope.

4. Clinical AD Investigation

Clinical investigation of Alzheimer's disease is defined as a stage of disease that symptoms emerge. The biological changes can be assessed anatomically and functionally in order to perform classification of the

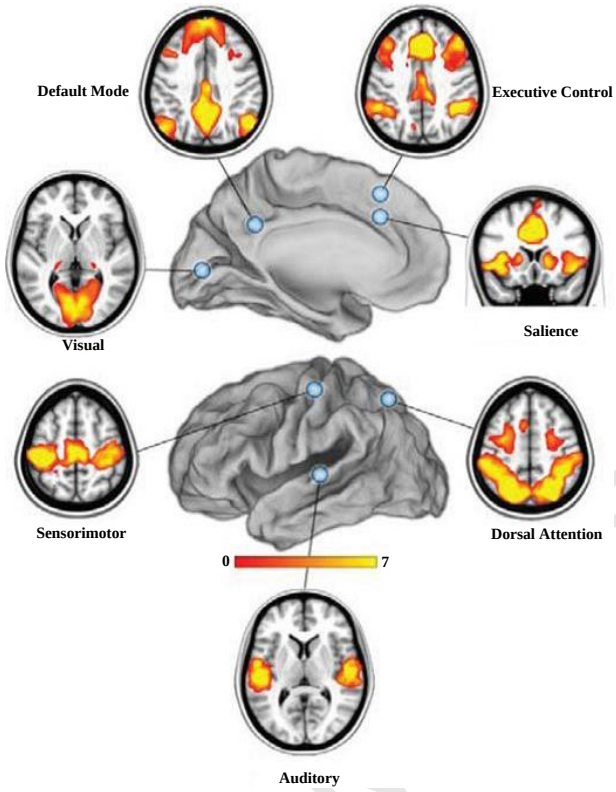

Figure 3: Functional organization of the main networks in the brain. Reprinted from [92]

different stages of AD, with a focus placed on the early phase of MCI. Brain changes caused by AD may have begun many years before clinical symptoms like memory loss and cognitive decline appear; ; however, there is no specific criteria to diagnose the AD in this stage.

4.1. Differentiation of neurodegenerative dementias using rs-fMRI

Recently, some clinical applications for fMRI signal have been reported that include presurgical localization for tumor operation, diagnosis of schizophrenia, depressive disorder, and neurodegenerative diseases such as AD. In addition, such applications are beginning to demonstrate the ability to distinguish variant types of dementias such as AD and behavioral variant frontotemporal dementia (bvFTD). These two types of dementia have an overlap of symptoms that makes diagnosis challenging specifically in early stage of the disease which proves the need for early biomarkers. Some studies investigated these two types of dementia using MRI [96, 97, 98], motor and cognitive tasks [99], and social cognition assessments [100]; however, there are fewer studies investigated the fMRI application.

Zhou and colleagues studied connectivity differences of bvFTD and AD and found that these two diseases exhibited inverse patterns to each other [101]. They observed attenuation functional connectivity in salience network and enhanced functional connectivity in DMN in bvFTD group, which is what inversely happened in the AD group. Applying the intrinsic connectivity network (ICN) fMRI which detects the changes in the network before brain atrophy, and using ICA on 36 subjects (12 people in every group of CN, AD, and

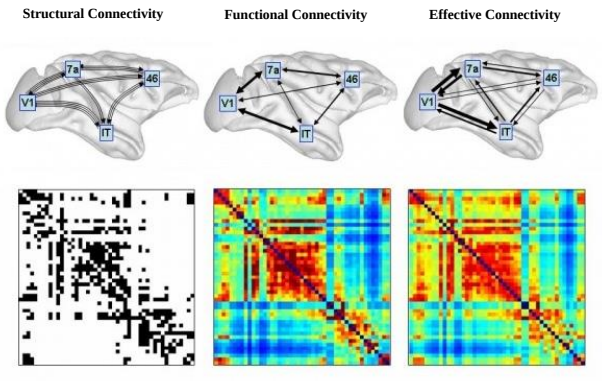

Figure 4: Different modes of connectivity using graph theory. Reprinted from [94]

bvFTD) led to 92% of classification accuracy. However, bvFTD subjects showed decreasing FC between the auditory network and angular gyrus and also between the lateral visual network and lateral occipital cortex compared to the AD group [102]. Furthermore, gray matter atrophy in posterior cingulate, lateral occipital and frontal medial cortices, temporal gyrus and hippocampus in patients with AD have been observed as well as a reduction in functional connectivity of AD patients compared to the healthy participants in DMN, posterior cingulate gyrus, lateral occipital, and precuneus cortices. Moreover, FC between the lateral occipital cortex and dorsal visual network, and between dorsal visual and parietal cortices were perceived in AD patient. Tuovinen et al. observed decreasing in functional connectivity in the salient network in bvFTD and posterior DMN in AD group using ICA dual regression [103]. In addition, decreasing of FC between right frontoparietal network and precuneus in AD differ from the left frontoparietal network, and inferior frontal gyrus in bvFTD have been achieved longitudinally for 20 AD, 22 CN, and 12 bvFTD using network-to-region analysis [104]. Multimodal neuroimaging will better diagnose AD patients from CN people as well as differentiating the bvFTD and Alzheimer's disease [105]. They demonstrated that the combination of fMRI and grey matter density would be associated with the more accurate diagnosis.

4.2. Functional connectivity investigation using task-based fMRI

Task-based fMRI activation function has been investigated in some studies as a biomarker for people at risk for developing AD. Enhanced FC in AD patients has been reported by many researchers. Hamalainen et al. reported increased fMRI responses in parahippocampus, hippocampus, and fusiform areas for MCI patients during the encoding task [106]. Machulda et al. tried to discriminate CN, MCI, and AD groups according to the fMRI encoding task memory [12]. In addition, passive sensory fMRI was performed on the subjects as a control parameter to show that subjects have the potential to have an equivalent response. Then, correlation coefficients between fMRI signal intensity and activation timing were obtained using sinusoidal stimulus waveform for both memory and sensory tasks. Considering medial temporal lobe as ROI for memory task and hand region of cortical homunculus for sensory task and receiver operating characteristic (ROC) analysis, they found out there was no significant difference in memory region activation for recogni-

tion and free recall name between MCI and AD subjects. Moreover, they realized that activation in medial temporal lobe was greater in CN subjects than MCI and AD groups which could be a reason for dysfunction of the medial temporal region due to neurodegenerative disease. Donald G. McLaren and his colleagues applied a generalized psychophysiological interaction method using $gPPI$ toolbox on 24 mild AD subjects to assess the task-based connectivity of the hippocampus and the rest of the brain regions [107]. They used face-name pairs encoding task for fMRI data acquisition in 3 conditions of novel face-name, repeated face-name, and fixation cross. Using connectivity-behavior regression analysis, they concluded that behavioral and clinical measures of memory and cognition are associated and found out that this relationship is even stronger and more complicated than the results of previous studies.

In another study, a significantly lower level of functional activity in the hippocampus, and more level of activity in medial parietal cortex and posterior cingulate cortex in AD patients have been found by using face-name encoding task [108]. they observed a significant attenuation of FC in the left hippocampus and bilateral parahippocampal gyrus during the color picture memory encoding. AD patients have a memory loss due to the fact that the most inclination of functional activity is observed in the hippocampal formation. Although most studies focus on the hippocampus and medial temporal lobe (MTL) to investigate memory task encoding in patients with Alzheimer, some other studies tried to find the FC patterns of that patients during visual encoding due to the importance of visual function as a neuropsychological biomarker of Alzheimer [109, 110]. In [109], decreasing functional activity in the superior parietal lobe (SPL) that might be explained by SPL atrophy and increasing activity in the occipitotemporal cortex (OTC) in AD group during the angle discrimination task. This abnormality proved that in the early stages of Alzheimer, the parietal dysfunction was compensated by using ventral visual stream. However, they observed a higher magnitude of fMRI signal but a not higher number of fusiform gyrus (FG) voxels which indicates that the ventral visual recruitment is supported by only a small section of the FG that prevents the activation spread in that area. In addition, failure of activation in temporal lobe and prefrontal area which is associated with the visual area have been reported during visual encoding task for mild AD [110].

On the other hand, some studies applied the auditory stimulation in order to investigate the functional neuroanatomy alternations in an auditory scene of CN and AD subjects [**?**]. They proposed four stimulation of naturally and spectrally rotated sounds (NI and RI, respectively), and naturally and spectrally rotated name superimposed (NS and RS, respectively). Although they observed alternations in right posterior superior temporal cortex in CN and AD subjects using auditory object segregation stimuli, [(NI+RI)-(NS+RS)], they could not find any significant differences between these two groups. However, they found out increasing functional activity in the right supramarginal gyrus in AD subjects in comparison to the CN group using the cocktail party effect stimuli, [(NI-RI)-(NS-RS)]. This alternations of functional neuroanatomy in inferior parietal cortex which is the main region of the auditory scene in the brain proves that central auditory functions have been impaired in AD group and suggests that they have the difficulty of discovering the auditory

information in the noisy environment.

4.3. Functional connectivity investigation using rs-fMRI

Brain network mapping in patients with Alzheimer's disease is one of the important applications of fMRI studies, and among the brain network mapping methods, DMN is one of the most interesting networks measuring at resting state. DMN consists of several spatially distinct regions in the cortex lobes mostly includes posterior cingulate, medial prefrontal and lateral temporal cortices and also hippocampus [111]. DMN is associated with remembering events of the past, envisioning events of the future, self-relevant mental processing, and monitoring of external information [liu2013impaired]. The alternation of the functional activity of DMN is associated with neurological disorders [112, 113, 50, 114].

Decreased functional connectivity in DMN is reported in most studies. In [115], the power of DMN in rs-fMRI was investigated for three groups of CN, MCI, and AD in order to detect the AD and MCI from the healthy group. They provided the magnitude of the rs-fMRI signal in DMN for three groups as shown in Figure 5 which clearly illustrates the disruption of functional connectivity in DMN as the disease progress from normal to MCI and from MCI to AD.

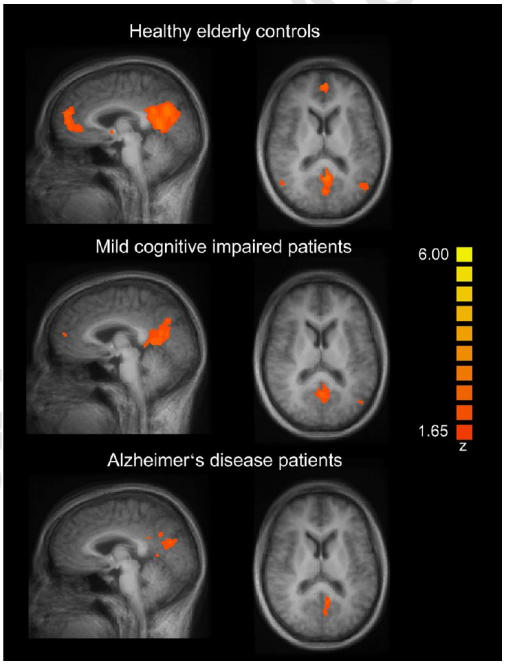

Figure 5: Magnitude of DMN for three groups of normal, MCI and AD. Reprinted from [115]

In [116], Toussaint et. al. used 40 spatial ICA for every fMRI signal and applied a hierarchical clustering algorithm to individual independent components to determine group maps. They observed inclination correlations between precuneus posterior cingulate (PPC) and frontal regions and also between PPC and bilateral temporal region of the brain for aging subjects comparing to the young people. In addition, decreased correlations between frontal and parietal regions were beheld; however, intra-network interactions of

the subsystem of DMN in parietal and frontal regions were increased for the same groups. Moreover, DMN inter-region and intra-region correlations within the parietal, temporal, and frontal areas were significantly higher in aging than the AD group. Liang Wang and colleagues focused on changes in brain connectivity between the hippocampus and other regions of the brain for mild AD [117]. This seed-based study exhibited the disruption of FC between the right hippocampus and some other regions of DMN such as medial prefrontal cortex and posterior cingulate cortex in AD patients. Also, disruption observed between the right hippocampus and ventral anterior cortex, and between right and left cuneus as well. Furthermore, they explored increasing FC between the right prefrontal cortex and the left hippocampus and in AD compared to the healthy group.

Zheng et al. studied cerebellar subregions functional connectivity [118]. In order to assess within-group functional connectivity, one sample t tests was performed for each cerebellar subregion and between groups. They realized that AD group had disrupted functional connectivity patterns within DMN, Visual network (VN) and SMN in comparison to the healthy group. DMN, VN, and SMN are important regions that are crucially associated with the cognition in the brain which demonstrates cognitive decline as a result of disrupted functional connectivity in AD patients. Moreover, they found gray matter atrophy in some regions such as dorsal cortex, medial frontal cortex, lateral temporal cortex, MTL, posterior cingulate cortex, lateral parietal regions, and subcortical areas in patients with AD. Badhwar et al. observed changes in functional connectivity of SAN, limbic network (LIM) including entorhinal cortex and hippocampus, and DMN including PCC and precuneus in MCI subjects [119]. The dysfunction of SAN and DMN may lead to deficits in attention in MCI and AD patients [120].

In [121], voxel-based graph theory approach was used to study the FC patterns of the brain for 75 subjects including 34 AD and 41 healthy. In their research, they used Functional connectivity strength (FCS), a metric that showed what regions associated with the abnormality and how they were distributed in the brain. They found disrupted connectivity distance-dependent in most regions in DMN such as inferior parietal cortex and medial prefrontal gyrus and in some other hubs such as insula, thalamus, and supplemental motor area. Although the functional connectivity strength also decreased in the healthy group, it showed more significant changes in patients with AD. In addition, they realized widespread gray matter atrophy specifically very strong at the inferior parietal cortex, posterior cingulate gyrus, medial prefrontal gyrus, and insula. In [122], authors considered fusiform left and right gyri as the seed regions and found that functional connectivity was increased between these regions and regions of left middle occipital gyrus and right anterior cingulate cortex. Furthermore, they represented altered functional connectivity between seed regions and some other brain regions such as inferior temporal gyrus (ITG) which were involved in visual cognition. ITG is known as the long-term visual memory which is located on the visual stream similar to left and right fusiform gyri. Therefore, volume and functional connectivity reduction of these areas may lead to visual processing deficit such as failure in face recognition. The results revealed that functional connectivity reduction between two seed regions in amnestic MCI (aMCI) group which may explain why AD or MCI patients are unable to

recognize familiar faces. Brier and colleagues studied intra-network and inter-network functional connectivity concerning the different amount of clinical dementia rating (CDR) using PCC as the region of interest [123]. They perceived the FC of three pairs of DMN with DAN, SMN, and CON was significantly changed with increasing AD severity (CDR from 0 to 1). The other pairs did not illustrate too many changes which suggested that dysfunction of one abnormal resting state network of a pair may lead to dysfunction of another network of that pair.

Damoiseaux et al. discovered that in early Alzheimer's disease the connectivity of the anterior and ventral regions of DMN started to be increased while the posterior regions began to be detached and both eventually disrupted as disease progression [124]. They used dual regression method which included obtaining data driven from running ICA, applying the dual regression to the independent components, and finally performing the voxel-wise analysis. Wang et al. performed temporal permutation of entropy, a method based on adjacent data comparison in arbitrary time series, for 4 groups of CN, early MCI (EMCI), late MCI (LMCI) and AD to study the abnormal complexity of resting-state fMRI and observed that the average permutation entropy decreased from MCI to AD [125]. They used whole-brain entropy preprocessing and Gaussian smoothing which resulted in showing the least complexity of AD group which is significantly correlated with the neuropsychological measurements such as mini-mental state examination (MMSE) and CDR. Considering the same type of EMCI and LMCI groups, Niu et al. found that the complexity of the BOLD signal associating with different ROIs is significantly contributed to the cognitive decline in MCI and AD groups [126].

Brier and the colleagues demonstrated brain network deterioration [127]. Also, they observed that clustering coefficients and modularity reduction were contributed to the degree of cognitive impairment. J. Xiang et al. studied abnormality in the functional connectivity of 16 people as CN, 17 EMCI, 19 LMCI, and 18 AD subjects using graph theory [128]. They represented increasing of shortest path and decreasing of clustering coefficients along with increasing the cognitive loss. Daianu et al. used the k-core decomposition method of the anatomical network to assess brain functional connectivity [129]. They analyzed the diffusion-weighted imaging (DWI) of 111 subjects including 28 CN, 15 AD patients, and 68 MCI from ADNI2. Applying graph theory and comparing the connectivity matrices of left and right hemispheres and considering only edges, more than half of the valid connections were asymmetry in all groups which intensified with AD progression. Left hemisphere showed a lower proportion of fiber density among regions in AD subjects that proved core connection was broken down in left hemisphere compared to the CN group. They discovered that path length and efficiency were decreased in AD patients compared to the CN group; however, normalized small-word was increased in all analyses of the right hemisphere and whole brain. Y. Zhan et al. indicated abnormal network components in DMN, SMN, VSN (visual-sensory network) and VAN (visual-attention network), using a network-based statistic (NBS) with 264 ROIs [130]. They considered NBS as components of interest (COIs) in order to study the relationship between the strength of the connectivity and the severity of the disease. They proved that the increase in the degree of cognitive impairment was associated with a de-

crease in FC of the COIs which was distributed through the several brain networks. Liu et al. investigated long-distance functional connectivity that led to magnitude and homogeneity reduction of fluctuation of low-frequency fMRI data and functional connectivity reduction between farther regions in the brain of the severe AD subjects [131]. They explored matches results for MCI and aMCI that the degree of disruption of FC of the areas contributed to the physical distance of those regions, e.g., the areas of the anterior-posterior within the DMN were most affected in these patients. Also, they realized that the disconnection of connectivity and disruption of fMRI fluctuations led to the reduction of the efficiency in the nodal and global networks.

4.3.1. Classification

Recently, there has been a great interest for machine learning applications in diagnosis of Alzheimer's disease in its different stages. Graph and topological measures of fMRI data can be used in order to classify or predict the early onset of the AD. Variety of machine learning algorithms have successfully applied to the fMRI data which among them support vector machine (SVM), random forest (RF), Baysian network (BN), and neural network are deemed the most powerful methods. Most machine learning algorithms have been applied to the rs-fMRI, although recently a developed deep convolution neural network was applied to the task-based fMRI [132].

Authors in [133] divided the cortex into 1024 regions and using wavelet transform based statistical analysis; they obtained the correlation of time courses of those regions. They proved that disruption of functional connectivity happened at three levels of global, nodal, and connectional in aMCI subjects that associates with memory loss. Moreover, the classification of aMCI from the CN group with relatively high sensitivity and specificity (86.5% and 85.1%, respectively) was achieved. Wee et al. used an SVM classifier combined with a nonlinear radial basis function (RBF) based neural network (NN) to classify the BOLD signal changes triggered by pathological attacks [134]. This classification was used to diagnose the MCI. In their technique, they employed times series of ROIs and relations among clustering coefficients of different ROIs were used as features for classification. Using this approach, they reached a classification accuracy of 86.5%. In [135], the authors used rs-fMRI data to investigate the functional connectivity of the brain based on Pearson's correlation coefficients. The classification was applied on the ROIs time series using an L2-regularized logistic regression classifier. The Pearson's correlation coefficients were defined based on changes between time series of each pair of RIOs. They demonstrated that functional connectivity changes can be used as features for MCI classification. Using this methodology, they obtained the accuracy of 87.5% in the diagnosis of MCI.

Jie et al. introduced a new method of brain connectivity classification by integrating a vector-based kernel and a graph-based kernel corresponding to local network properties and global topological properties, respectively [136]. The classification was applied on the mean time series of each ROI by calculating the average of the fMRI over all the voxels in the target ROI. This integration helped to reach the accuracy of 91.5% in the diagnosis of MCI. Koch et al. compared two methods of time series correlation with voxel of interest and ICA, and they found out that the correlation analysis was more accurate [115]. Using the

combination of two methods, they could achieve 97% of the accuracy of classification among CN and AD groups. In another study, an accuracy of 94.4% for CN and AD groups was achieved applying random SVM to the rs-fMRI [137]. Bi et al. used the random neural network cluster method on 61 subjects and achieved the classification accuracy of 92.31% between 36 CN and 25 AD besides finding 23 abnormal regions including frontal and precentral gyrus [138]. Using FC and regional volume atrophy in 10 subcortical regions of the brain and applying random forest, 53.33% accuracy has been achieved for multiclass of three groups of MCI, CN, and AD [139]. Khazaee et al. obtained accuracy of 87.29% for classification of CN vs. MCI and AD using abnormalities of the brain connectivity [140]. They used graph theory and extracted the graph parameters such as global efficiency and shortest path length in order to find the functional connectivity pattern and applied SVM with RBF kernel.

In another study, an accuracy of 97.14% for CN vs. AD classification has been achieved using SVM and sequential minimal optimization classifier and using SPM toolbox for statistical analysis of the fMRI [141]. De et al. used the combination of three different parameters of FC obtained using ICA, dynamic of the FC, and the amplitude of low-frequency fluctuations and achieved area under the curve (AUC) of 0.85 for classification of CN vs. AD using logistic regression as the classifier [142]. They found out that only FC and dynamic of FC are enough to obtain the optimal accuracy. Recently, some studies tried to investigate the progression of the disease from MCI to AD. Hojjati et al. used converter MCI (c-MCI) and non-converter MCI (nc-MCI) groups to predict progressed patients. They obtained an accuracy of 91.4% using SVM for nc-MCI and c-MCI applying rs-fMRI [143]

4.4. Effective connectivity investigation

Effective connectivity estimates the directionality of influence of one region in the brain on the other functionally connected areas. It is crucial to study how the brain regions, e.g. in DMN interact with each other and how the Alzheimer affects these patterns of interaction which reflects the shifting in the cognitive process. In [144], effective connectivity using DCM was studied on 14 AD and 16 CN subjects during a visual task known as interhemispheric integration. They examined the strength of top-down inhibitory effects of the visual cortex and discovered that this inhibition attenuated in the early AD. Impaired deactivation in DMN in both AD and CN groups during the active task that can be explained by attenuation of inhibitory feedback connections at least in AD subjects. All the intrinsic connections, especially at the left hemisphere, were significantly weakened. This reduction of effective connectivity was in agreement with cortico-cortical connectivity changes of the visual network of AD patients. Indeed, reduced inhibitory influence of top-down connections was explored in elderly subjects and more significantly in early AD led to the functional deactivation in primary visual areas.

Hampstead and colleagues [145] applied multivariate GCM using autoregressive modeling in order to study effective connectivity pattern of MCI subjects during memory encoding task and retrieval object location task. They used GLM to identify the active regions during encoding and retrieval tasks and found 45 ROIs for effective connectivity analyses. They observed more significant paths in right hemisphere from

anterior hippocampus during retrieval in CN group that are attenuated in MCI subjects. During retrieval, the right inferior frontal junction (rIFJ) and right anterior thalamus were the primary driver of activation indicating hippocampus dysfunction in MCI. Moreover, they found frontoparietal network including IFJ and PCC drove activation in the left hemisphere in CN group while it shifted to right frontal eye field (rFEF) in MCI patients during the encoding task. The CN subjects relied on parietal eye field while frontal eye field was engaged in MCI patients during the encoding task which illustrated top-down loss control in this group. This shift from posterior cingulate cortex to the retrosplenial cortex in MCI patients was contributed to the memory and learning impairment. Zhong et al. studied effective connectivity using multivariate GCM in the DMN and subregions of DMN to find the casual interaction changes associated with AD [146]. They applied ICA to identify the DMN core regions and applied signed path coefficients of GCM to investigate the casual interaction among these regions. They found degradation of effective connectivity in both terms of strength and quantity as illustrated in Figure 6. It is obvious that PCC that had more connections in the CN group showed weakening interactions in the AD. They believed that since PCC is the most metabolic active and most connected region in the CN group, the reduced interaction of PCC proportion to the memory decline could be considered as a clinical index. Furthermore, the inhibited activity of the right inferior temporal cortex (rITC) in subjects with AD represented the breakdown of visual networks caused the long-term visual memory decline of AD patients.

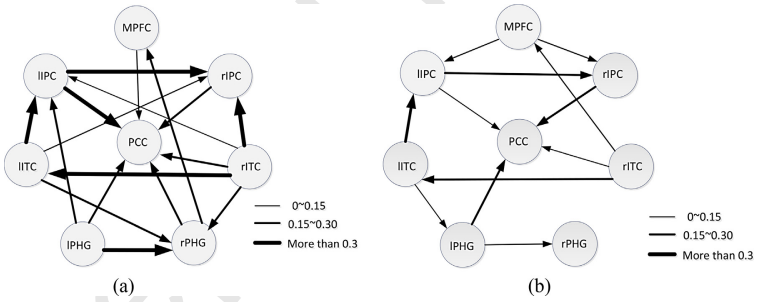

Figure 6: Effective connectivity patterns of default mode network in healthy group (a) and AD patients (b). The thickness of the lines determines the strength of the connections. Reprinted from [146]

Neufang et al. applied DCM on attention task-based fMRI data of 15 AD and 16 CN subjects [147]. They observed that effective connectivity was significantly decreased in fronto-parietal pathways (from frontal to parietal cortex) which was a function of gray matter volume reduction in those areas leading to top-down attentional control impairment in the early AD. Later in 2014, they found a relation between rs-fMRI functional connectivity and effective connectivity using task-based fMRI of CN and early AD within DAN [148]. They used seed-based partial coherence analysis to examine functional connectivity from rs-fMRI, and DCM to analyze the task fMRI. Then, by a combination of these two analyses in regression models, they explored that rs-fMRI functional connectivity was associated with the effective connectivity within cingulo-fronto-parietal network in the CN group. The connections from parietal to frontal lobe and connections within the parietal were contributed to the higher rs-fMRI frequencies, and bottom-up effective connectivity

was associated with lower frequencies while this pattern was disrupted in the early AD.

Although the effective connectivity studies the casual effects of the brain regions on each other and provides the possible shifts in learning and memory process in MCI and AD, there are fewer studies focused on this field. Most studies relied on functional connectivity investigation that may not reflect the cognitive process as well as effective connectivity which proves the need for more attention to effective connectivity investigation using task-based fMRI.

5. Preclinical studies

In recent decades, many researchers studied the abnormal amyloid plaques and neurofibrillary tangles including β-amyloid and tau proteins aggregation proceed to neurodegeneration in the brain of AD patients [149]. This accumulation in the brain generally includes temporal and hippocampal regions which are detectable before symptoms onset using fluorodeoxyglucose positron emission tomography (FDG-PET) [150, 151]. The β-amyloid load is associated with AD; however, sometimes it is observed in cognitively normal aging prior to symptoms onset that can be considered as a biomarker of preclinical pathology which will be developed to AD. Indeed, increased $A\beta$ aggregation is contributed to the greater risk of Alzheimer leads to cognitive decline and gray matter atrophy [152]. Figure 7 widespread atrophy most in the frontal region which is overlapped with amyloid burden in the mild AD. In this section, we reviewed preclinical studies due to the importance of the events leading up to dementia before clinical symptoms [153].

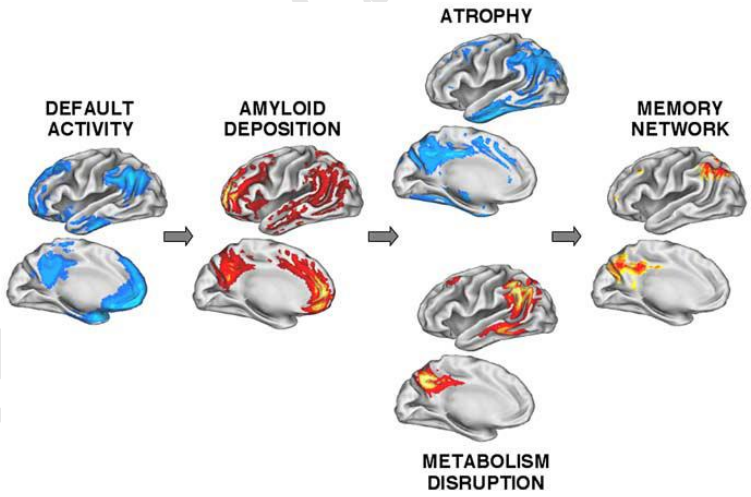

Figure 7: Relationship of structural, molecular, and functional measurements. Functional activity of DMN in young adults and amyloid burden in AD patients, have been represented in first and second steps. These activities that are highly similar include anterior and posterior cortex. Metabolism abnormality and gray matter atrophy in the next step are strongly observed in posterior cortical areas more than the anterior areas affected by amyloid burden. Reprinted from [153]

Some studies investigated the relationship of the tau/amyloid deposition and functional connectivity in MCI and AD patients. The amyloid deposition is correlated with the increased functional activity of left posterior temporal and contributed to the language network of cognitively intact subjects [152]. were also

contributed to medial temporal lobe volume reduction and disrupted functional activity during memory encoding in normal aging [154]. Hansson et al. investigated the relationship of the regional distribution of tau pathology and related pattern to a functional network of the brain in AD using BioFINDER [155]. They corroborated that tau accumulation increased in parts of DMN, higher visual network, limbic, and DAN that proved tau deposition effects on the sensory network and motor network.

As mentioned before, since DMN is engaged with memory retrieval, the focus of studies of the preclinical AD is primarily on DMN [156]. Elman et al. used ICA and dual regression analyses to find the relationship between functional connectivity disruption and $A\beta$ load measured by Pittsburgh compound B-PET (PIB-PET) in cognitively normal aging. Alternations in FC in parietal and temporal cortices, represent dysfunction of the local network, compensatory mechanism, and impaired control network. Indeed, they found the disrupted FC not only in DMN but also in the right CON and DAN as well. The changes in higher PIB-PET associated with FC were observed in the posterior cortex that could be a compensatory response of the visual system. Increased neural activity in the hippocampus with $A\beta$ accumulation during episodic memory task was reported in [157]. Increased neural activity in the hippocampus may arouse the neural activity of other connected regions to the hippocampal area and prone to β-amyloid accumulation. They monitored 33 patients with MCI over 36 months to assess the contribution of $A\beta$ accumulation and longitudinal progression of the disease. At baseline, they observed increased hippocampal activity along decreased its volume, slightly functional impairment and higher cognitive decline for $A\beta$ positive subjects than $A\beta$ negative patients. Longitudinally, they found the same results but more significant with faster clinical progression. Kazemifar et al. used ICA with 30 independent components followed by three steps template matching approach including goodness of fit calculation to assess the similarity between 30 components, multiple template matching, and finally SVM to find the neuronal components [158]. Afterward, the brain activity map was created using statistical parametric mapping (SPM8) toolbox. They observed overall lower brain activity and lower glucose standard uptake value ratio (SUVR) metabolism in amygdala and hippocampus in the mild AD which proved their significant correlation.

However, some other studies failed to find this relationship between hippocampal activity and high $A\beta$ burden in cortical during memory encoding. Huijber et al. [159] and Song et al. [160] explored that higher cortical $A\beta$ deposition is contributed to the lower hippocampal activity in normal elderly subjects during the memory encoding task. This higher $A\beta$ deposition is a hallmark of functional connectivity changes in MTL and specifically in the hippocampus. However, this $A\beta$ load effect was decreased by increasing the age which may represent the different results of the relationship of the hippocampal activity and cortical $A\beta$ load.

Seo et al. studied two groups of amnestic MCI with and without $A\beta$ lload and confirmed that memory impairment in these two groups depended on distinct brain areas according to the amyloid deposition level [161]. In aMCI without amyloid burden, the attentional control network was activated while in the positive amyloid group, hippocampus, and parahippocampal gyrus were activated for the episodic memory function

as a result of disruption in the memory-related network. Hyperactivation in occipital and parietal cortices associated with $A\beta$ burden played a compensatory role in subjects with amyloid deposition during memory encoding [162]. TThey found that subjects with A aggregation illustrated less neural activity in task-negative regions (regions that are not active during the memory encoding) and increased neural activity in task-positive regions (regions that are active during the memory encoding). Ref. [163], suggested that increasing $A\beta$-related hyperactivation during working memory task in frontoparietal cortex (FPC) support the fact that this hyperactivation not only occurs in episodic memory (EM) system but in FPC as well. Some studies are suggesting that hypometabolism in the brain follow the amyloid accumulation; however, its development is a mixture of events that can not be explained by only amyloid deposition [164]. They suggested that amyloid accumulation in remote regions of the brain which are functionally connected and unaffected by local amyloid accumulation was associated with longitudinal hypometabolism in that areas.

DMN consists of several distinct regions in the cortex mostly includes posterior cingulate, medial prefrontal and lateral temporal cortices and also hippocampus in which its functional activity is associated with internal tasks such as envisioning events of the future, multimodal sensory, and level of consciousness. Pathogenic protein deposition could be the cause of atrophy patterns and neurodegenerative disease as a result [165]. DMN as the main network under investigation in rs-fMRI measurement demonstrates the pathogenic protein accumulation even in the early stage of AD [166]. The subjects with a high value of $A\beta$ A in their DMN show DMN functional connectivity disruption specially in the hippocampal formation. In addition, this earliest $A\beta$ burden is contributed to the frontoparietal network and DMN decreasing connectivity as a result which is exhibited in preclinical AD [167]. The DMN cortical neurons produce more amyloid will result in more $A\beta$ and tau accumulation as a consequence in the DMN. However, Warren et al. suggested that interaction of tau and $A\beta$ as the main two pathogenic protein causes difficulty in association between the specific pathology and network dysfunction [168]. In addition, some elements of DMN involve in active cognitive tasks such as visuospatial processing. Therefore, the incorporation of the cognitive function would be uncertain and required to more functional connectivity and structural investigations.

In addition to the $A\beta$ burden, there is also APOE $\varepsilon 4$ allele as a genetic factor associated with developing AD in cognitively normal people [169]. Ref. [170] proved that regions contributed to memory and cognitive functions were affected by increasing activity in anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC), and decreasing functional activity in precuneus and middle temporal gyrus (MTG) related to episodic memory in normal elderly subjects with APOE $\varepsilon 4$ carrier. Sheline et al. explored abnormalities of functional connectivity in APOE$\varepsilon 4$ carriers within the DMN even in the absence of $A\beta$ accumulation [171]. Figure 8 exhibits altered functional connectivity in normal APOE$\varepsilon 4$ carriers compared to APOE$\varepsilon 4$ noncarriers. Machulda and colleagues [172] observed a reduction of functional connectivity in DMN including bilateral anterior temporal lobe, left middle temporal gyrus, and left inferior parietal lobe considering the posterior cingular cortex as the seed. In addition, they observed an increase in SAN included bilateral insular cortex, medial prefrontal cortex, cingular gyrus, thalamus and striatum considering the anterior cingulate

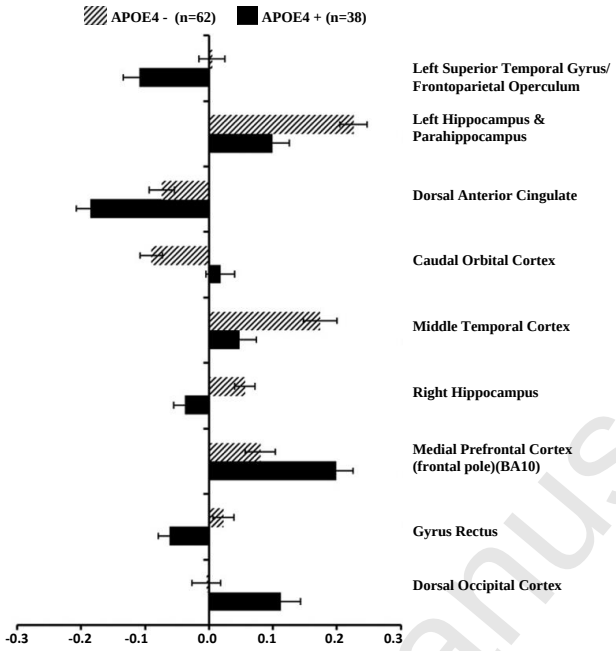

Figure 8: Disrupted FC of the precuneus in healthy elderly APOE4 carriers (APOE4+) compared to the APOE4 noncarriers (APOE4-) participants. It shows the correlation magnitudes for these two groups. reprinted from [171]

cortex as the seed for the APOEε4 carrier subjects compared to noncarriers. They found this changes in rs-fMRI as balance disruption between DMN and SAN which could be considered as an early hallmark for AD. Ref. [173], exhibited that APOEε4 disrupted FC in executive control network (ECN) and posterior DMN and at the nodal and connectional level that was the reason for disruption at the global level in AD subjects.

et al. observed that the FC is increased in left middle frontal gyrus and decreased in left lingual gyrus and medial temporal lobe in APOE 4 carriers [174]. Chen et al. demonstrated dysfunction in white matter (structural disruption) and functional abnormalities are contributed to cognitive and specifically memory network in APOE ε4 carriers [175]. They demonstrated later alternations in functional connectivity in the DMN of precuneus as a pivotal APOE effect and other regions [176]. They observed the increasing FC of precuneus and regions in insula including inferior parietal lobe and superior temporal gyrus and decreasing FC between precuneus and anterior areas such as superior frontal gyrus in APOE ε4 carriers compared with non-carriers. The evidence studied in this section suggests that alternations of fMRI are detectable before clinical symptoms of dementia among individuals. There are many studies that prove functional abnormalities of the preclinical AD, however, preclinical fMRI still requires more investigation to understand the relation of these abnormalities with AD.

McKenna et al. compared the ROI-to-ROI connectivity with the whole brain ROI functional network in APOE ε4 carriers and non-carries between two groups of CN and EMCI [177]. They observed functional connectivity decreasing in precuneus, visual cortices, temporal gyrus, PCC, and anterior cingulate cortices in

EMCI subjects with a strong overlap of functional connectivity abnormalities in APOE $\varepsilon 4$ carriers. However, they found that effect of APOE $\varepsilon 4$ on EMCI and CN groups is almost similar which opens up the question of what other important factors lead to developing the APOE $\varepsilon 4$ to EMCI.

6. Advantages, Limitations and Future Perspective

The fMRI modality is a non-invasive imaging modality which provides high spatial resolution in comparison to the other modalities such as PET imaging. Deployment of BOLD-based signal analysis techniques does provide valuable information through the constructed functional networks of the brain at rest (or even under anesthesia). FMRI could also yield more complicated functional connectivity during tasks such as visual, auditory, and language. Abnormalities in functional networks due to pathological changes can be used for the diagnosis of neurodegenerative diseases such as Alzheimer's disease. Another important advantage of fMRI over the FDG-PET imaging is that not only it is less costly and easier to administer, although both fMRI and PET are relatively safe, PET exposes subjects to radiation and injection of radioactive agents [178]. In addition, fMRI which has a higher spatial resolution can be taken simultaneously during the MRI session for structural imaging. The main advantage of discovering the functional connectivity abnormalities over the structural imaging is its great potential in detecting through the functional activities the early stage of Alzheimer's disease before any structural damage observed through MRI can be detected. The BOLD signal abnormality of the lingual gyrus, precuneus, auditory, prefrontal regions, and alternations in medial temporal lobe activity could be considered as clinical biomarkers for mild cognitive impairment. In addition, a great deal of research in fMRI application in rehabilitation will help gauge the treatment effect and in evaluating the pharmacologic effect on the functional cognitive network in Alzheimer's disease.

Although so many studies investigated the white matter and grey matter atrophy due to neuron loss, finding the relationship of pathological and biological changes of AD with functional network abnormalities still requires more thorough investigations. One major deficiency in fMRI studies is the lack of longitudinal data to investigate the progression of the disease. The majority of the studies compare the functional connectivity of the healthy control subjects with those who are diagnosed with AD or MCI; however, there is not enough knowledge about longitudinal alternations and the relationship between disease progression and functional connectivity disruption [179]. Furthermore, there is a crucial need for advanced techniques in fMRI acquisition and analysis. Using a more powerful magnet to improve the temporal resolution, a real-time motion correction could overcome the sensitivity to head motion, and at the same time improve the signal to noise ratio, especially for the task-based fMRI which more complicated to administer than the rs-fMRI. It should be emphasized that because of the lack of large datasets, many of the reviewed studies have relied on a limited number of subjects.

As we discussed before, fMRI can also serve as a helpful tool for differentiating AD from other neurodegenerative diseases; however, more investigations are necessary to distinguish the brain connectivity disruption in AD and other forms of dementia. Recently, many studies demonstrated that multimodal neuroimaging

provides more insightful and integrated information about human brain mapping and Alzheimer classification which is bound to help clinicians plan for subject-specific therapies [180]. For example, Jacobs et al. observed increased functional activity in parietal and temporal regions which have increased diffusion and decreased activation in orbitofrontal with decreased diffusion in MCI subjects [181]. They showed structural evidence from diffusion MRI as a functional reorganization to reflect a compensatory process which may be associated with cingulum connectivity loss. Rahimi et al. demonstrated that prediction and classification of MCI and AD from CN group have been increased due to the consolidation of fMRI and FDG-PET imaging [182].

Although the fMRI is a non-invasive tool to assess brain function and connectivity, there are some limitations for using this imaging technique. The fMRI modality does not associate directly to the neural activity but indirectly to the blood flow, and this makes it challenging because of the limited spatial resolution, and the low temporal resolution for observing the hemodynamic response [183]. Most fMRI analysis techniques consider the resting state networks constant while they can be changed voluntarily [184] or by learning [185]. The fMRI analysis techniques have been poorly investigated for correlating the neurovascular BOLD signal with disease, age, and medication which may cause changes in the BOLD response due to impaired vascular response. Disrupted functional connectivity even in DMN could be associated with other diseases such as migraines, depression, addiction, or with other types of dementia [92]. For example, subjects with subcortical vascular dementia and AD exhibited similar cortical activation regions [186]. Also, the BOLD fMRI signal is associated with the neurovascular coupling which means the hemodynamic properties and the neural activations during fMRI procedures can be altered by natural aging or disease [187]. Therefore interpretation of this signal for investigations of subjects with different pathologies could be extremely challenging.

7. Conclusion

In this paper, we reviewed several research and survey articles that study brain functional connectivity, with focus placed on Alzheimer's disease (AD). Resting state fMRI and task-based fMRI are non-invasive methods that provide functional mapping of the brain with significant implications on early detection, classification and prediction for both cross-sectional and longitudinal data. All the studies in this review demonstrate disruptions in brain connectivity patterns in AD and MCI as compared to the cognitively normal (CN) group. These studies also prove that brain network disconnections could be associated to cognitive deficits in AD in its different prodromal stages.

The DMN, which is a large scale brain network of interacting brain regions that reflects brain behavior of a subject at rest with no external stimuli, is seen as the primary network capable of elucidating the subtle changes of cognitive deficit in the earliest stage of the disease. AD investigations typically include decreasing functional connectivity in posterior DMN and sometimes increasing FC in frontal areas. However, other networks of the brain are affected by AD progression as well including dorsal attention network, control network, salience network, and sensorimotor networks. Furthermore, some areas of the brain that exhibit

increased functional connectivity at an early stage of the disease like the salience network, tend to decline in the later stages, which may indicate a form of compensatory mechanism of the brain. Moreover, interneuron dysfunction in fMRI could be considered as a potential biomarker for cognitive decline in AD. Perhaps a limitation of fMRI could be in its use in mostly cross-sectional studies. Diseases like AD which is progressive in nature require the use of longitudinal data. It seems that deployment of fMRI in the study of longitudinal data remains limited in scope. In longitudinal fMRI analysis we are confronted by the notion that in order to gauge the functional changes and disruptions in the resting state fMRI or task-induced fMRI, we must first understand changes that could be related to disease in relation to those that emanate from natural evolution due to aging or through brain neuroplasticity and brain reorganization to overcome deficit. Moreover, the cause of the pathophysiological effects in functional network abnormality remains unresolved. All these uncertainties obviously emphasize the need for multimodal imaging. In addition, we reviewed main data-driven and model-based approaches that analyze fMRI data. Among all these methods, graph theory has attracted more interest due to its ability to perform complex network analysis and still provide both functional and effective connectivity information. The graph-based network hence provides the means for both visualizing the overall functional connectivity patterns and for characterizing the organization of such patterns quantitatively. Different graph-based parameters such as small-word and modularity demonstrated a great potential to evaluate the subtle changes in brain connectivity at the different stages of AD.

Moreover, multimodal neuroimaging provides more clinical application of brain functional and structural mapping specifically for identification of AD. Gray matter and white matter atrophy, amyloid deposition, and reduced level of glucose metabolism were reported in multimodal neuroimaging. Since early detection of cognitive decline is very important for early diagnosis of AD and for the planning of treatment and therapeutic protocols, more research needs to be done to fully understand this complex neurological disorder. The fMRI modality through changes in its functional connectivity patterns in concert with other modalities could augment the prospects for an early diagnosis.

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Highlights

- Discussions of methods have been used in functional magnetic resonance imaging analysis.
- Investigation of pre-clinical and clinical applications of functional magnetic resonance imaging in Alzheimer's disease.
- Investigation of functional brain connectivity in mild cognitive impairment and Alzheimer's disease subjects.
- There is a need for new methods to understand the functional pattern alternation in earlystage of Alzheimer's disease.
- Importance of multimodal neuroimaging in early diagnosis of mild cognitive impairment.