Whole brain structure-function analysis predicts impacts of aging in cognitive functions

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Human brain function emerges from complex mechanisms involving multiple sensory modalities. Aging entails processes that are primarily responsible for Cognitive and Motor decline. Such brain wide changes result from loss of gray (GM) and white matter (WM) integrity, neurovascular and functional connectivity alterations. Regarding connectivity, reduced resting-state fMRI connectivity between anterior and posterior nodes of the Default Mode Network (DMN) relates to cognitive function and has been postulated to be a hallmark of ageing. However, the relationship between age-related connectivity changes and other neuroimaging-based measures in ageing is fragmentarily investigated. We employed resting state functional MRI in 50 individual participants (ranging from age 19-82 years) and graph theoretical, multivariate statistical techniques to systematically chart whole brain structure-function topological organizations across life spans. Here, we report a snapshot of our results demonstrating SC-FC relationship breakdown in aging over brain modules mainly located in the hub areas (e.g. DMN, dorsal attention network (DAN)). DMN connectivity decreases in ageing and an association between anterior-posterior DMN connectivity. These results resembled patterns of age-related SC-FC changes which was studied by comparing the Pearson's rank correlation in the blood-oxygenation-level-dependent (BOLD) temporal fluctuations recorded from anterior-posterior DMN with age-effect maps (structural and functional increase, decrease). Further quantitative analysis with Partial least square (PLS) methods revealed that modularity linearly decreases (cingulate cortex, parietal cortex, occipital cortex) and moreover there is a systematic reorganization within, distant module pairwise correlations suggesting age dependent variability of functional brain networks. These results may have important implications for structural and functional brain networks involved in cognition that links development, aging related decline, and vulnerability to disease.

Introduction

As demographic changes in developing countries like India push up the proportion of elderly adults in the population, age-related cognitive decline is emerging as a major concern. Cognitive domains affected by age include speed of processing, working memory capacity, inhibitory function and long-term episodic memory (Park and Reuter-Lorenz (2009); Vidal-Piñeiro D et al. (2014)). Lateral and medial temporal lobes and posterior midline structures are also significantly affected by age-related atrophy (Fjell et al. (2014)). Most structures show a linear decline, though specific structures such as the hippocampus may exhibit an increased rate of atrophy with ageing (Fjell et al., 2013).

These changes are believed to impair the efficiency of communication between neural regions and to contribute to the functional decline in elders (Bartozokis et al. (2004)). Diffusion Tensor Imaging (DTI) techniques are sensitive to the degree and direction of water molecule permeability and are able to characterize microstructural properties of WM *in vivo*. Increased Fractional Anisotropy (FA) and reduced Mean Diffusivity (MD) are the most frequently used

DTI measures associated with WM integrity, as they are able to provide summarized information on the state of WM.

More recently, though, brain connectivity at rest has consistently been found to be altered in ageing using the fMRI technique (rs-fMRI; Ferreira and Busatto, 2013). rs-fMRI is able to detect interregional correlations in low-frequency spontaneous BOLD fluctuations (Biswal et al., 1995). A significant finding in rs-fMRI ageing literature is the observation of decreased long-range functional connectivity in elders (Meunier et al., 2009; Tomasi and Volkow, 2012) usually complemented by increased local clustering. Age-related decreases in rs-fMRI mainly affect the Default Mode Network (DMN); a resting state network (RSN) that comprises several structures including posterior midline structures (precuneus/posterior cingulate cortex [PCU/PCC]), medial prefrontal cortex (mPFC), inferior parietal lobule (IPL), and middle and medial (entorhinal/hippocampus) temporal cortex (Vidal-Piñeiro D et al. (2014)).

The main objective of this study was to assess the relationship between mPFC-PCU DMN connectivity across subjects using multivariate analysis with varied age (young and elderly cohorts). The specific hypotheses tested were: (1) mPFC-PCU connectivity will be reduced in ageing; (2) regions correlating with mPFC-PCU coupling strength will be located in areas of high age-related vulnerability.

Materials and methods

Acquisition of fMRI, DTI/DSI in Human subjects under eyes open resting state conditions

The study protocol was reviewed and approved by the Charité University Medicine, Berlin, Germany. After obtaining written informed consent in accordance with institutional guidelines, 49 resting state simultaneous EEG–fMRI data sets acquired at Berlin Center for Advanced Imaging, Charité University Medicine, Berlin, Germany (age ranged from 18 to 80 years, mean 41.55 ± 18.44; 30 females and 19 males) and one simultaneous EEG–fMRI data set under task conditions acquired at Baycrest Centre, Toronto, Canada (54 year old female). Further details about data acquisition, preprocessing steps and reconstruction of the data followed (Schriner et al. (2015)). Following diffusion spectrum and T1-weighted MRI acquisitions, the segmented gray matter was partitioned into 68 anatomical regions according to anatomical landmarks using Freesurfer (surfer.nmr.mgh.harvard.edu) and as described in (Schriner et al. (2015)). White matter tractography was performed with a custom streamline algorithm and finally, fiber connectivity was aggregated across all voxels within each of the 998 predefined ROIs (pipeline is fully automated and currently available from github (https://github.com/BrainModes/TVB-empirical-data-pipeline). For more details please see (Schriner et al. (2015)).

Correlation analyses of BOLD regional time series

Pearson's linear correlation coefficients were calculated for BOLD hemodynamic time series signals extracted from each ROI (high resolution 998 or low resolution 68 nodes), and functional correlation is obtained for each pair of ROI's. Normality of the data was ensured by the Anderson-Darling test. Finally data from all subjects (all ages) are collated over individual modules defined as Temporal, Cingulate, Frontal, Parietal and Insula covering all the 68 brain

nodes used for analysis. This to test out the SC-FC relationship change across age over individual modules as accessed via correlation analysis.

Multivariate analysis of BOLD time series

The term partial least squares refers to the computation of the optimal least-squares fit to part of a correlation or covariance. PLS is similar to principal components analysis (PCA), but one important feature of PLS is that the solutions are constrained to the part of the covariance structure that is attributable to experimental manipulations or that relates to behavior. Moreover, PLS is ideal for data sets where the dependent measures within a block are highly correlated (e.g., neuroimaging data) because items within a block are not adjusted for these correlations (c.f., canonical correlation) (McIntosh et al. 2004). First we compute Pearson's rank correlation matrix between regionwise obtained BOLD time series. Subsequently, PLS measure is applied on the generated correlation matrix. Given there are 68 anatomical regions we obtain a least square fit for all 68×68 correlation matrix and construct the confidence interval across aging parameters.

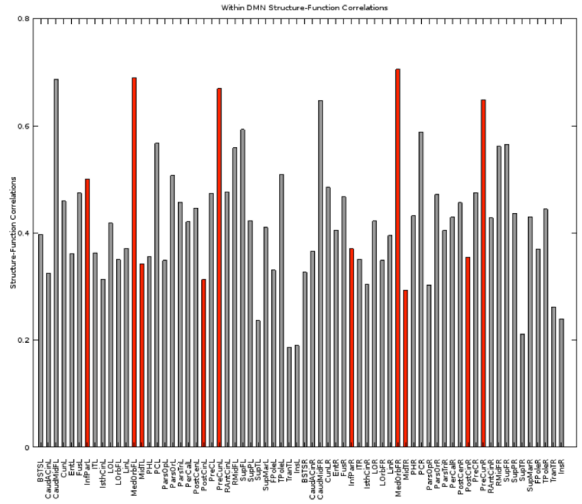
Results

Using correlation analysis pairwise (node pairs) we try to first estimate the whole network structure-function relationship for all 50 subjects (various age groups). In **Fig. 1A**, we look at the coupling strength between DMN nodes; as it seems to be supported by the cingulum bundle integrity in ageing which connects posterior to anterior and temporal DMN areas (Vidal-Piñeiro D et al. (2014)). More specifically we look at the connectivity between DMN node mPFC and posterior midline structures which are the key nodes of the DMN as shown in red bar plot **Fig. 1A**. We find that within DMN structure-function correlation is stronger however structure-function correlation with other nodes decreases. Next, we plot function correlation values as a function of the age of the participants (18-82 years) in **Fig. 1B**. Result indicates function decrease is strongest in elderly participants (age=50 and above) and over specific brain areas.

Conclusions

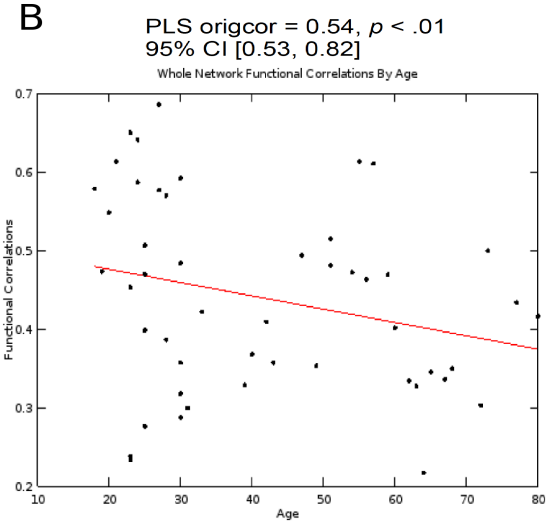
Our results on structure-function relationship modulation with aging and over multiple brain areas are in fact in line with many previous findings in aging studies where accelerated decreases occurs during senescence (Vidal-Piñeiro D et al. (2014)). In our study, we find strongest structure and function change is observed over cingulate, occipital, parietal cortex in both hemispheres (not shown). Structure-function correlations within DMN nodes (ACC, rpCUN, mPFC, MTL) are stronger. In addition, we find that the whole brain network structure-function relationship is modulated by age (partially shown). Studying the relationship of DMN with other neuroimaging modalities may help to unify disparate findings of the neuroimaging literature and provide a more comprehensive description of altered connectivity in aging. So far, despite almost unequivocal evidence that DMN connectivity is highly vulnerable to the effects of aging, our understanding of the causes and consequences of decreased antero-posterior DMN connectivity remains limited. We plan to investigate this systematically in our future study to gain insight whether structural architecture supports functional modularity in a different way in the aging brain.

A



Abbreviation	Brain region
BSTS	Bank of the superior temporal sulcus
CAC	Caudal anterior cingulate cortex
CMF	Caudal middle frontal cortex
CUN	Cuneus
ENT	Entorhinal cortex
FP	Frontal pole
FUS	Fusiform gyrus
IP	Inferior parietal cortex
ISTC	Isthmus of the cingulate cortex
IT	Inferior temporal cortex
LING	Lingual gyrus
LOCC	Lateral occipital cortex
LOF	Lateral orbitofrontal cortex
MOF	Medial orbitofrontal cortex
MT	Middle temporal cortex
PARC	Paracentral lobule
PARH	Parahippocampal cortex
PC	Posterior cingulate cortex
PCAL	Pericalcarine cortex
PCUN	Precuneus
POPE	Pars opercularis
PORB	Pars orbitalis
PREC	Precentralgyrus
PSTC	Postcentralgyrus
PTRI	Pars triangularis
RAC	Rostral anterior cingulate cortex
RMF	Rostral middle frontal cortex
SF	Superior frontal cortex
SMAR	Supramarginalgyrus
SP	Superior parietal cortex
ST	Superior temporal cortex
TP	Temporal pole
TT	Transverse temporal cortex.

B



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