Ageing Research Reviews 15 (2014) 44–50

Contents lists available at ScienceDirect

Ageing Research Reviews

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

Review

A quantitative neural network approach to understanding aging phenotypes

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ARTICLE INFO

Article history:
Received 4 December 2013
Accepted 5 February 2014
Available online 15 February 2014

Keywords:
Graph theory
Neural networks
Neurocognitive aging

ABSTRACT

Basic research on neurocognitive aging has traditionally adopted a reductionist approach in the search for the basis of cognitive preservation versus decline. However, increasing evidence suggests that a network level understanding of the brain can provide additional novel insight into the structural and functional organization from which complex behavior and dysfunction emerge. Using graph theory as a mathematical framework to characterize neural networks, recent data suggest that alterations in structural and functional networks may contribute to individual differences in cognitive phenotypes in advanced aging. This paper reviews literature that defines network changes in healthy and pathological aging phenotypes, while highlighting the substantial overlap in key features and patterns observed across aging phenotypes. Consistent with current efforts in this area, here we outline one analytic strategy that attempts to quantify graph theory metrics more precisely, with the goal of improving diagnostic sensitivity and predictive accuracy for differential trajectories in neurocognitive aging. Ultimately, such an approach may yield useful measures for gauging the efficacy of potential preventative interventions and disease modifying treatments early in the course of aging.

Published by Elsevier B.V.

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1. Introduction

Dramatic increases in life expectancy over the last century have led to an escalating aging population. The potential impact of this demographic trend is tremendous not only in terms of the financial burden to society but also the devastating personal toll for afflicted individuals and their caregivers. Given the urgency of the issue, major efforts are underway to advance a more comprehensive neurobiological account of neurocognitive aging. A critical, and yet unrealized goal, has been to differentiate indicators of 'normal' aging from those that signal pathological processes, and ultimately, to identify the mechanisms that support optimal cognitive health.

It seems clear on the basis of available evidence that no single neurobiological abnormality or defect fully accounts for age-related cognitive impairment, and instead, that the interaction among causative factors gives rise to a multifaceted etiology. Nevertheless, research in this area has traditionally adopted a reductionist

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http://dx.doi.org/10.1016/j.arr.2014.02.001
1568-1637/Published by Elsevier B.V.

approach that, while illuminating critical neurobiological signatures (see Fletcher and Rapp, 2013; Lister and Barnes, 2009 for reviews), presents an oversimplification of the aging process itself and risks obscuring the synergistic interactions across multiple levels of analysis that are collectively responsible for cognitive outcomes. Indeed, it is plausible that profiles of age-related decline in cognitive function simply are not traceable to a narrow cell biological account. An alternate view is that the diversity of cognitive aging phenotypes is more appropriately conceived as an *emergent* property of the interactions among neural networks involving multiple brain regions and information processing capacities (Menon, 2011). Leveraging advances in neuroimaging technology, here we suggest that the field is poised to accelerate an integrative network science of brain and cognitive aging.

An important element of an integrative systems approach in this area is to describe the dynamical relationships between structural and functional networks and how they change as a function of age, health, and disease (Bassett and Bullmore, 2009). An initial step is to establish whether age-related network alterations are coupled with the maintenance or decline of cognitive function, suggesting that a network level description might be useful in tracking and predicting differential trajectories of neurocognitive aging. Validation hinges on evidence that aging is associated with variability in structural and functional connectivity that generates divergent neurocognitive outcomes. The purpose of this paper is twofold: (1) to briefly review current literature using graph theory to characterize patterns of functional and structural connectivity in healthy and diseased aging, and (2) to propose a conceptual framework that quantifies graph theory measures as a foundation for better prediction of aging trajectories. Thus, this mini-review is not intended to be a formal "proof of concept" in testing specific hypotheses, but instead to provide an introductory resource for scientific stakeholders across a range of interests, from neural circuit dynamics to the psychology of aging, for moving forward toward an integrated account.

2. Applying graph theory to whole brain networks

Networks of all types and sizes follow similar organizing principles that can be characterized using graph theory (Fig. 1). The application of graph theory in neuroimaging studies has advanced significant progress in mapping the connectivity of structural (SC) and functional (FC) brain networks that support cognitive function (Sporns, 2011). The basic elements of a graph (nodes) represent brain regions or voxels, whereas the connections between nodes (edges) represent their statistical associations in time or space. In this scheme, FC graphs signify the degree of coordinated activity in different brain areas under either resting-state (RS) or stimulus/task-induced conditions, measured by functional magnetic resonance imaging (fMRI) or electroencephalography/magnetoencephalography (EEG/MEG; Fig. 2 right; Sporns, 2011). Connectivity in this case refers to shared functional attributes, independent of assumptions about the anatomical relationships that directly or indirectly give rise to such associations (Honey et al., 2009). SC graphs, by comparison, represent either white matter connections between brain regions, probabilistically derived by diffusion tensor imaging (DTI), or associations between brains areas for morphometric parameters such as cortical thickness or volumes, calculated from structural MRI (Fig. 2 left; Sporns, 2011). An overarching goal in modeling these networks is to determine the nature of the SC–FC relationship and how these network dynamics map onto cognition and behavior. Graph theory may provide new insight into understanding SC and FC network organization throughout the course of aging and how these networks are disrupted in neuropsychiatric and degenerative diseases. However, there are several methodological issues to consider when interpreting graph theory studies that can affect the results, including choice of parcellation scheme, reliability of FC and SC networks across subjects and sessions, and control of extraneous noise, as described below.

2.1. Considerations in interpreting graph theory studies

A crucial step in graph theory applications involves selecting the method and spatial resolution for parcellating the brain into nodes and edges (Behrens and Sporns, 2012; Wig et al., 2011). Studies have varied in their approach, from using independently derived anatomical templates (e.g. Gong et al., 2009), to randomly dividing the brain into equally sized regions (e.g. Hagmann et al., 2008), to deriving nodes on the basis of similarities in FC or SC profiles across subjects (e.g.'s Cohen et al., 2008; Johansen-Berg et al., 2004). The choice of methodology is inherently linked to the spatial

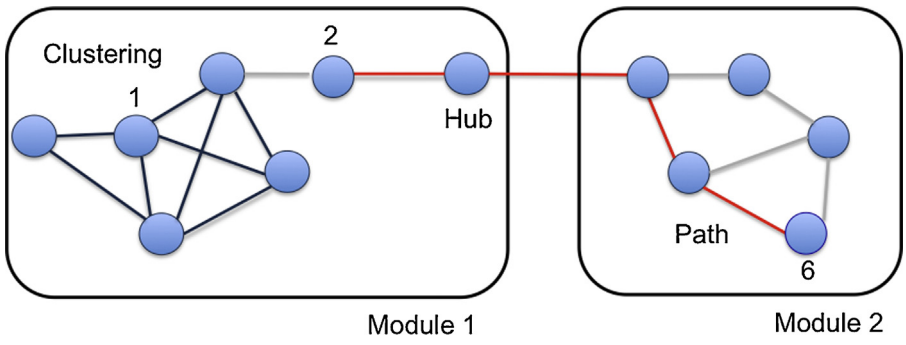

Fig. 1. Simple concepts in graph theory. A network consists of *nodes*, the basic elements of a system (depicted as circles), and the relationships between nodes, referred to as *edges* (all lines connecting circles). Once nodes and edges are defined, graph theory measures can be applied which characterize three basic features of a system: *segregation*, *integration*, and *influence* (Rubinov and Sporns, 2010). Measures of *segregation* describe the degree of interconnectedness among nodes. Clustering coefficient, for example, measures the degree of segregation of a network; in this example clustering for an individual node is high if that node's neighbors are also connected (e.g., node 1 shows a high level of clustering). A high clustering coefficient for an entire system suggests multiple segregated communities of nodes (referred to as modules, as indicated in figure). Related measures include local efficiency and modularity of a system. *Integration* measures describe how effectively information is transferred across networks by calculating the number of connections or paths between nodes (characteristic path length), with a shorter path length reflecting more efficient information exchange (e.g., shortest path between nodes 2 and 6 is four, indicated in red). A similar measure used in characterizing disconnected networks, such as those in aging and disease, is global efficiency calculated as the inverse of the average path length. Measures of *influence* describe the importance of individual nodes (hubs) in coordinating interactions amongst nodes or across modules. Hubs are determined on the basis of a high number of connections or by their inclusion in the shortest path lengths across a network (centrality measures). In sum, measures of *segregation*, *integration* and *influence*, may provide a new framework from which to understand the topology and function of the healthy, aged, and diseased brain.

Adapted from He and Evans (2010) and Rubinov and Sporns (2010).