Neurobiology of Aging 34 (2013) 2023–2036

Contents lists available at SciVerse ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Review

Alzheimer's disease: connecting findings from graph theoretical studies of brain networks

Betty M. Tijms [a,*], Alle Meije Wink [b], Willem de Haan [a], Wiesje M. van der Flier [a,c], Cornelis J. Stam [d], Philip Scheltens [a], Frederik Barkhof [b]

[a] Alzheimer Center and Department of Neurology, VU University Medical Center, Amsterdam, the Netherlands
[b] Department of Radiology, VU University Medical Center, Amsterdam, the Netherlands
[c] Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, the Netherlands
[d] Department of Clinical Neurophysiology and MEG, VU University Medical Center, Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 10 October 2012
Received in revised form 19 February 2013
Accepted 25 February 2013
Available online 28 March 2013

Keywords:
Dementia
Graph theory
Connectivity
Brain networks
MRI
DTI
EEG
MEG

ABSTRACT

The interrelationships between pathological processes and emerging clinical phenotypes in Alzheimer's disease (AD) are important yet complicated to study, because the brain is a complex network where local disruptions can have widespread effects. Recently, properties in brain networks obtained with neuroimaging techniques have been studied in AD with tools from graph theory. However, the interpretation of graph alterations remains unclear, because the definition of connectivity depends on the imaging modality used. Here we examined which graph properties have been consistently reported to be disturbed in AD studies, using a heuristically defined "graph space" to investigate which theoretical models can best explain graph alterations in AD. Findings from structural and functional graphs point to a loss of highly connected areas in AD. However, studies showed considerable variability in reported group differences of most graph properties. This suggests that brain graphs might not be isometric, which complicates the interpretation of graph measurements. We highlight confounding factors such as differences in graph construction methods and provide recommendations for future research.

1. Introduction

Alzheimer's disease (AD) is a progressive, disabling neurodegenerative disorder that accounts for approximately 50%–80% of all dementia cases. AD is histopathologically defined by the presence of amyloid-β plaques and tau-related neurofibrillary tangles. These plaques and tangles have been associated with local synaptic disruptions, suggesting that AD is a dysconnectivity disease (Arendt, 2009; Blennow et al., 1996; Delbeuck et al., 2003; Takahashi et al., 2010). At later stages of the disease, cortical atrophy progresses in an orderly fashion from subcortical structures such as the hippocampus into associative cortical areas and finally primary sensory areas (Braak and Braak, 1991; Jack et al., 2010). These observations suggest that specific cortical areas are vulnerable for AD pathology, which may determine how the disease propagates along specific paths in a network. If AD is indeed a dysconnectivity disease then this can only be captured with a network approach, because the structural elements of the brain form an intricate network at different spatial scales (ranging from neurons to anatomical regions) from which functional dynamics emerge. Local disruptions in such complex networks can have unpredictable and widespread effects (see e.g., Gratton et al., 2012).

Graph theory provides tools to concisely quantify the properties of complex networks that describe interrelationships (represented by edges) between objects (represented by nodes; see Section 2 for an explanation of graph theoretical concepts). It has been proposed that a detailed understanding of structural connectivity between cortical areas (i.e., the 'human connectome') will provide a mechanistic understanding of the dynamic function that can emerge (Sporns et al., 2005). Graph theory offers at least 2 important advantages in comparison with other network approaches. First, it provides for each node quantitative measurements that incorporate connectivity information from the complete network, reflecting the

* Corresponding author at: Alzheimer Center and Department of Neurology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands. Tel.: +31 204440816; fax: +31 204440816.
E-mail address: betty.tijms@gmail.com (B.M. Tijms).

0197-4580/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2013.02.020

integrated nature of local brain activity. For example, hubs can be defined as nodes that make information processing in a graph more efficient and increase a network's robustness to random failure (Albert et al., 2000; see section 2). However, such nodes are also bottlenecks, because the loss of a hub is likely to fragment a network into disconnected parts. Interestingly, hubs have been associated with epidemic transfer, and might therefore be important to study how a disease propagates in a network (Pastor-Satorras and Vespignani, 2001).

A second advantage of graph theory is that it provides a general language that enables direct comparison of graphs that describe different types of data (e.g., functional connectivity vs. anatomical connectivity). For these reasons, graph theory seems to be a promising framework to disentangle how various pathological processes in AD, such as spatial patterns of cortical atrophy and functional disruptions, are associated with each other and why the disease propagates along specific routes.

Up to now graph theory has been mainly used to describe brain graphs that were obtained with anatomical, morphological, and functional neuroimaging techniques, because a detailed a description of the human connectome is difficult to obtain (for reviews see Bassett and Bullmore, 2006; Bullmore and Bassett, 2011; Bullmore and Sporns, 2009, 2012, 2013; Stam and Reijneveld, 2007). It has been argued that if graphs constructed from different imaging modalities reflect true brain connectivity, they should have corresponding network topologies. Yet, it is still an open question whether connectivity as defined across neuroimaging modalities measure the same underlying construct (although associations across modalities have been reported: Gong et al., 2012; Honey et al., 2007, 2009).

Recently, brain networks in AD have been investigated by applying the theoretical framework of graph theory to neuroimaging data (Çiftçi, 2011; de Haan et al., 2009, 2012b, 2012c; He et al., 2008; Li et al., 2012; Lo et al., 2010; Sanz-Arigita et al., 2010; Stam et al., 2009; Supekar et al., 2008; Tijms et al., 2013; Yao et al., 2010; Zhao et al., 2012. For AD-specific reviews see: He et al., 2009; Xie and He, 2012; and for neurodegenerative diseases in general, see: Greicius and Kimmel, 2012). Importantly, these studies have reported altered local and global graph properties in AD, supporting the clinical relevance of brain graphs. However, the interpretation of 'disturbance' might be ambiguous, because the definition for connectivity depends on the imaging modality used.

It could be hypothesized that if brain graphs are robust across neuroimaging modalities and of an isometric nature, then group differences in graph measurements between AD and control subjects should converge across studies. Here we investigate this question by reviewing graph studies in AD and we will introduce a heuristically defined graph space to investigate which theoretical models best explain converging network alterations.

2. Studies of AD and graph theory

A literature search was carried out in the following online resources: PubMed, Web of Science, and Google Scholar. Combinations of the following key words were used: structural magnetic resonance imaging (sMRI), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), diffusion spectrum imaging (DSI), EEG (electroencephalography), magnetoencephalography (MEG), gray matter, white matter, connectivity, AD, networks, small world. From this search articles were selected that used graph theory to analyze networks at the whole-brain level and that reported the network size and connectivity density (i.e., the ratio of the number of existing connections to maximum possible number of connections). Table 1 shows an overview of the studies found.

2.1. Graph theoretical concepts

The building blocks of networks are nodes (i.e., vertices) that represent the objects of interest and the edges that connect them. Presently, no general consensus exists as to how to best choose nodes and a connectivity function, mostly because the exact mapping of neuronal connectivity at the cell and/or population level to the macroscopic level of neuroimaging data is unknown (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010; Sporns, 2011; Sporns et al., 2005).

Nodes in all brain graphs represent anatomical areas. Table 2 shows that network sizes varied across studies from 21 (EEG) to 8683 (sMRI). In magnetic resonance imaging (MRI) research, most studies have defined nodes using 90 regions from the Automated Anatomical Labeling atlas (AAL) (Tzourio-Mazoyer et al., 2002), apart from Lo et al. (2010), who used 78 AAL regions, He et al. (2008), who used 54 regions defined with automated nonlinear image matching and anatomical labeling software (Collins et al., 1995), and Tijms et al. (2013), who used a template-free approach resulting in an average graph size of 8683 nodes.

Edges connect nodes according to some connectivity function: the existence and/or integrity of a DTI traced white matter tract, temporal associations (measured with either linear or nonlinear techniques in fMRI, MEG, and EEG) or covariation of cortical thickness or volume between anatomical areas across subjects (sMRI) or similarity of cortical structure within an individual (sMRI). In graph theoretical context the term 'connection' indicates the existence of an edge, which in sMRI and functional networks might exist in the absence of white matter tracts. Defining the relationships between nodes is not a trivial task, because even within a modality different association metrics can lead to different connectivity patterns (see Liang et al., 2012; Smith et al., 2011). Preprocessing procedures can also influence connectivity. For example, spatial smoothing of signals to reduce the influence of normalization errors introduces (spurious) correlations between spatially nearby voxels (Li et al., 2012; Supekar et al., 2008; Yao et al., 2010).

Finally, the edges can be weighted, thresholded weighted, and unweighted (i.e., binarized). In contrast to binarized networks, weighted networks convey information about the strength of connectivity, including weak relationships that might even be spurious (introducing noise into the network). Weak relationships are given 0 weight in thresholded networks, but setting a threshold involves an arbitrary decision. Therefore, topologies of thresholded networks are usually studied for a range of different threshold values. When studying patient populations, including AD, a priori group differences in global connectivity will introduce group differences in connectivity densities of weighted and unweighted networks, complicating group comparisons of other graph properties.

2.2. A heuristic model of graph space

The studies in this review investigated 13 different graph properties in total, which are illustrated in Fig. 1 along with the theoretical models that explain them (for more details see Table 3. Readers unfamiliar with graph theoretical concepts are referred to Section 1 of the Supplementary data).

These graph properties derive their meaning from the fact that they are defined in the context of specific structural models of complex networks, from which functional dynamics can emerge. However, the precise structural description, also called the 'connectome', of the human brain is largely unknown, because at different spatial scales it is difficult to measure; at the micro level of neurons, their sheer number hinders the mapping of all synaptic