Review

Graph Theory and Brain Connectivity in Alzheimer's Disease

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Abstract

This article presents a review of recent advances in neuroscience research in the specific area of brain connectivity as a potential biomarker of Alzheimer's disease with a focus on the application of graph theory. The review will begin with a brief overview of connectivity and graph theory. Then resent advances in connectivity as a biomarker for Alzheimer's disease will be presented and analyzed.

Keywords

Alzheimer's disease, graph theory, EEG, fMRI, computational neuroscience

Introduction

Throughout a human's lifetime the brain is constantly changing. This change over a lifespan typically produces a decline in cognitive abilities (Grady 2012). This decline can be exacerbated by the onset of Alzheimer's disease (AD). AD is a neurodegenerative disease that starts during an individual's mid-late life. It progressively and greatly affects memory and cognitive performance and eventually results in dementia (Martinez-Murcia and others 2016; Ortiz-Garcia and others 2016). AD is estimated to be responsible for 60% to 80% of dementia cases and is the fifth leading cause of death among people over 65 years of age (Alzheimer's Association 2015).

AD has received a significant amount of attention from researchers (Adeli and others 2005a, 2005b; Amezquita-Sanchez and others 2016; Romero-Garcia and others 2016). While there is general agreement that the brain of a patient with AD compared to normal is different, AD is difficult to diagnose, especially in early-onset stages, and cannot be confirmed until post mortem (McKhann and others 1984). A big issue with the diagnosis of AD is that it has no known localized cause (Hu and others 2015). This has sparked an effort to find biomarkers that can be used to diagnose AD as early as possible.

Biomarkers for AD are being researched on a variety of different scopes such as biochemical (Bajo and others 2015; D'Amelio and Rossini 2012; Jardanhazy and others 2008), genetic (De Jager and others 2014; Hawrylycz and others 2015), neurophysiological, and neuroimaging (Kim and others 2015b). For a review on the differences between these methods, see Mirzaei and others (2016). The present review will focus on research using neurophysiological and neuroimaging techniques such as functional magnetic resonance imaging (fMRI) (Michalopoulos and Bourbakis 2015), electroencephalogram (EEG) (Sankari and Adeli 2011; Sankari and others 2011), and positron emission tomography (PET).

Neurophysiological and neuroimaging studies establish networks of connectivity in the brain (Yang and others 2016a, 2016b). There are three main forms of connectivity, anatomical, functional, and effective. Anatomical connectivity has to do with the physical connections between areas of the brain. Functional connectivity is regarded as interaction of the neurons and neural ensembles regardless of physical connection (Ahmadlou and others 2014; Yuvaraj and others 2016). Effective connectivity is a deeper notion of functional connectivity by utilizing all aspects of functional connectivity and assessing how regions of the brain influence other regions (Friston 2011). Different imaging techniques lend themselves to utilize different forms of connectivity (Bullmore and Sporns 2009). Investigating more than one type of connectivity in a study has been tried but no clear conclusions have been drawn (Fitzsimmons and others 2013). This review will target changes in functional and effective and thus will not

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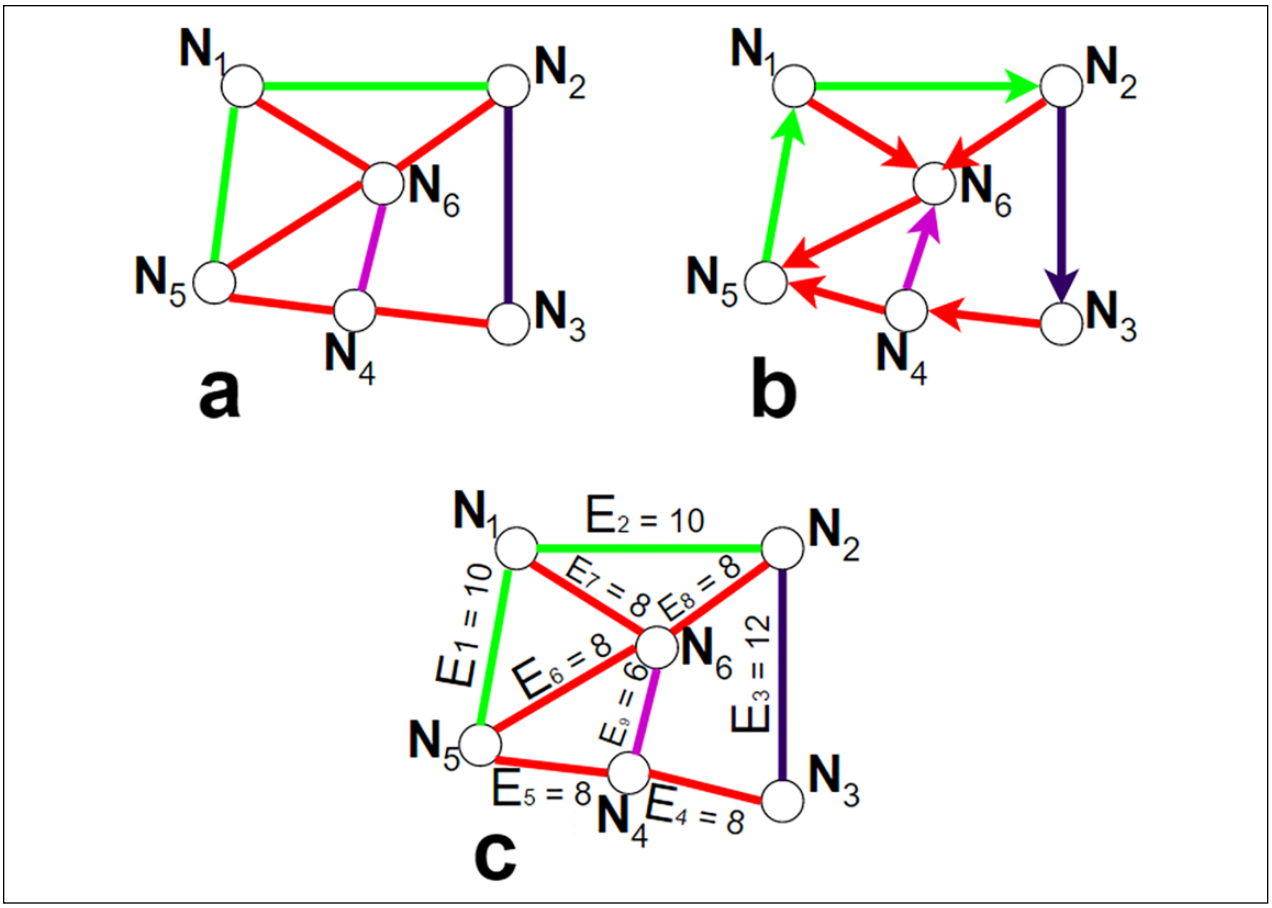

Figure 1. Basic graphs: (a) is a basic graph consisting of 6 nodes N_1, N_2, . . . , N_6, and 9 edges; (b) is a basic directional graph. The arrows indicate where the information is flowing; (c) is a basic graph with weighted edges.

differentiate between the two types. The next section will present a brief review of graph theory, which is the mathematical principles behind connectivity.

Graph Theory

Definition

Graph theory is employed in computational and imaging brain studies extensively because it can be used to quantify brain connectivity (Michalopoulos and others 2016). In this section, some common elements and terminology used in this area of research are described briefly. Figure 1 shows three basic graphs: Figure 1a is a basic graph, Figure 1b is a directional graph called digraph, and Figure 1c is a graph with weighted edges. Graphs are a pictorial representation of the interactions of objects presented as nodes. Relationships among the objects are delineated through links connecting the nodes. All three example graphs in Figure 1 have 6 nodes, N1, N2, . . . , N6, and 9 edges, E1, E2, . . . , E9. Figure 1a has no directionality and its edges have no weight. Figure 1b has directionality to its unweighted edges, which indicates the direction of information flow. Edges may be assigned weights to represent an associated magnitude such as time or distance between nodes. For example, in Figure 1c number 10 on edge E2 may mean it takes 10 seconds for information to get from N1 to N2 or may mean they are 10 mm apart.

In neuroscience research the graphs usually stand for specialized neural populations such as the prefrontal cortex or medial temporal lobe. Most research in this field deals with functional connectivity between neural populations. Functional connectivity is represented as a graph with no directionality to the edges (Fig. 1a) and may have weight (Fig.1c). Effective connectivity is created by adding directionality to the edges to indicate not only which areas of the brain are connected but also how the information flows between two nodes (Fig. 1b). Box 1 shows an overview of graph theory.

Box 1. Overview of Graph Theory Application.

- Simplified network with minimum loss of information
- Graphs are easily generated from MRI, fMRI, EEG, PET, and NMR data
- Can show spatial and temporal dynamics

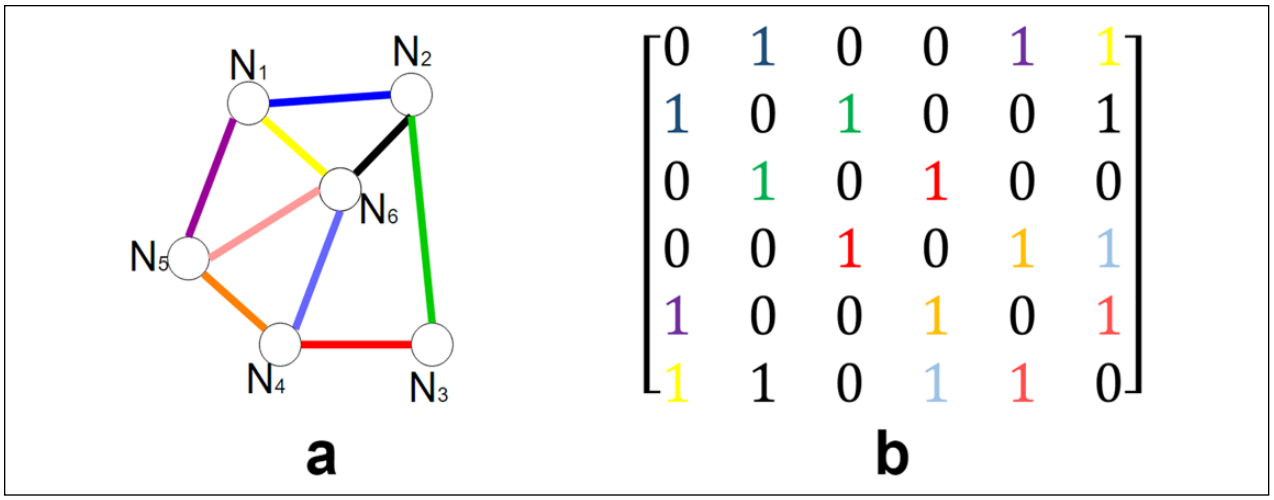

Figure 2. (a) A basic graph. (b) The corresponding adjacency matrix.

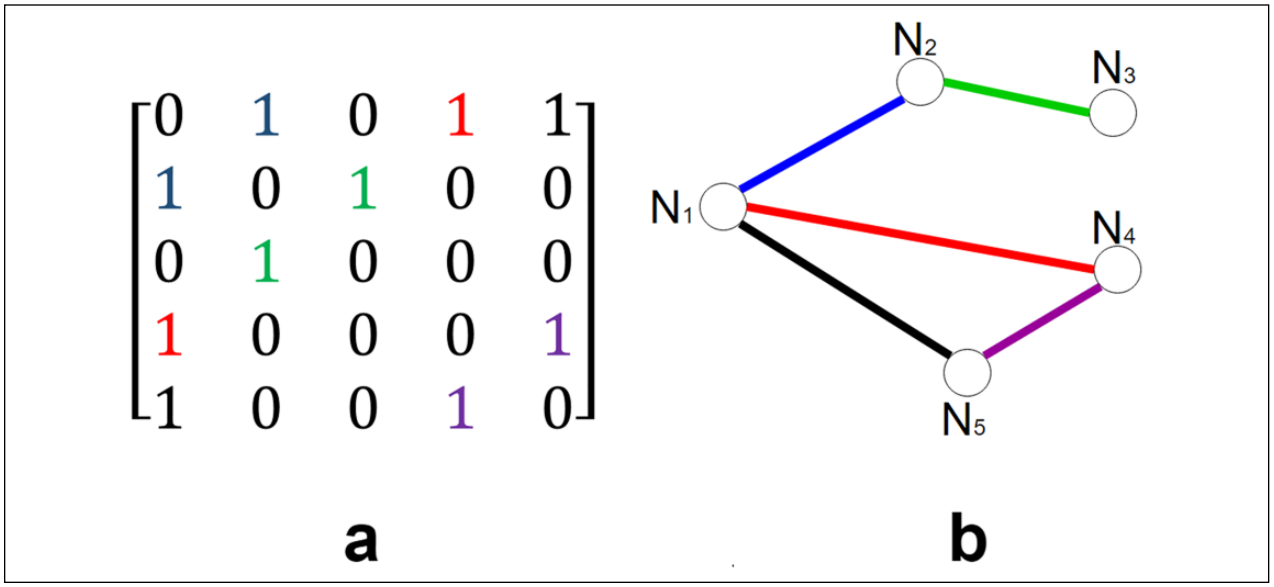

Figure 3. (a) An arbitrary matrix. (b) The graph of the matrix.

Matrix Representation of Graphs

Graphs can be represented as $N \times N$ matrices where N is the number of nodes. This representation is called the adjacency matrix (Daianu and others 2014). It is produced by creating an entry a_{ij} where i and j represent two nodes, respectively. If the nodes are connected $a_{ij} = 1$ otherwise $a_{ij} = 0$. The adjacency matrix for graph of Figure 1a is presented in Figure 2b.

Matrix representation is particularly useful in neuroscience because data acquisition techniques such as fMRI record data as a matrix. Just as a graph is converted to a matrix, a matrix can be converted to a graph. This is done by moving across a row i and if $a_{ij} = 1$ the two nodes are directly connected and if $a_{ij} = 0$ the two nodes are not directly connected. Figure 3a shows an arbitrary matrix B. It is converted into a graph in Figure 3b.

Visibility Graph

A very specific type of graph called a visibility graph (VG) is particularly useful when looking at time series data (Lacasa and others 2008). A VG is a technique to turn temporal data into a network and thus visualize it as a graph. This works by taking each data point to be a node and linking nodes based on whether they can *see* other nodes. Developing a VG from a temporal data set involves two steps. The first step is to establish the nodes and

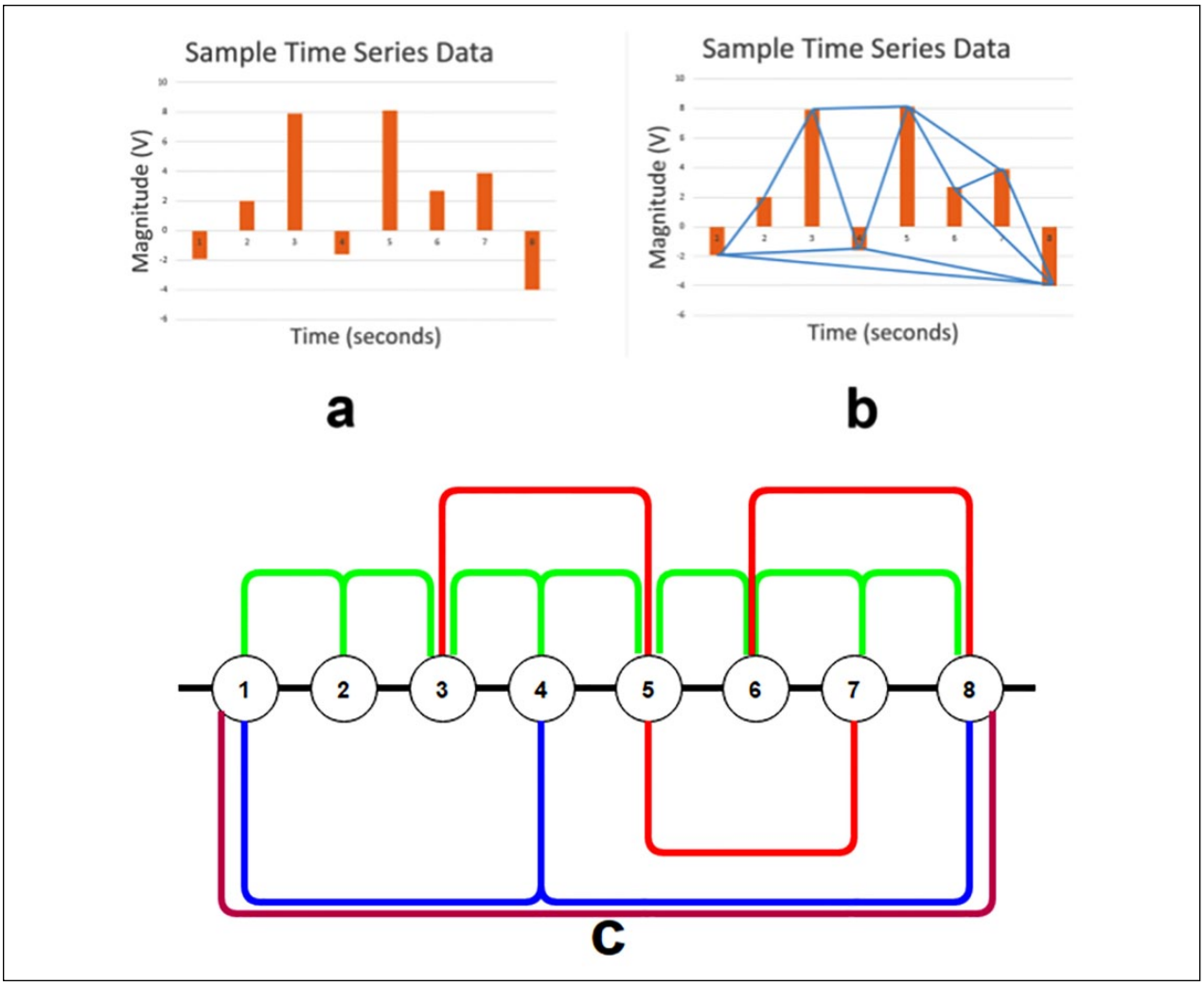

Figure 4. (a) A sample time series data set. (b) Visibility graph for "a." (C) Visibility graph as a line graph.

edges where nodes correspond to the peaks of the graphs and edges are found based on whether nodes can see each other. If two nodes can see each other it means that there is no other node lying on the edge drawn between them. An example of creating a VG is shown in Figure 4. Figure 4a shows a sample time series. Figure 4b is the VG for Figure 4a superimposed on the time series. In Figure 4b, nodes 2 and 4 are not connected directly because node 4 cannot see node 2. Figure 4c shows visibility graph as a line graph. A line graph is an adequate representation of the visibility graph because the visibility graph's edges represent the shortest distance between two nodes. Ahmadlou and others (2010) present diagnostic EEG markers of AD using VG.

Improved Visibility Graph

In real systems there is always noise. Noise can effect time series data and can in turn affect the VG generated. In order to produce a more robust VG, Ahmadlou and others (2012) presented an improved VG. Improved VG examines fractal systems on different scales using their self-similar patterns to produce a VG that is less susceptible to effects of noise.

Hubs

Hubs are highly connected regions of a network (Ahmadlou and others 2010). They derive from fractal dimension visibility graphs. A fractal dimension is a ratio of how the detail in a pattern changes with scale (Xu and others 2016). Fractal systems are self-similar in that they follow patterns that are similar on both the micro and macro scales (Goldberger and others 2002). In the brain neurons are distributed into fractal networks that have complex topologies. The distribution of connections is neither random nor uniform. The connectivity distribution follows a power law dependence (Kim and Lim

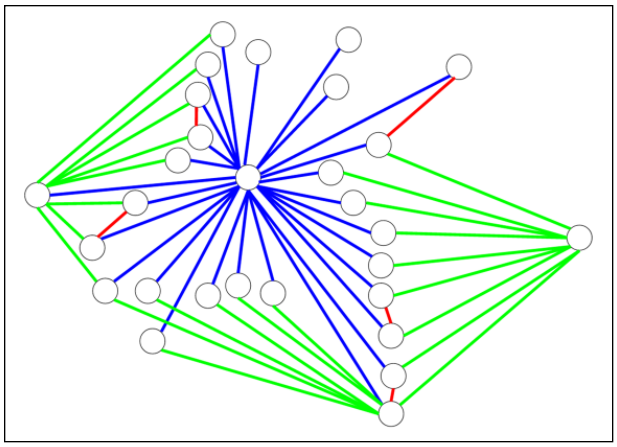

Figure 5. A sample scale free network with a power law dependence of 3.

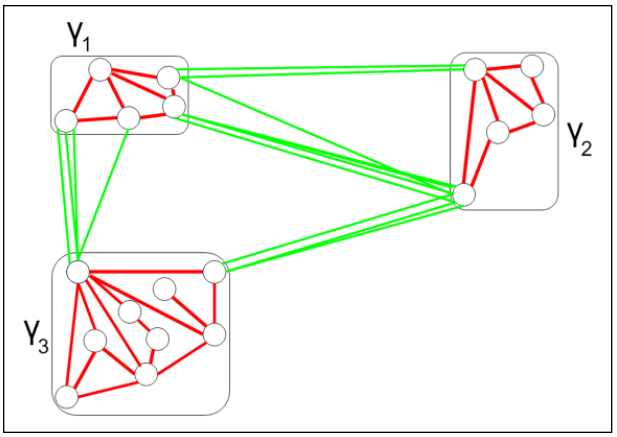

Figure 6. A small world network.

2016). This produces a scale free network with hubs. For example, if the power law dependence of a network is 3 then a network may exhibit one node with 3^3 edges, three nodes with 3^2 edges, and nine nodes with 3^1 edges, as shown in Figure 5.

Small Worldness

Small worldness (SW) is the "balance between integration and segregation, maximizing both global and nodal efficiency" (Dennis and Thompson 2014). It is modeled using two parameters. The first is the clustering coefficient (γ), which is how densely confined and connected local nodes are. The totality of local nodes and their connectivity is called a cluster. The second parameter is the characteristic path length (λ), which is the distance between connected clusters. SW is then quantified as $\sigma = \gamma / \lambda$ (Supekar and others 2008). Many of the studies use this as a primary or subordinate means to quantify connectivity (Prasad and others 2015; Supekar and others 2008; Zippo and others 2015). Figure 6 shows an arbitrary network that has three distinct clusters, γ_1, γ_2, and γ_3 connected by edges that represent the characteristic path between them.

Global and Local Changes

One way to assess the viability of connectivity as a biomarker is to look at global and local changes in the brain. In the parlance of the graph theory, global connectivity refers to the binary state of connectivity among nodes. That means two nodes are either connected or not. Local connectivity, on the other hand, refers to the strength of the connection between two nodes. The strength of the connection between two nodes is reflected in the local connectivity only. Figure 7 presents an example of global and local network changes. Figure 7a shows a network of 5 nodes where the strength of connectivity or weight of the edge is represented by the thickness of the edge with a thicker line denoting a stronger connection. Figure 7b shows a network where local connectivity between nodes has changed with no change in their global connectivity. Figure 7c present a network where both local and global connections have changed. SW plays a key role in accessing both local and global connectivity.

Other Methods

While this review focuses on graph theory, there are other methods that can be used to quantify connectivity. Among the most common are Granger causality (GC) (Deshpande and others 2009), wavelet analysis (Adeli and Ghosh-Dastidar 2010; Başar and others 2015; Sankari and others 2012), spectral coherence (Chan and others 2013), entropy (Houmani and others 2015), and synchronization likelihood (SL) (Ahmadlou and Adeli 2011; Schutte and others 2013).

Furthermore, these analyses can be used in combination with graph theory. Yan and others (2013) use effective connectivity and GC to evaluate changes in the default mode network between healthy and mild cognitive impairment. Schutte and others (2013) used SL and function connectivity to show that twins inherited similar functional connectivity patterns.

Connectivity Changes as a Biomarker

Many studies have concluded that functional connectivity changes are prevalent in AD. Furthermore, there is a growing notion that the decrease in functional connectivity in AD can be a viable biomarker for the disease (Dai and others 2015; Zhan and others 2016). A review of

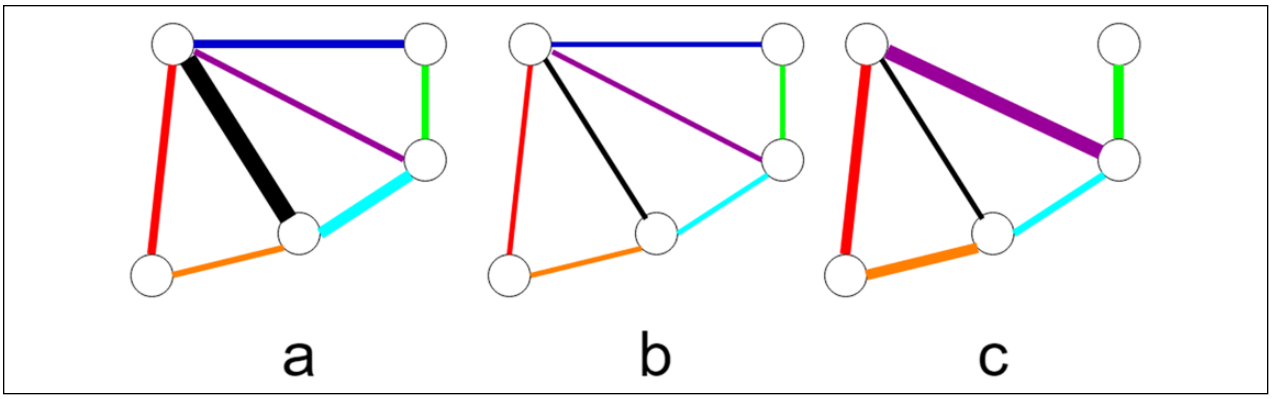

Figure 7. (a) An example network (the strength of connectivity or weight of the edge is represented by the thickness of the edge). (b) Change in local connectivity from network "a." (C) Change in local and global connectivity from network "a."

current AD brain connectivity research using fMRI and EEG imaging techniques is presented in this section.

Functional Magnetic Resonance Imaging

fMRI is commonly used to examine networks such as the default mode network (DMN), sensorimotor network (SMN), and the salience network (SN). The DMN is a specific group of neural regions whose activity increases when not performing a task and is thought to be crucial in memory consolidation. SMN refers to the regions of the brain that aid in movement (Xiao and others 2015). SN is often viewed as the network that automatically monitors for conflict and houses reward processing centers (Dennis and Thompson 2014). These networks and their connectivity patterns have been studied extensively.

Default Mode Network

Ciftci (2011) uses the graph theory measure of a minimum spanning tree to study the DMN in healthy controls versus AD patients. A minimum spanning tree is a graph that minimizes the path from any node to another given node, thus reducing energetic cost. The study reports that those with AD developed more segregated clusters and have less interconnectivity. Hahn and others (2013) investigate the structural and functional changes in the DMN. Their study indicates that AD affects certain networks such as the DMN negatively, and as the disease progresses, the functional connectivity of the network continues to break down. As a result, the functional connectivity is impaired.

Bernard and others (2015) examine memory decline over a 10-year span. By using the graph theory measure of SW they observed a decrease in functional connectivity among those with memory decline. While the global network remained stable they found most of the alteration takes place in regions highly involved in the DMN. Dai and others (2015) identify hubs using Pearson correlations of time series data. The hubs and connections are mapped as a weighted graph, which represents the subjects' whole brain network. They report that the connection density is slightly lower among AD patients; however, the DMN in particular is significantly deteriorated relative to the DMN of healthy controls.

Chen and others (2016) study the resting state fMRI (rsfMRI) of mild cognitive impairment (MCI) and AD patients. Resting state refers to the absence of a task; in other words, the subject is not engaged in anything specific. They present a methodology to detect rsfMRI networks by calculating the inflow and outflow of information in each network. They identify and study five networks and conclude that the networks are structured similarly. However, the connectivity in these networks in general is impaired in both MCI and AD patients. Furthermore, they report a major connectivity decrease in the DMN for AD patients.

Local Regions

More recently, fMRI has been used to evaluate the functional connectivity of specific regions of the brain. Chen and others (2013) used a graph theory measure of modularity that is similar to SW to examine the density of connection in a network. They report that those with AD have less symmetric networks and the insula is greatly affected by AD. Xia and others (2014) study the connectivity of the posteromedial cortex. With the use of an edge deletion algorithm, they identify subregions in the posteromedial cortex. Their results reveal a decrease in connectivity in all identified subregions but not all the same way. They found three different patterns of disruption. Burggren and Brown (2014) report the medial temporal lobe is highly affected even before cognitive decline manifests in AD.

Specifically, the hippocampus lying within the medial temporal lobe is greatly affected and connectivity in the medial temporal lobe is altered significantly in AD patients. The authors argue that this change in connectivity can provide insights into the disease pathology.

Wang and others (2016) investigate the connectivity disruptions of the amygdala. They identified three areas of interest within the amygdala that is present in both hemispheres. They report that the connectivity among many of the subregions within the amygdala decreases in patients with AD compared with healthy controls. Similar disruptions were also observed by Yao and others (2013), who examined the role of amygdala connectivity in AD and found that the functional connectivity decreases in those with AD.

Global Connectivity

Connectivity and its changes can also be studied on a global basis where the interaction among many different regions are examined. Brier and others (2014) use SW on a large sample of data to identify network characteristics of the progression of AD. They report that the clustering coefficient changes with the progression of the disease. The change in clustering coefficient also correlates with the known cognitive decline of those with AD. Suckling and others (2015) study the global pathways of AD patients compared to healthy controls and report that the brain of AD patients tends to form more circuits-based paths with reduced intra-connections. The paths change because of deletion of minor edges (a nonhub edge).

Ortiz and others (2015) find that patients with AD have less densely packed neural connections and thus a less optimal small world network (SWN) is developed. Toussaint and others (2014) report that the DMN SW decreases in patients with AD. The same observation is made by Xiang and others (2013) and Canu and others (2014). Khazaee and others (2016) use a slew of graph theory measures such as in and out degree, node strength, clustering coefficient, and characteristic path length to develop an algorithm to differentiate healthy, MCI, and AD. By setting up a global network of prevalent hubs and comparing to previously studied hubs in all conditions, they diagnosis AD patients with a false negative value of zero.

Deng and others (2016) investigate the differences between healthy, MCI, and AD patients' high-level visual functions by generating two matrices from which graphs are generated and the components of SW are calculated. The study concludes that the visual network is compromised in those with AD. Jie and others (2016) develop a hyper graph approach to overcome a limitation of simple graphs, that is, stagnant representation of a given network. They report that hyper graphs lead to a better classification/differentiation of AD and MCI toward a viable biomarker for the disease.

Electroencephalography

EEG is often analyzed using signal processing methods such as wavelets (Ahmadlou and Adeli 2010) or statistical approaches such as synchronization likelihood (SL) (Ahmadlou and Adeli 2011). In recent years, researchers have advanced the idea of integrating these tools with the graph theory. de Haan and others (2009) examined the frontal temporal region focusing on the lobar within the frontal temporal region in AD patients and those with frontal temporal lobar degeneration. They report AD patients have more sparse connections in the alpha and beta bands and longer average connection lengths in the lower alpha and gamma bands. Adeli and others (2008) present a spatiotemporal wavelet-chaos methodology for EEG-based diagnosis of the AD. Ahmadlou and others (2011) present fractality and a wavelet-chaos methodology for EEG-based diagnosis of AD.

Engels and others (2015) use the graph theory measurement of minimum spanning tree to study how networks change as AD progresses. They conclude that the functional connectivity in the lower alpha band and a transition of network hubs migrating to the anterior of the brain is connected to the severity of AD. Morabito and others (2015) present a longitudinal EEG study of the Alzheimer's disease progression based on a complex network approach. Yu and others (2016) use EEG with a graph theory measure known as minimum tree spanning. Minimum tree spanning develops a graph with the least amount of edges possible to connect nodes. This is implemented to examine the difference between functional connectivity among patients with AD and behavioral variant of frontal temporal dementia (bvFTD). They conclude that both groups of patients have disrupted connectivity. For AD patients, most of the connectivity disruption is in the posterior regions of the brain whereas for bvFTD patients it is in the frontal regions.

Small Worldness

EEG can be used to explore the SW of a network. Stam and others (2007) use graphs converted from SL to assess the SW of patient with AD. They find that AD patients have a longer characteristic path lengths and less dense local clusters in the beta-band frequency, corresponding to a less connected SWN. Similarly, de Haan and others (2009) report that the clustering coefficient of those with AD is significantly diminished compared to healthy controls and patients with frontotemporal lobar degeneration. Wang and others (2014) examine SWN components such as local clustering and mean path lengths and conclude that SWN among AD patient is diminished.

Wang and others (2014) report that functional connectivity decreases in individual brain regions corresponding to a weaker SWN. Vecchio and others (2016) use exact

Table 1. A Summary of Recent Research on the Application of Graph Theory in the Study of Brain Connectivity in Alzheimer's Disease.

Author	Method	Focus	Main Finding
Ciftci (2011)	fMRI	DMN	Minimum spanning tree reveals affected DMN
Hahn and others (2013)	fMRI	DMN	Connectivity of DMN decreased
Bernard and others (2015)	fMRI	DMN	Globally stable network, connectivity of DMN decreased
Dai and others (2015)	fMRI	DMN	Connectivity of DMN decreased
Chen and others (2016)	fMRI	DMN	Connectivity of DMN decreased
Chen and others (2013)	fMRI	Insula	Affected connectivity in patients
Xia and others (2014)	fMRI	Posteromedial cortex	Affected connectivity in patients
Burggren and Brown (2014)	fMRI	Medial temporal lobe	Affected connectivity in patients
Wang and others (2016)	fMRI	Amygdala	Affected connectivity in patients
Yao and others (2013)	fMRI	Amygdala	Affected connectivity in patients
McCarthy and others (2014)	fMRI	Global	Posterior-anterior shift enhanced
Brier and others (2014)	fMRI	Global	SW decreases
Suckling and others (2015)	fMRI	Global	Neural networks become more circuit like
Ortiz and others (2015)	fMRI	Global	Less optimal SW networks develop
Toussaint and others (2014)	fMRI	Global	SW decreases
Xiang and others (2013)	fMRI	Global	SW decreases
Canu and others (2014)	fMRI	Global	SW decreases
Khazaee and others (2016)	fMRI	Global	Diagnosis
Deng and others (2016)	fMRI	Global	Patients take more time to find visual targets
Jie and others (2016)	fMRI	Method	Hyper graphs better classify AD, MCI
Lee and others (2016)	fMRI	Method	Graph theory voxel algorithm better tracks DMN change
de Haan and others (2009)	EEG	Frequency bands	SW components are compromised
Engels and others (2015)	EEG	Frequency bands	Hubs migrate and connectivity decreases
Yu and others (2016)	EEG	Frequency bands	Posterior regions compromised
Stam and others (2007)	EEG	SW	SW decreases
de Haan and others (2009)	EEG	SW	SW decreases
Wang and others (2014)	EEG	SW	SW decreases
Wang and others (2016)	EEG	SW	SW decreases
Miraglia and others (2016)	EEG	SW	SW decreases

fMRI = functional magnetic resonance imaging; DMN = default mode network; SW = small worldness; AD =Alzheimer's disease; MCI = mild cognitive impairment; EEG = electroencephalography.

low-resolution brain electromagnetic tomography (eLORETA) to extract information about memory and combine it with graph theory. Using eLORETA they found that the SW of AD patients is compromised. Additionally, they report that the weakening of the SW affects neural pathways and memory. Miraglia and others (2016) investigate attention differences using eyes open and eyes closed resting state EEG. This study also used eLORETA to extract the EEG data for graph theory analysis, focusing on SW. They find that AD patients have less SW in the alpha band, possibly due to the brain's inability to register nonspecific visual information.

Conclusion

Table 1 presents a summary of recent research on the application of graph theory in the study of brain connectivity in Alzheimer's disease. In general, patients with AD show a decrease in local connectivity relative to healthy controls (Brier and others 2014; Dai and others 2015; Dillen and others 2016; Khazaee and others 2016; Serra and others 2016; Sui and others 2015). An interesting secondary conclusion with AD patients is that although connectivity decreases in general, the brain also reorganizes itself, known as brain plasticity (Dillen and others 2016; Khazaee and others 2016; Kim and others 2015a; Toussaint and others 2014). This has led to conflicting results based on the presumptions of the study. Most studies conclude that local connectivity decreases and global connectivity remains stable (Brier and others 2014; Daianu and others 2013; Engels and others 2015).

While there is good evidence that the decrease of functional connectivity correlates well with distinguishing healthy patients from AD there is still more research to be done. The horizon of this work points toward quantifying the amount of network decay to distinguish AD from

healthy or perhaps ranking the hubs most affected by AD. The regions of the major networks such as the DMN or SN need more research in order to complete the picture of the overall network breakdown. Furthermore, an interesting aspect of the reported research is the reorganization of the brains' networks among those with AD, providing a glimmer of hope, even farfetched, for rehabilitation of the AD brain. Reorganization has been seldom studied, and on an individual basis may serve as a potential biomarker for detecting the onset of AD.

Declaration of Conflicting Interests

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