Published in final edited form as:

Ageing Res Rev. 2014 May ; 15: 44–50. doi:10.1016/j.arr.2014.02.001.

A quantitative neural network approach to understanding aging phenotypes

Jessica A. Ash^{*} and Peter R. Rapp

Laboratory of Behavioral Neuroscience, Neurocognitive Aging Section, National Institute on Aging, Biomedical Research Center, 251 Bayview Blvd, Baltimore, MD 21224, USA

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.

Keywords

Graph theory; Neural networks; Neurocognitive aging

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.

^{*}Corresponding author at: Laboratory of Behavioral Neuroscience, National Institute on Aging, Biomedical Research Center, 251 Bayview Boulevard, Baltimore, MD 21224, United States. Tel.: +1 410 558 8672. jessica.ash@nih.gov, ja7421@gmail.com (J.A. Ash).

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 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 brain 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. Cohen et al., 2008; Johansen-Berg et al., 2004). The choice of methodology is inherently linked to the spatial resolution (i.e. the number of nodes and edges), which can influence specific graph theory measures such as clustering or path length, in contrast to more global inferences of whole brain topology (e.g. small-worldness) that are more robust to various parcellation resolutions (Fornito et al., 2010; Hayasaka and Laurienti, 2010; Wang et al., 2009; Zalesky et al., 2010). Importantly, individual differences are largely preserved with resolutions that exceed 200 nodes, at least for resting-state FC networks (Fornito et al., 2010). This is especially relevant for aging and clinical studies where individual differences are substantial and the relationships between variability in behavior and network properties of great interest (Fornito et al., 2010). Future studies could benefit from comparing graph theory parameters across differing spatial resolutions to ensure that the results are not dependent upon a specific parcellation method or scale. For instance, Hagmann et al. (2010) computed graph theory metrics from development through adulthood for low (66 nodes) and high (241 nodes) resolutions, showing equivalent results with either scale. Until such a strategy is common practice or a standardized node definition is established, aggregating findings across aging studies may be confounded where divergent parcellation schemes and resolutions are used.

Another unresolved issue relates to the reliability of FC and SC networks across time. Graph theory analyses depend upon the spatial consistency and reproducibility of these networks in order to allow accurate between-group comparisons and document within-subject longitudinal change. Studies tend to show moderate to good reliability measures for resting-state FC networks across short (up to a few hours) and long (several months to a year) inter-session intervals, with even greater reproducibility for SC or task-based FC networks over time (Damoiseaux et al., 2006; Honey et al., 2009; Shehzad et al., 2009; Van Dijk et al., 2010; Wang et al., 2011). However, several questions remain about these reliability measures in normal and pathological aging groups. Among the few studies that have addressed this issue, all report moderate multi-scan reliability scores for RS networks within

young, aged cognitively normal (CN), and MCI subjects (Blautzik et al., 2013; Guo et al., 2012; Song et al., 2012), although young adults show the highest test–retest reliability (Song et al., 2012) and MCI patients the lowest (Blautzik et al., 2013), relative to CN populations. The most reproducible RS networks, regardless of age or cognitive phenotype, are those that are highly interconnected, such as the default mode network (DMN) (Blautzik et al., 2013; Guo et al., 2012; Van Dijk et al., 2010). The degree of network reliability depends on several factors including the parcellation scheme (Wang et al., 2011), as discussed earlier, the type of graph theory metrics used to characterize network patterns (Braun et al., 2012; Deuker et al., 2009; Guo et al., 2012), and whether a global signal correction is applied (Guo et al., 2012; Wang et al., 2011). Clearly, standardization of analytic fMRI methods would facilitate the consistent characterization of FC and SC networks in the field. Nevertheless, the general consensus is that graph theory measures derived from FC and SC networks are sufficiently reliable to be used as indices of neural networks across subjects and sessions.

A final consideration is the influence and control of experimental noise associated with various subject-related variables and imaging equipment itself. These factors can be especially problematic for RS fMRI studies where the low intensity neural signal of interest is in the same spectrum as other non-neural signals and therefore difficult to disentangle (Power et al., 2012; Van Dijk et al., 2012). Head movement is a particularly common source of noise and although a variety of correction strategies have been developed, none completely eliminate the possibility that movement artifacts give rise to spurious FC patterns (Power et al., 2012; Van Dijk et al., 2012). This problem is compounded in studies of aging and clinical populations where the degree of movement varies across groups and there are large individual differences. Fortunately, almost all studies adopt some type of approach to regress out variability attributable to experimental noise, although the field lacks standardized methods in this regard. Future studies are needed to determine the best approach to model and eliminate motion artifacts as well as other noise factors, in order to enhance the sensitivity of neuroimaging features for biomarker detection in aging and disease.

2.2. Reviewing graph theory studies

These methodological constraints notwithstanding, graph theory studies show relatively consistent findings from early development through young adulthood, although the patterns in advanced aging are less clear. In reviewing these studies below, there are three broad categories of measures for FC and SC networks to consider as important features of brain organization (Rubinov and Sporns, 2010): (i) *segregation*, describing the degree to which neighboring nodes are interconnected, often forming communities of specialized functions (e.g., clustering coefficient, modularity, local efficiency); (ii) *integration*, defining the global interactions between these local communities of nodes (e.g., path length, global efficiency); and (iii) *influence*, representing the importance and influence of certain nodes in orchestrating dynamic neural activity (e.g., hubs, centrality).

2.3. SC and FC networks from development to young adulthood

Starting in childhood and continuing through young adulthood, the brain can be characterized by its small-world architecture, referring to the balance between functional

segregation of communities of nodes (modules) with global integration across these modules supporting efficient system-wide processing (Fig. 1; Bullmore and Sporns, 2009). The defining elements of these two aspects of brain topology, segregation and integration, are a high clustering coefficient, and short paths lengths, respectively (Watts and Strogatz, 1998; Fig. 1). This balance between segregation and integration changes as a function of age (Hagmann et al., 2010). In early development, the brain shows a tendency toward functional segregation of modules until long-range white matter projections mature in adolescence, facilitating global integration (Fair et al., 2009; Hagmann et al., 2010; Supekar et al., 2009). The correlation between SC and FC continues to strengthen over this period as well (Hagmann et al., 2010), coinciding with the elaboration of increasingly sophisticated cognitive capacities, including enhanced cognitive control and dynamical switching between networks (Supekar and Menon, 2012; Uddin et al., 2011).

2.4. SC and FC networks across advanced aging phenotypes

Advanced aging can be characterized by an imbalance between integration and segregation of neural networks as well as aberrant deviations in the influence and importance of specific nodes (hubs) that enable efficient information processing. Notably, the overall patterns of network change reveal a number of shared characteristics across aging phenotypes, suggesting that current network characterizations may not be sufficient for discriminating normal versus pathological outcomes.

One pattern that emerges in normal aging, with greater decline in AD, is a reduced capacity for global network integration, as revealed by increasing path lengths between pairs of nodes (He et al., 2008; Lo et al., 2010; Yao et al., 2010), and a trend toward decreasing global efficiency of information transfer (Achard and Bullmore, 2007; Gong et al., 2009). The distributed loss of interactions between networks may in turn alter dynamics on a local level. Several studies point to decreased local efficiency of information processing in normal aging relative to young adults (Achard and Bullmore, 2007; Gong et al., 2009). Using a related measure, AD patients exhibit a similar pattern of decreased clustering coefficient compared to aged CN controls (de Haan et al., 2009; Stam et al., 2009; Supekar et al., 2008), although others have reported increased clustering coefficient in AD as well (He et al., 2008). Regardless of the direction of change, there appears to be a shift in advanced aging away from the small-world architecture of the adult brain, with varying degrees of deviation from normal to pathological conditions. Interestingly, MCI subjects exhibit network values intermediate between CN and AD groups (Yao et al., 2010), consistent with the idea that network alterations give rise to a continuum of differential cognitive outcomes.

Parallel to declining internetwork connectivity, aging also results in reduced intranetwork connectivity, especially in the DMN. The DMN shows graded degrees of hypoconnectivity starting in normal aging compared to healthy adult subjects (Andrews-Hanna et al., 2007; Chen et al., 2011; Hedden et al., 2009) and becomes progressively worse beginning in very mild stages of AD, mimicking a pattern apparent in other RS networks (Brier et al., 2012). Although qualitative differences in regional FC of the DMN also exist between groups, the overall loss in connectivity predominates and becomes more pervasive throughout the DMN as AD progresses (Greicius et al., 2004; Qi et al., 2010; Sorg et al., 2007; Wang et al., 2007).

Aberrant connectivity and dysfunction of the DMN is a feature of several other neurological disorders as well (e.g. Schizophrenia, Camchong et al., 2011). How graded variations within the DMN and other RS networks contribute to such a diversity of cognitive phenotypes, from normal aging to psychiatric disease, remains an important but unanswered question.

Another pattern shared across groups may arise partly as a result of global deterioration: alterations in the influence of hubs in coordinating network communication (centrality measures). In normal aging this is revealed by topological reorganization between and within modules (Chen et al., 2011; Meunier et al., 2009), potentially impacting the way information is processed relative to young adults. For instance, aged CN subjects show declining centrality among frontal and parietal hubs compared with young adults, but increased centrality in DMN regions including the precuneus and anterior cingulate cortex under memory activated conditions (Wang et al., 2010). Increased centrality for these DMN hubs is also reported in MCI and AD (Yao et al., 2010), significantly different from aged CN individuals. In general, however, MCI patients fall intermediate between phenotypes, more similar to AD overall in altered centrality patterns, although not always significantly different from CN subjects (Yao et al., 2010).

More extensive changes in centrality have been noted in AD, revealing decreases in several multimodal association regions and increases in some unimodal cortical areas (He et al., 2008). Importantly, the hub reorganization in AD may render these networks especially vulnerable to pathological attack (He et al., 2008; Stam et al., 2009), consistent with findings that elevated aerobic glycolysis among hubs is correlated with regional amyloid-beta deposition, especially within the DMN (Buckner et al., 2005, 2009; Vaishnavi et al., 2010; Vlassenko et al., 2010). Recent computational data suggest that the high activity and metabolism generated within hubs may contribute to pathological progression in AD (de Haan et al., 2012).

3. Developing a quantitative network model of aging: segregation, integration, and influence (SII)

Current evidence reveals varying degrees of similarity in patterns of network topology across aging phenotypes, calling into question the utility of graph theory in its current application for distinguishing these cognitive trajectories. One reason may relate to a reliance on more qualitative rather than quantitative classifications of network properties. For instance, many studies discuss the loss of small-world networks in aging and AD without reporting the magnitude of the difference relative to other groups in quantitative terms. The full range of cognitive phenotypes (young adult, CN, MCI, and AD) is also unavailable for examination in many studies, compounding the difficulty of developing network metrics with the required precision and specificity.

Here, we propose a strategy for systematically testing the sensitivity of neural network analyses to differentiate and predict healthy versus pathological cognitive aging trajectories. Recent guidelines from the Food and Drug Administration (FDA) highlight the need for such diagnostic frameworks early in aging given the continued failure of phase 3 clinical trials to modify late-stages of AD and the emerging realization that successful treatment of

AD and sustainment of cognitive health will require much earlier intervention (Kozauer and Katz, 2013). The quantification of neural networks using graph theory measures could potentially yield surrogate biomarkers to detect early and subtle signs of cognitive decline, and importantly, sensitive metrics for tracking the efficacy of early therapeutic intervention. The method outlined here offers a first step in the evaluation process.

As an overview, the first goal is to select and quantify network measures that represent key aspects of brain structure and function across well-defined, age-matched CN, MCI, and AD subjects (Fig. 3: #1). The second goal is to select suitable cutpoints for these network measures to be used as screening criteria for AD. If network cutpoints are effective in differentiating CN, MCI, and AD populations, the third goal is to then determine the predictive validity of these cutpoints in longitudinal studies that include both subjects who start as CN and subsequently progress to MCI or AD and those who do not. The approach advocated here could be tested taking advantage of large-scale longitudinal studies such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), where within-subject fMRI data are collected across many years. A potential implementation strategy for pursuing these goals is elaborated below.

First, we suggest quantifying the three categories of graph theory measures described earlier – segregation, integration, and influence (SII) – for subjects from each of the independently defined target populations of interest (CN, MCI, AD). Given that there are multiple network measures within each SII category, one strategy toward quantification is to construct composite z -scores for each SII category, which may provide more robust indicators of network organization than univariate measures alone (Fig. 3, Step #1). To accomplish this, all graph theory measures representing a single SII category could be included in a principal component analysis to determine which load onto the factor accounting for the greatest variance. Among these highly inter-correlated measures, each could then be z -transformed and then averaged together to provide a single composite measure for individual SII categories.

Previous studies have taken a conceptually similar approach combining clustering coefficient and path length into a single small-world index, for instance, to quantify this topological characteristic across whole-brain networks (Humphries and Gurney, 2008). Quantifying network measures in this way has the benefit of standardizing the use of graph theory for grading aging phenotypes and potentially improving replication across studies. For the model proposed here, we suggest constructing SII composite z -scores for SC networks initially, given that structure more reliably predicts function than the converse (Hagmann et al., 2008; Honey et al., 2009). Another possibility is to obtain SII measures for specific RS networks or subsystems, which might prove more sensitive to age-related changes than whole brain networks.

The second step involves defining the SII estimates considered abnormal based on AD standards. We propose identifying cutpoints for each SII category that correspond to the 90th or higher percentile of the AD population under study (Fig. 3: Step #2). This selection method of cutpoints is similar to that used by Jack et al. (2012). The cumulative distributions for the CN and MCI populations would then be plotted to determine the percentile cutpoints

of these populations that share the same SII scores as the AD population in order to reveal the degree of overlap in SII scores across phenotypes (i.e., the percentage of the CN and MCI populations with scores overlapping the abnormal AD distribution; Fig. 3: Steps #2a and 2b).

Third, receiver operating curves (ROC) could be used to identify the percentile cutpoints that maximally differentiate phenotypes for each SII category, balancing sensitivity versus specificity preferences (Fig. 3: Step #3). For instance, as an initial proof-of-concept, it may be advantageous to choose SII cutpoints that favor high sensitivity at the risk of low specificity to ensure that all AD patients are identified using this method. Other study aims, however, will dictate the selection of different cutpoints.

Finally, the last step examines the accuracy of the derived SII cut-points for predicting differential cognitive trajectories in aging and their potential utility as prognostic biomarkers. This could be confirmed in longitudinal studies where the neurocognitive outcomes are known (Fig. 3: Step #4), such as ADNI. Critical comparisons would include the proportion of CN subjects with abnormal SII values at baseline that later develop MCI or AD versus those that remain cognitively normal. Ideally, some combination of SII scores would correctly predict 100% of the CN population destined to develop pathology, without yielding false positives among those who will in fact escape disease. Although accuracy of this sort may be unrealistic, the proposed approach is a starting point for establishing a more quantitative neural network perspective on differential trajectories of cognitive aging, and for developing new tools to track the influence of promising interventions.

4. Conclusion

Scientific progress often comes from examining old problems in new ways. Adopting a network approach to the aging brain could inaugurate a new conceptual understanding of changes beyond the linear thinking that the reductionist tradition has encouraged in the past. Here, we outline a quantitative strategy consistent with the directions of AD research to test the possibility of using network metrics as biomarkers to predict cognitive aging trajectories beyond their current descriptive nature. Whether or not this particular approach proves useful, the development of tools for capturing neural network organization in brain may be key to understanding and treating AD and other complex disorders of mind.

Acknowledgments

We would like to thank Dr. Yihong Yang for his invaluable comments on this manuscript. This is original work supported by the Intramural Research Program of the National Institute on Aging.

References

- Achard S, Bullmore E. Efficiency and cost of economical brain functional networks. *PLoS Computational Biology*. 2007; 3:e17. [PubMed: 17274684]
- Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. *Journal of Neuroscience*. 2006; 26:63–72. [PubMed: 16399673]
- Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle ME, Buckner RL. Disruption of large-scale brain systems in advanced aging. *Neuron*. 2007; 56:924–935. [PubMed: 18054866]

- Bassett DS, Bullmore ET. Human brain networks in health and disease. *Current Opinion in Neurology*. 2009; 22:340–347. [PubMed: 19494774]
- Behrens TE, Sporns O. Human connectomics. *Current Opinion in Neurobiology*. 2012; 22:144–153. [PubMed: 21908183]
- Blautzik J, Keeser D, Berman A, Paolini M, Kirsch V, Mueller S, Coates U, Reiser M, Teipel SJ, Meindl T. Long-term test–retest reliability of resting-state networks in healthy elderly subjects and with amnesic mild cognitive impairment patients. *Journal of Alzheimer's Disease*. 2013; 34:741–754.
- Braun U, Plichta MM, Esslinger C, Sauer C, Haddad L, Grimm O, Mier D, Mohnke S, Heinz A, Erk S, Walter H, Seiferth N, Kirsch P, Meyer-Lindenberg A. Test–retest reliability of resting-state connectivity network characteristics using fMRI and graph theoretical measures. *Neuro Image*. 2012; 59:1404–1412. [PubMed: 21888983]
- Brier MR, Thomas JB, Snyder AZ, Benzinger TL, Zhang D, Raichle ME, Holtzman DM, Morris JC, Ances BM. Loss of intranetwork and internetwork resting state functional connections with Alzheimer's disease progression. *Journal of Neuroscience*. 2012; 32:8890–8899. [PubMed: 22745490]
- Buckner RL, Sepulcre J, Talukdar T, Krienen FM, Liu H, Hedden T, Andrews-Hanna JR, Sperling RA, Johnson KA. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. *Journal of Neuroscience*. 2009; 29:1860–1873. [PubMed: 19211893]
- Buckner RL, Snyder AZ, Shannon BJ, LaRossa G, Sachs R, Fotenos AF, Sheline YI, Klunk WE, Mathis CA, Morris JC, Mintun MA. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *Journal of Neuroscience*. 2005; 25:7709–7717. [PubMed: 16120771]
- Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews Neuroscience*. 2009; 10:186–198. [PubMed: 19190637]
- Camchong J, MacDonald AW 3rd, Bell C, Mueller BA, Lim KO. Altered functional and anatomical connectivity in schizophrenia. *Schizophrenia Bulletin*. 2011; 37:640–650. [PubMed: 19920062]
- Chen ZJ, He Y, Rosa-Neto P, Gong G, Evans AC. Age-related alterations in the modular organization of structural cortical network by using cortical thickness from MRI. *Neuro Image*. 2011; 56:235–245. [PubMed: 21238595]
- Cohen AL, Fair DA, Dosenbach NU, Miezin FM, Dierker D, Van Essen DC, Schlaggar BL, Petersen SE. Defining functional areas in individual human brains using resting functional connectivity MRI. *Neuro Image*. 2008; 41:45–57. [PubMed: 18367410]
- Damoiseaux JS, Rombouts SA, Barkhof F, Scheltens P, Stam CJ, Smith SM, Beckmann CF. Consistent resting-state networks across healthy subjects. *Proceedings of the National Academy of Sciences of the United States of America*. 2006; 103:13848–13853. [PubMed: 16945915]
- de Haan W, Mott K, van Straaten EC, Scheltens P, Stam CJ. Activity dependent degeneration explains hub vulnerability in Alzheimer's disease. *PLoS Computational Biology*. 2012; 8:e1002582. [PubMed: 22915996]
- de Haan W, Pijnenburg YA, Strijers RL, van der Made Y, van der Flier WM, Scheltens P, Stam CJ. Functional neural network analysis in frontotemporal dementia and Alzheimer's disease using EEG and graph theory. *BMC Neuroscience*. 2009; 10:101. [PubMed: 19698093]
- Deuker L, Bullmore ET, Smith M, Christensen S, Nathan PJ, Rockstroh B, Bassett DS. Reproducibility of graph metrics of human brain functional networks. *Neuro Image*. 2009; 47:1460–1468. [PubMed: 19463959]
- Fair DA, Cohen AL, Power JD, Dosenbach NU, Church JA, Miezin FM, Schlaggar BL, Petersen SE. Functional brain networks develop from a local to distributed organization. *PLoS Computational Biology*. 2009; 5:e1000381. [PubMed: 19412534]
- Fletcher, BR.; Rapp, PR. Normal neurocognitive aging. In: Weiner, IB., editor. *Handbook of Psychology Biological Psychology and Neuroscience*. 2. Vol. 3. Wiley; New Jersey: 2013. p. 643–663.
- Fornito A, Zalesky A, Bullmore ET. Network scaling effects in graph analytic studies of human resting-state FMRI data. *Frontiers in Systems Neuroscience*. 2010; 4:22. [PubMed: 20592949]

- Gong G, Rosa-Neto P, Carbonell F, Chen ZJ, He Y, Evans AC. Age- and gender-related differences in the cortical anatomical network. *Journal of Neuroscience*. 2009; 29:15684–15693. [PubMed: 20016083]
- Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America*. 2004; 101:4637–4642. [PubMed: 15070770]
- Guo CC, Kurth F, Zhou J, Mayer EA, Eickhoff SB, Kramer JH, Seeley WW. One-year test–retest reliability of intrinsic connectivity network fMRI in older adults. *Neuro Image*. 2012; 61:1471–1483. [PubMed: 22446491]
- Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O. Mapping the structural core of human cerebral cortex. *PLoS Biology*. 2008; 6:e159. [PubMed: 18597554]
- Hagmann P, Sporns O, Madan N, Cammoun L, Pienaar R, Wedeen VJ, Meuli R, Thiran JP, Grant PE. White matter maturation reshapes structural connectivity in the late developing human brain. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107:19067–19072. [PubMed: 20956328]
- Hayasaka S, Laurienti PJ. Comparison of characteristics between region-and voxel-based network analyses in resting-state fMRI data. *Neuro Image*. 2010; 50:499–508. [PubMed: 20026219]
- He Y, Chen Z, Evans A. Structural insights into aberrant topological patterns of large-scale cortical networks in Alzheimer's disease. *Journal of Neuroscience*. 2008; 28:4756–4766. [PubMed: 18448652]
- He Y, Evans A. Graph theoretical modeling of brain connectivity. *Current Opinion in Neurology*. 2010; 23:341–350. [PubMed: 20581686]
- Hedden T, Van Dijk KR, Becker JA, Mehta A, Sperling RA, Johnson KA, Buckner RL. Disruption of functional connectivity in clinically normal older adults harboring amyloid burden. *Journal of Neuroscience*. 2009; 29:12686–12694. [PubMed: 19812343]
- Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, Hagmann P. Predicting human resting-state functional connectivity from structural connectivity. *Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106:2035–2040. [PubMed: 19188601]
- Humphries MD, Gurney K. Network 'small-world-ness': a quantitative method for determining canonical network equivalence. *PLoS ONE*. 2008; 3:e0002051. [PubMed: 18446219]
- Jack CR Jr, Knopman DS, Weigand SD, Wiste HJ, Vemuri P, Lowe V, Kantarci K, Gunter JL, Senjem ML, Ivnik RJ, Roberts RO, Rocca WA, Boeve BF, Petersen RC. An operational approach to National Institute on Aging-Alzheimer's Association criteria for preclinical Alzheimer disease. *Annals of Neurology*. 2012; 71:765–775. [PubMed: 22488240]
- Johansen-Berg H, Behrens TE, Robson MD, Drobniak I, Rushworth MF, Brady JM, Smith SM, Higham DJ, Matthews PM. Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*. 2004; 101:13335–13340. [PubMed: 15340158]
- Kozauer N, Katz R. Regulatory innovation and drug development for early-stage Alzheimer's disease. *New England Journal of Medicine*. 2013; 368:1169–1171. [PubMed: 23484795]
- Lister JP, Barnes CA. Neurobiological changes in the hippocampus during normative aging. *Archives of Neurology*. 2009; 66:829–833. [PubMed: 19597084]
- Lo CY, Wang PN, Chou KH, Wang J, He Y, Lin CP. Diffusion tensor tractography reveals abnormal topological organization in structural cortical networks in Alzheimer's disease. *Journal of Neuroscience*. 2010; 30:16876–16885. [PubMed: 21159959]
- Menon V. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends in Cognitive Sciences*. 2011; 15:483–506. [PubMed: 21908230]
- Meunier D, Achard S, Morcom A, Bullmore E. Age-related changes in modular organization of human brain functional networks. *Neuro Image*. 2009; 44:715–723. [PubMed: 19027073]
- Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuro Image*. 2012; 59:2142–2154. [PubMed: 22019881]

- Qi Z, Wu X, Wang Z, Zhang N, Dong H, Yao L, Li K. Impairment and compensation coexist in amnesic MCI default mode network. *Neuro Image*. 2010; 50:48–55. [PubMed: 20006713]
- Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuro Image*. 2010; 52:1059–1069. [PubMed: 19819337]
- Shehzad Z, Kelly AM, Reiss PT, Gee DG, Gotimer K, Uddin LQ, Lee SH, Margulies DS, Roy AK, Biswal BB, Petkova E, Castellanos FX, Milham MP. The resting brain: unconstrained yet reliable. *Cerebral Cortex*. 2009; 19:2209–2229. [PubMed: 19221144]
- Song J, Desphande AS, Meier TB, Tudorascu DL, Vergun S, Nair VA, Biswal BB, Meyerand ME, Birn RM, Bellec P, Prabhakaran V. Age-related differences in test-retest reliability in resting-state brain functional connectivity. *PLoS One*. 2012; 12:e49847. [PubMed: 23227153]
- Sorg C, Riedl V, Muhlau M, Calhoun VD, Eichele T, Laer L, Drzezga A, Forstl H, Kurz A, Zimmer C, Wohlschlaeger AM. Selective changes of resting-state networks in individuals at risk for Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104:18760–18765. [PubMed: 18003904]
- Sporns O. The human connectome: a complex network. *Annals of the New York Academy of Sciences*. 2011; 1224:109–125. [PubMed: 21251014]
- Stam CJ, de Haan W, Daffertshofer A, Jones BF, Manshanden I, van Cappellen van Walsum AM, Montez T, Verbunt JP, de Munck JC, van Dijk BW, Berendse HW, Scheltens P. Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer's disease. *Brain*. 2009; 132:213–224. [PubMed: 18952674]
- Supekar K, Menon V. Developmental maturation of dynamic causal control signals in higher-order cognition: a neurocognitive network model. *PLoS Computational Biology*. 2012; 8:e1002374. [PubMed: 22319436]
- Supekar K, Menon V, Rubin D, Musen M, Greicius MD. Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. *PLoS Computational Biology*. 2008; 4:e1000100. [PubMed: 18584043]
- Supekar K, Musen M, Menon V. Development of large-scale functional brain networks in children. *PLoS Biology*. 2009; 7:e1000157. [PubMed: 19621066]
- Uddin LQ, Supekar KS, Ryali S, Menon V. Dynamic reconfiguration of structural and functional connectivity across core neurocognitive brain networks with development. *Journal of Neuroscience*. 2011; 31:18578–18589. [PubMed: 22171056]
- Vaishnavi SN, Vlassenko AG, Rundle MM, Snyder AZ, Mintun MA, Raichle ME. Regional aerobic glycolysis in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107:17757–17762. [PubMed: 20837536]
- Van Dijk KR, Hedden T, Venkataraman A, Evans KC, Lazar SW, Buckner RL. Intrinsic functional connectivity as a tool for human connectomics: theory, properties, and optimization. *Journal of Neurophysiology*. 2010; 103:297–321. [PubMed: 19889849]
- Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. *Neuro Image*. 2012; 59:431–438. [PubMed: 21810475]
- Vlassenko AG, Vaishnavi SN, Couture L, Sacco D, Shannon BJ, Mach RH, Morris JC, Raichle ME, Mintun MA. Spatial correlation between brain aerobic glycolysis and amyloid-beta (A β) deposition. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107:17763–17767. [PubMed: 20837517]
- Wang J, Wang L, Zang Y, Yang H, Tang H, Gong Q, Chen Z, Zhu C, He Y. Parcellation-dependent small-world brain functional networks: a resting-state fMRI study. *Human Brain Mapping*. 2009; 30:1511–1523. [PubMed: 18649353]
- Wang JH, Zuo XN, Gohel S, Milham MP, Biswal BB, He Y. Graph theoretical analysis of functional brain networks: test–retest evaluation on short-and long-term resting-state functional MRI data. *PLoS ONE*. 2011; 6:e21976. [PubMed: 21818285]
- Wang K, Liang M, Wang L, Tian L, Zhang X, Li K, Jiang T. Altered functional connectivity in early Alzheimer's disease: a resting-state fMRI study. *Human Brain Mapping*. 2007; 28:967–978. [PubMed: 17133390]

- Wang L, Li Y, Metzak P, He Y, Woodward TS. Age-related changes in topological patterns of large-scale brain functional networks during memory encoding and recognition. *Neuro Image*. 2010; 50:862–872. [PubMed: 20093190]
- Watts DJ, Strogatz SH. Collective dynamics of ‘small-world’ networks. *Nature*. 1998; 393:440–442. [PubMed: 9623998]
- Wig GS, Schlaggar BL, Petersen SE. Concepts and principles in the analysis of brain networks. *Annals of the New York Academy of Sciences*. 2011; 1224:126–146. [PubMed: 21486299]
- Yao Z, Zhang Y, Lin L, Zhou Y, Xu C, Jiang T. Abnormal cortical networks in mild cognitive impairment and Alzheimer’s disease. *PLoS Computational Biology*. 2010; 6:e1001006. [PubMed: 21124954]
- Zalesky A, Fornito A, Harding IH, Cocchi L, Yucel M, Pantelis C, Bullmore ET. Whole-brain anatomical networks: does the choice of nodes matter? *Neuro Image*. 2010; 50:970–983. [PubMed: 20035887]

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).

Fig. 2.

Construction of structural (left) and functional (right) connectivity networks. (1) Nodes are typically defined as voxels or brain regions with connections (edges) between nodes characterized by (2) structural data using MRI (left) or DTI (not shown), or functional data using fMRI or EEG/MEG (right). (3) These data are then used to create structural connectivity maps (left), which define connections between nodes in terms of their direct anatomical connections or correlations between regions based on cortical thickness or volume measures. Alternatively, functional connectivity maps (right) reflect temporal correlations of activity at rest, or under conditions of cognitive demand. Graph theory measures are then applied to network maps (4). A network graph is compared to a random network containing the same number of nodes and edges to ensure that the observed connections are greater than that expected by chance. Finally, network parameters are aggregated for groups to determine differences in connectivity that may underlie traits of interest (The structural and functional network images are reproduced with permission from Bullmore and Sporns (2009) and Achard et al. (2006)).

Fig. 3.

SII model. The proposed analytic strategy aims to enhance the diagnostic and prognostic potential of a network approach to neurocognitive aging. (1) Construct composite z-scores of network measures for segregation, integration, and influence (SII) for CN, MCI, and AD populations. Principal component analysis may be used to determine which network measures load onto a single factor for each SII category. (2) Plot cumulative distributions for the AD population for each SII biomarker and identify the SII scores associated with 90th–99th percentiles. Next, plot the CN and MCI distributions for SII and determine the percentile cutpoints of these populations that share the same SII scores as the AD population. This will determine the degree of overlap in SII scores across phenotypes. A hypothetical example is illustrated in (2). Here, ~90% of the AD population has a standardized score of –1.5 or less for a segregation metric whereas 58% of MCI subjects and 10% of CN subjects share that same score or more extreme values. (2a) Shows an ideal example with no overlap between CN, MCI and AD populations indicating that SII scores fully differentiate the groups. Alternatively, (2b) shows a hypothetical example where SII provides no diagnostic potential because all populations overlap substantially. (3) The next step is to determine the criterion point that optimally identifies the transition in phenotype from CN to MCI to AD. Receiver operation curves (ROC) may help to determine the cutpoints for SII that maximally differentiate these groups. Identifying the most appropriate criterion values for SII will depend upon balancing false positive and false negative rates. It may be best initially to determine SII criterion with high sensitivity for AD, assuming that prevention and treatment are possible. As illustrated in the hypothetical example of (2) above, a segregation score of –1.5 correctly identifies 90% of the AD population (sensitivity) and 58% of the non-AD population who have not converted (specificity). (4) The next step would be to determine if a priori knowledge of this segregation score accurately predicts those who develop AD versus those who do not. Longitudinal studies, where neurocognitive outcomes are known, are needed to test this possibility, for example by examining CN subjects who later transitioned to MCI or AD and determining what percentage of this population had one or more abnormal SII scores at baseline compared to

CN cases who remained intact over time. Overall, this method provides a starting point to determine whether a network approach can predict neurocognitive outcomes, which if successful can be used prospectively in the study of aging.