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# Reduced functional segregation between the default mode network and the executive control network in healthy older adults: A longitudinal study

Kwun Kei Ng [a], June C. Lo [a], Joseph K.W. Lim [a], Michael W.L. Chee [a], Juan Zhou [a,b,*]

[a] Center for Cognitive Neuroscience, Neuroscience and Behavioral Disorders Program, Duke-NUS Medical School, Singapore
[b] Clinical Imaging Research Centre, the Agency for Science, Technology and Research and National University of Singapore, Singapore

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ABSTRACT

The effects of age on functional connectivity (FC) of intrinsic connectivity networks (ICNs) have largely been derived from cross-sectional studies. Far less is known about longitudinal changes in FC and how they relate to ageing-related cognitive decline. We evaluated intra- and inter-network FC in 78 healthy older adults two or three times over a period of 4 years. Using linear mixed modeling we found progressive loss of functional specialization with ageing, evidenced by a decline in intra-network FC within the executive control (ECN) and default mode networks (DMN). In contrast, longitudinal inter-network FC between ECN and DMN showed a u-shaped trajectory whereby functional segregation between these two networks initially increased over time and later decreased as participants aged. The rate of loss in functional segregation between ECN and DMN was associated with ageing-related decline in processing speed. The observed longitudinal FC changes and their associations with processing speed remained after correcting for longitudinal reduction in gray matter volume. These findings help connect ageing-related changes in FC with ageing-related decline in cognitive performance and underscore the value of collecting concurrent longitudinal imaging and behavioral data.



## Introduction

Neuroimaging has proven informative about the structural and functional changes in the ageing brain and how these relate to accompanying cognitive changes (Grady, 2012). Degradation of processing speed, perception, memory, and executive function (Cabeza et al., 2005; Craik and Salthouse, 2008; Lindenberger and Baltes, 1994; Park and Reuter-Lorenz, 2009) erode the benefits of increased longevity and motivate the search for the underlying mechanisms of these functional losses. Task-free fMRI provides information about the integrity of several highly reproducible intrinsic connectivity networks (ICNs) and is well suited for characterizing age and ageing related changes in brain function, as it requires minimal participant input.

Of the multiple ICNs that exist, three are particularly relevant to the study of loss of cognitive function in older adults because their age-related changes and associated cognitive alterations have been replicated in multiple studies (Damoiseaux et al., 2008; Fjell et al., 2015a, 2015b; Shaw et al., 2015). The three ICNS are: the default mode network (DMN), the executive control network (ECN), and the salience network (SN) (Menon, 2011; Voss et al., 2013). The DMN is associated with internally oriented mentation and autobiographical memory (Buckner et al., 2008), while the ECN is associated with demanding externally oriented processes that have a high cognitive load or require cognitive control (Seeley et al., 2007; Turner and Spreng, 2015). The SN serves as the 'dynamic switch', biasing activation of one or the other network when a salient external event is detected (Menon and Uddin, 2010; Seeley et al., 2007). The integrity of these three networks and their interactions appear fundamental to higher-level cognition and are therefore relevant to our understanding of the ageing brain (Greicius and Kimmel, 2012).

Indicative of their functional specialization, each ICN typically demonstrates high intra-network functional connectivity (Honey et al., 2010; Sporns, 2013; Zhang and Raichle, 2010). High signal coherence within a network renders its sub-components more functionally coupled, possibly resulting in greater distinctiveness of functional specialization (Dennis and Thompson, 2014; Sternberg, 2011; Wig et al., 2011). Cross-sectional studies of older adults have highlighted the loss of functional specialization evidenced by decreased intra-network FC in the ECN (Allen et al., 2011; Geerligs et al., 2015) or DMN (Andrews-Hanna et al., 2007; Ferreira and Busatto, 2013; Sambataro et al., 2010). Loss of DMN and/or ECN connectivity has been associated with poorer executive function, memory, and processing speed (Andrews-Hanna et al., 2007; Mevel et al., 2013). Less commonly,

* Corresponding author at: Center for Cognitive Neuroscience, Neuroscience and Behavioral Disorders Program, Duke-National University of Singapore Medical School, 8 College Road, #06-15, Singapore 169857. Fax: +65 62218685.
*E-mail address:* helen.zhou@duke-nus.edu.sg (J. Zhou).

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intra-network FC can also increase with age, for example within the SN (Voss et al., 2013), where increased connectivity has been linked to superior emotional regulation in old adults (Mather, 2012; Sze et al., 2012).

Complementing changes in intra-network connectivity are those involving inter-network FC, which denote functional segregation between ICNs, for example, between task-positive ICNs (ECN and SN) and task-negative ICN (DMN). The negative correlation of spontaneous oscillations (labeled as 'anti-correlation' in seminal studies) between these networks suggests that they normally have opposing functional roles, such that when one network is engaged, the other has to be suppressed (Chen et al., 2013; Fox et al., 2005; see Fig. 6 in Yeo et al., 2015 for an illustration).

Specifically negatively correlated fluctuations in BOLD signal between 'segregated' networks are thought to mediate transitions between internal and externally oriented cognition (Uddin et al., 2009). Reduced segregation between DMN and task-positive networks is characteristic of reduced functioning in many psychiatric conditions (Mattfeld et al., 2014; Whitfield-Gabrieli and Ford, 2012) as well as states associated with reduced cognitive performance like sleep-deprivation (De Havas et al., 2012; Yeo et al., 2015).

Age-related alteration in between-ICN connectivity manifests in the form of either reduced negative correlation or increased positive correlation among various ICNs (Biswal et al., 2010; Ferreira et al., 2015). A higher degree of network segregation at rest may be associated with better episodic (Chan et al., 2014) and working memory (Keller et al., 2015). During task performance, increased coupling (reduced negative correlation) between the DMN and task-positive ICNs was also associated with poorer cognitive performance (Spreng and Schacter, 2011).

While cross-sectional studies are pertinent to the construction of new hypotheses, longitudinal studies are equally or maybe even more important because it may not be appropriate to extrapolate cross-sectional findings to predict the effects of ageing (Kraemer et al., 2000; Mungas et al., 2010; Salthouse, 2009). Longitudinal studies are necessary to demonstrate with-subject ageing trajectories and the possible interactions between ageing with other factors (Li et al., 2014; Raz and Lindenberger, 2011; Voss et al., 2010). Relative to the wealth of cross-sectional data amassed to date, there is relatively little longitudinal data on changes in FC with ageing (Bernard et al., 2015). For instance, Bernard et al. (2015) reported greater decline in the functional connectivity of the posterior cingulate cortex and the DMN in memory decliners; Fjell et al. (2015a) found that recall change was related to change in functional connectivity over time and such positive relationship differed between young and older adults.

Here, we examined the longitudinal intra- and inter-network FC changes in a cohort of relatively healthy older adults. We focused on task-free FC within and between three ICNs (DMN, ECN, and SN) and their relationships with cognitive performance across five domains. We expected intra-network FC in the three ICNs, i.e. functional specialization, to decrease as participants age (Ferreira and Busatto, 2013; Onoda et al., 2012), although that in the SN may increase or remain unchanged given previous mixing results (Geerligs et al., 2015; Voss et al., 2013). Secondly, we anticipated reduced segregation of inter-network FC between task-positive networks (ECN and SN) and default mode network with ageing, commensurate with expectations of reduced regulation (Menon and Uddin, 2010) and functional segregation (Chan et al., 2014; Geerligs et al., 2015) of brain networks. Lastly, we sought to determine whether the rate of change in intra- and inter-network FC would be associated with longitudinal cognitive decline.

## Methods

### Participants

We studied 78 relatively healthy Chinese older adults (38 females; 4 left-handed; mean age = 68.03 years, SD = 5.73 years at the baseline; mean education = 12.48 years, SD = 3.15 years) from the Singapore-Longitudinal Ageing Brain Study (S-LABS) (Chee et al., 2009). Participants who met study criteria underwent brain imaging at approximately 2-year intervals between 2009 and 2014. Eligible participants had to have participated in at least two time points of the longitudinal study and to have completed both neuropsychological assessment and brain imaging (with satisfactory data quality[1]). Second, they had a Mini-Mental State Examination (MMSE) (Folstein et al., 1975) score of 26 or greater (mean = 28.15, SD = 1.40) and a modified-Geriatric Depression Screening Scale (GDS) (Yesavage and Sheikh, 1986) score of less than 9 (mean = 0.98, SD = 1.10) at the baseline. Third, they did not have any of the following at any time point: (1) a history of significant vascular events (i.e., myocardial infarction, stroke, or peripheral vascular disease); (2) a history of malignant neoplasia of any form; (3) a history of cardiac, lung, liver, or kidney failure; (4) active or inadequately treated thyroid disease; (5) active neurological or psychiatric conditions; or (6) a history of head trauma with loss of consciousness. The study was approved by the Institutional Review Board of the National University of Singapore. All participants provided written informed consent prior to participation.

### Neuropsychological assessments

Within 3 months of undergoing magnetic resonance imaging (MRI), all participants underwent neuropsychological assessment by trained researchers (Chee et al., 2009; Lo et al., 2014). Five cognitive domains were evaluated: processing speed, attention, verbal memory, visuospatial memory, and executive functioning. Processing speed was assessed with the Symbol Digit Modalities Test (Smith, 1991), the Symbol Search Task in the Wechsler Memory Scale-Third Edition (WMS-III) (Wechsler, 1997), and the Trail Making Test A (Reitan and Wolfson, 1985). Attention was assessed with the Digit Span Test and the Spatial Span Test in WMS-III. Verbal memory was assessed with the Rey Auditory Verbal Learning Test (Lezak et al., 2004). Visuospatial memory was assessed with a Visual Paired Associates Test. Executive functioning was assessed with the Categorical Verbal Fluency Test (Lezak et al., 2004), the Design Fluency Test in the Delis-Kaplan Executive Function System (Delis Kaplan et al., 2001), and the Trail Making Test B (Reitan and Wolfson, 1985). The scores of each test at each time point were standardized to *T* scores (mean = 50, SD = 10) with respect to the baseline. For domains evaluated with multiple tests, the domain-average composite scores per participant per time point were computed by taking the mean of the summated *T* scores from the relevant tests.

### Image acquisition

MRI scans were conducted on a 3 T Siemens Magnetom Tim Trio System (Siemens, Erlangen, Germany). All participants performed an 8-min task-free fMRI scan when they fixated on a cross at the center of a projector screen (36 continuous axial slices, TR/TE = 2000/30 ms, flip angle = 90°, FOV = 192 × 192, matrix size = 64 × 64, isotropic voxel size = 3.0 × 3.0 × 3.0 $mm^3$, bandwidth = 2112 Hz/pixel). High-resolution T1-weighted structural MRI was acquired using magnetization-prepared rapid gradient echo sequence (MPRAGE; 192 continuous sagittal slices, TR/TE/TI = 2300/2.98/900 ms, flip angle = 9°, FOV = 256 × 240 $mm^2$, matrix = 256 × 240, isotropic voxel size = 1.0 × 1.0 × 1.0 $mm^3$, bandwidth = 240 Hz/pixel).

### Image processing

Both functional and structural images were preprocessed using a standard pipeline (Susanto et al., 2015; Zhou et al., 2012) based on FSL (Jenkinson et al., 2012) and AFNI (Cox, 1996). For the structural

[1] Thirty-eight participants provided data from all three phases, 37 provided data from two consecutive phases, and 3 provided data from the first and third phases.