NeuroImage 100 (2014) 558–563

Contents lists available at ScienceDirect

NeuroImage

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

Structural brain complexity and cognitive decline in late life — A longitudinal study in the Aberdeen 1936 Birth Cohort

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ARTICLE INFO

Article history:
Accepted 23 June 2014
Available online 30 June 2014

Keywords:
Cortical complexity
Fractal dimension
White matter
Cognition
Aging
Brain magnetic resonance imaging

ABSTRACT

Brain morphology and cognitive ability change with age. Gray and white matter volumes decrease markedly by the 7th decade of life when cognitive decreases first become readily detectable. As a consequence, the shape complexity of the cortical mantle may also change. The purposes of this study are to examine changes over a five year period in brain structural complexity in late life, and to investigate cognitive correlates of any changes.

Brain magnetic resonance images at 1.5 Tesla were acquired from the Aberdeen 1936 Birth Cohort at about ages 68 years (243 participants) and 73 years (148 participants returned). Measures of brain complexity were extracted using Fractal Dimension (FD) and calculated using the box-counting method. White matter complexity, brain volumes and cognitive performance were measured at both 68 and 73 years. Childhood ability was measured at age 11 using the Moray House Test.

FD and brain volume decrease significantly from age 68 to 73 years. Using a multilevel linear modeling approach, we conclude that individual decreases in late life white matter complexity are not associated with differences in executive function but are linked to information processing speed, auditory–verbal learning, and reasoning in specific models—with adjustment for childhood mental ability. A significant association was found after adjustment for age, brain volume and childhood mental ability.

Complexity of white matter is associated with higher fluid cognitive ability and, in a longitudinal study, predicts retention of cognitive ability within late life.

Introduction

Age-related cognitive decline is a poorly understood and increasing public health problem. Successful cognitive aging is associated with higher cortical volumes (Harrison et al., 2012; Staff, 2012) and greater retention of brain volumes in late life (Staff et al., 2006). Over the life course, gray matter (GM) volume reaches a maximum in the first decade of life, followed by a gradual decline, which accelerates later in life such that 13% is lost by the eighth decade (Courchesne et al., 2000); while white matter (WM) volume increases until late adulthood before it declines. Between ages 63 and 75, brain anatomy is characterized by shrinkage due to approximate equal loss of GM and WM but with a non-homogeneous pattern of atrophy (Lemaitre et al., 2005).

Volumetric measurements provide important information about the relative anatomy of cortical regions, but can explain only a small proportion of cognitive variance and do not represent fine structural changes in shape and integrity that accompany age-related changes in volume. Cortical sulcal anatomy is highly variable across different ages and between individuals (Kochunov et al., 2005). Cortical structural variability is partly captured by brain complexity using Fractal Dimension (FD), which measures the complexity of cortical folding described by gyri and thus characterizes the architectural pattern of cortex (Bullmore et al., 1994; Free et al., 1996). FD is a single numerical value representing brain morphological complexity, allowing inter- and intra-individual comparisons. In general, higher FD values represent greater complexity of cortical surface. FD has been compared between children and adolescents and also between young and old adults (Blanton et al., 2001; Zhang et al., 2007) using cross-sectional observations. These studies found higher cortical complexity in adolescents and less complexity in adulthood (Farahibozorg et al., 2014) with the lowest values of FD for people in the eighth and ninth decades. FD has also been investigated in schizophrenia (Narr et al., 2004; Sandu et al., 2008b; Yotter et al., 2011), manic depression (Bullmore et al., 1994), obsessive–compulsive disorder (Ha et al., 2005), Alzheimer's disease (King et al., 2010), intellectual disability (Sandu et al., 2014), epilepsy (Free et al., 1996), Williams syndrome (Thompson et al., 2005) and dyslexia (Sandu

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http://dx.doi.org/10.1016/j.neuroimage.2014.06.054
1053-8119/

et al., 2008a). Cortical complexity measured by FD is also positively correlated with the number of years of education and the intelligence quotient (Im et al., 2006). Brain complexity has also provided an insight into variation of cognitive performance throughout the human life span (Mustafa et al., 2012). FD thus provides information that is complementary to volumetric measurements of the brain and correlates with aging, cognitive ability and presence of neurological disorders.

Ontogenetic mechanisms of cortical self-organization strongly influence the complex shape of the cerebral hemispheres with mechanical tension along axons being currently thought to be the main factor for generation of cortical sulci and gyri (Hilgetag and Barbas, 2005; Van Essen, 1997). Mota and Herculano-Houzel (2012) have suggested that folding increases with connectivity through the WM and for the same number of neurons higher connectivity through the WM becomes responsible for a higher degree of folding. If confirmed, this implies that different degrees of folding exist for the same neuronal volume and suggest that folding complexity is likely to be an independent measure with functional significance.

The literature provides a logical mechanism for the formation of structural complexity (Hilgetag and Barbas, 2005; Mota and Herculano-Houzel, 2012; Van Essen, 1997) and has described cross-sectional observations that indicate its variation across the life span (Blanton et al., 2001; Esteban et al., 2010; Farahibozorg et al., 2014; Zhang et al., 2007). There is some limited cross-sectional evidence that complexity is associated with cognitive performance (Im et al., 2006; Mustafa et al., 2012). What is unclear is how, during non-pathological cognitive development and aging, inter- and intra-individual changes of cortical complexity are related to cognitive change. Our particular interest is to investigate whether changes in brain complexity reflect performance on different cognitive tasks. More broadly, we are concerned with examining if complexity can be used as a more subtle estimate of structural 'brain aging', in addition to or as an alternative to volumetric loss.

We hypothesize that individual differences in WM complexity are associated with differences in cognitive ability in a group of well characterized older adults who were imaged and completed a range of cognitive tests on two occasions at age about 68 and about 73 years. We used cross sectional and longitudinal modeling methods to test the association between change in cognition in late life and WM complexity, after adjustment for age, brain volume and childhood mental ability, that may potentially confound these hypothesized relationships.

Methods

Participants

T1 volumetric MR data were acquired from a well-characterized cohort of 243 individuals born in Aberdeen in 1936, known as the Aberdeen Birth Cohort of 1936 (ABC36) when aged around 68 years. We invited those previously recruited who were living independently in the community, were without dementia and gave informed consent to further study. 148 agreed and were imaged for a second time using an identical sequence and scanner, aged around 73 years (Whalley et al., 2011).

Cognitive tests

All participants took Raven's Standard Progressive Matrices (RPM) measuring nonverbal reasoning (Raven et al., 1977); the Digit Symbol Score (DS) evaluating the speed of information processing attention and visual short-term memory (Wechsler, 1997); Auditory Verbal Learning Test (AVLT) assessing short-term and longer-term memory and learning (Rey, 1964); Block Design (BLK) which test visuospatial skills (Wechsler, 1997); and Uses of Common Objects (UFO), a measure of executive function or purposive action (Guilford et al., 1978). The tests were applied at age 68 and repeated at age 73 by an experienced research psychologist. Data on childhood ability measured using the Moray House Test (MHT) at age 11, was archived by Scottish Council for Research in Education. The University of Aberdeen was granted access to these data.

Image acquisition

All brain MRI data at age 68 and 73 years were acquired on a 1.5 Tesla GE NVi system. Three dimensional (3D) images of the brain were acquired with a T1 SPGR (T1W) MR sequence with the following parameters; 20 ms repetition time (TR), 6 ms echo time (TE), 35° flip angle (α), number of slices 100 to 124, effective slice thickness 1.6 mm and matrix 256 × 256 with in-plane resolution 1 mm × 1 mm.

Image processing

MRI data pre-processing was completed using the free software FreeSurfer (FS) (http://surfer.nmr.mgh.harvard.edu/) that provides a set of semi-automated tools for creating computerized models of the brain from MR imaging data and measuring the brain's morphometric properties (Fischl et al., 2002). The pre-processing steps include motion correction, affine transformation to Talairach image space, non-uniform intensity normalization for intensity inhomogeneity correction and removal of non-brain tissues. The second step involves cortical parcellation of the GM and WM surface, topology correction and surface based warping to align anatomically homologous points. The segmentation is based on the voxel's location in the volume, the neighboring voxels' tissue classes, and the intensity value in each voxel. It has been shown that this automatic labeling procedure is comparable in accuracy to manual labeling (Fischl et al., 2002). After processing was completed, the left and right cerebral white matters were extracted from the subcortical structure to form a whole white matter mask ($256 \times 256 \times 256$ mm^3). The mask was not altered in any way (e.g. manual trimming). Segmented images with separated GM and WM are used for the calculation of white matter volume and whole brain volume (GM + WM).

Calculation of the fractal dimension

In order to characterize, in the second step of the analysis, the geometric complexity of WM, the WM obtained from the segmented images of the whole cerebrum served as a basis for the estimation of the fractal dimension. For the calculation of fractal dimension, the box-counting method is widely used and simple to apply. In the box-counting method, the object to be analyzed is covered with 3D boxes. The white matter structure is covered with boxes, which are arranged in a regular lattice and the boxes containing white matter are counted. The process is illustrated in Fig. 1 by a mid-coronal slice from one participant. WM volume is covered with boxes of increasing size. For illustration purposes, the linear size of the box is varied from 1 voxel, corresponding in our case to 1 cubic mm, to 6 voxels. Note that the slice is extracted after the construction of the boxes on the three dimensional volume.

The number of boxes (N) of a given length needed to cover the whole structure varies with the linear size (r) of the box as $N \sim r^{-D}$, where D is the fractal dimension given by the slope in a double logarithmic plot of number of boxes versus box size. For irregular structures, D is a non-integer number. This refers to the fine structure of the fractals: by decreasing the size of the ruler one covers more detail, thus the number of boxes varies in a different way than in smooth objects. In the case of the brain this property holds for a limited range of scales that has to be determined (Sandu et al., 2008b). The selected range was chosen as the maximum interval for which the linear correlation coefficient is above a threshold ($R^2 = 0.9995$). This describes the quality of the linear fit in the plot of logarithm of boxes size vs logarithm of number of boxes needed to assess the whole white mater structure. We illustrate this by showing how the edge length of the boxes increases by one voxel