Neurobiology of Aging 35 (2014) 42–54

Contents lists available at ScienceDirect

Neurobiology of Aging

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

Age-related functional reorganization, structural changes, and preserved cognition☆

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ARTICLE INFO

Article history:
Received 7 January 2013
Received in revised form 11 June 2013
Accepted 5 July 2013
Available online 12 August 2013

Keywords:
Aging
Complex networks
Functional MRI
Sentence processing

ABSTRACT

Although healthy aging is associated with general cognitive decline, there is considerable variability in the extent to which cognitive functions decline or are preserved. Preserved cognitive function in the context of age-related neuroanatomical and functional changes, has been attributed to compensatory mechanisms. However, the existing sparse evidence is largely focused on functions associated with the frontal cortex, leaving open the question of how wider age-related brain changes relate to compensation. We evaluated relationships between age-related neural and functional changes in the context of preserved cognitive function by combining measures of structure, function, and cognitive performance during spoken language comprehension using a paradigm that does not involve an explicit task. We used a graph theoretical approach to derive cognitive activation-related functional magnetic resonance imaging networks. Correlating network properties with age, neuroanatomical variations, and behavioral data, we found that decreased gray matter integrity was associated with decreased connectivity within key language regions but increased overall functional connectivity. However, this network reorganization was less efficient, suggesting that engagement of a more distributed network in aging might be triggered by reduced connectivity within specialized networks.

1. Introduction

Healthy aging is typically associated with deteriorating cognitive capacities in the context of structural and functional brain changes (Craik and Salthouse, 2000; Davis et al., 2009; Pfefferbaum et al., 2000; Raz et al., 2005). However, one of the hallmarks of healthy aging is its variability, with a range of preservation and losses in structure, function, and performance across several cognitive domains. The preservation of cognitive function in some individuals and in some cognitive domains (e.g., language comprehension; Tyler et al., 2010) more than others (e.g., working memory; Salthouse, 1991) has led to the hypothesis that preserved function is underpinned by compensatory mechanisms (Cabeza et al., 2002). Because a variety of neural changes occur with aging, cognitive changes in older adults might be mediated by underlying neural changes, through processes such as dedifferentiation (Park et al., 2004) or reduced hemispheric specialization (hemispheric asymmetry reduction in older adults; Cabeza, 2002; Ghisletta and Lindenberger, 2003). These findings support the "scaffolding theory of aging and cognition"; which claims that as neural structures decline over time because of natural aging, other structures from proximal or distal brain regions are recruited to preserve function.

However, evidence for compensation requires the integration of structural, functional, and behavioral data, a combination that is rarely obtained. Moreover, studies of compensation tend to focus primarily on age-related neural changes in the prefrontal cortex, in the context of age-related performance changes in cognitive domains that usually decline with age (e.g., memory, executive function). These studies reveal increased bilateral activation (Cabeza, 2002), and increased functional connectivity (Davis et al., 2012; Yang et al., 2009) in frontal cortex with age when performance is preserved. This focus on the frontal cortex, although generating important insights, involves studies that require participants to carry out an explicit task and thus might confound age-related changes to a specific cognitive domain and to those involved in more general task-related processes. In the present study we aimed to avoid this potential problem by minimizing the influence of task-related effects by using a paradigm that does not involve an overt task.

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http://dx.doi.org/10.1016/j.neurobiolaging.2013.07.003

We investigated a cognitive function that tends to be preserved across the adult life span—language comprehension (Burke and Shafto, 2008; Tyler et al., 2010). Language function involves a set of bilateral neural regions including bilateral inferior frontal gyrus (IFG), superior (STG) and middle temporal gyri (MTG), angular gyrus, supramarginal gyrus, and inferior parietal lobule (Indefrey and Cutler, 2004; Price, 2012). Within this extensive system, different aspects of language processing recruit different subnetworks, with syntactic processing depending on intact left MTG (LMTG) and left IFG (LIFG) and connectivity between them (Griffiths et al., 2013; Tyler et al., 2011). In our study we focused on syntactic processing because it has the advantage of being strongly left lateralized in the young, providing the ideal basis for determining whether age-related preservation of function necessarily involves increased bilateral activity and/or connectivity.

Our main research interest was in the relationship between gray matter changes, the functional network known to be essential for preserved syntax and the wider language system. Specifically, we asked whether preservation of syntax was underpinned by changes in the neural network with which it is associated (the left frontotemporal network) and its relationship to the wider bilateral language system. In investigating the influence of aging on hemispheric reorganization, we tested age-related hypotheses concerning the mechanisms involved, such as the dedifferentiation (Park et al., 2004), hemispheric asymmetry reduction in older adults (HAROLD; Cabeza, 2002), and scaffolding models (Park and Reuter-Lorenz, 2009).

Most studies of compensatory neural mechanisms in aging use region-specific analyses which bias toward describing local but not age-related global changes; consequently, they largely ignore the wider neural changes that take place in aging, except insofar as they are related to frontal function (Davis et al., 2008). Here we circumvent these limitations in a study that uses graph theoretic analyses to investigate the relationship between age-related changes in connectivity at local and more global levels.

Graph theoretic analysis enables the characterization of functional network properties in a unique manner not offered by other connectivity approaches. Previous attempts to characterize functional networks have mainly been carried out on resting-state functional magnetic resonance imaging (fMRI) (Ferreira and Busatto, 2013) using a variety of approaches such as machine learning (Meier et al., 2012) and seed-based functional connectivity analyses (Tomasi and Volkow, 2012). Resting-state networks have also been investigated using graph theory (Buckner et al., 2009; Bullmore and Sporns, 2009; He and Evans, 2010), but this approach has only occasionally been used with task fMRI studies (Bassett et al., 2011; Eguiluz et al., 2005; Ginestet and Simmons, 2011; Shinkareva et al., 2008). This trend is reflected in the investigation of age-related functional changes, in which most studies using graph theoretical approaches have focused on resting-state (Achard and Bullmore, 2007; Meunier et al., 2009; Wang et al., 2010) and one study examined task-related fMRI (working memory; Wang et al., 2012).

Graph theoretic analysis allows the detailed characterization of networks by examining the structural properties of graphs, where a graph is defined as a set of interactions (‘connections,’ or ‘edges’) between large numbers of areas or ‘nodes’ (Newman, 2003). Graph analysis provides the ideal means for studying changes in global connectivity and within local networks, and establishing relationships between neural changes and cognitive functions. Here we focus on average snapshots of brain connectivity and differences between those connectivity patterns when comparing younger with older adults responding to spoken sentences rather than the temporal evolution of connectivity in younger and older brains. We obtained functional networks using the weighted correlations method (Dodel et al., 2005), which permits quantification of network properties at the single participant level. We used a functional connectivity index (FCI) to relate network properties with age, local and global gray matter density (GMD), and behavioral performance acquired outside the scanner.

Current hypotheses regarding age-related functional reorganization in language processing in the context of network analyses and preserved language processing performance suggest the following outcomes: (1) according to the dedifferentiation hypothesis (Ghisletta and Lindenberger, 2003), functional connectivity is expected to increase in the overall language system with aging, leading to less specialized networks for older subjects; (2) in the HAROLD model (Cabeza, 2002), it is assumed that there is reduced hemispheric specialization in aging, and thus that there will be reduced connectivity between left frontotemporal regions for language processing for the older compared with the younger group; and (3) the “scaffolding theory of aging and cognition” model, in which an increase in bilateral functional connectivity for language processing in the older compared with the young group is predicted, and is associated with changes in neural structure (Park and Reuter-Lorenz, 2009). As far as structural reorganization is concerned, it is well known that GMD decreases with age (Sowell et al., 2003), and these decreases might be associated with modulation of functional connectivity, in particular between the LIFG and LMTG (Tyler et al., 2010).

2. Methods

2.1. Participants

Forty-three healthy adult volunteers (25 female), with an age range of 19 to 75 years (mean, 43.6 years; SD, 20.3 years) gave written consent to participate in the experiment. At the time of testing, 15 volunteers were between 18 and 30 years old, 12 volunteers were between 45 and 60 years old and 16 volunteers were between 60 and 75 years old (see Table 1). The study was approved by the East of England - Essex (formerly Suffolk) Research Ethics Committee. All were right-handed native British English speakers with no history of neurological illness or head injury and were free of psychiatric illness or psychoactive medication for at least one year before scanning. No participant had audiometer measurements indicating severe hearing impairment and 42 out of 43 participants scored 28 or higher on the Mini Mental State Examination and 30/36 or higher on the Ravens progressive matrices (Raven, 1995). One participant (aged 75, the oldest participant in our sample) scored 27 on the Mini Mental State Examination. Participant demographic characteristics are shown in Table 1.

2.2. Experimental paradigm

We avoided task-related effects by asking participants to listen to spoken sentences without carrying out an explicit task (see Tyler et al., 2011 for a description of the paradigm and stimuli). The sentences, all of which were fully grammatically correct and meaningful, contained a phrase which was either unambiguous (e.g., “The teacher knew that rehearsing plays is necessary for a good

Table 1
Ages and background behavioral test scores of participants

Age range (mean, SD), y	*n*	MMSE mean score, SD	NART mean score, SD	Shipley vocabulary mean score, SD
18–30 (21.01, 1.56)	15	29.57, 0.65	34.67, 4.39	32.20, 2.98
45–60 (51.69, 4.75)	12	29.08, 0.90	39.50, 4.10	36.92, 2.50
60–75 (66.88, 4.41)	16	28.81, 0.83	41.13, 5.43	37.69, 2.30

Key: MMSE, Mini Mental State Examination; NART, National Adult Reading Test.