Brain structural complexity and life course cognitive change

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ABSTRACT

Fractal measures such as fractal dimension (FD) can quantify the structural complexity of the brain. These have been used in clinical neuroscience to investigate brain development, ageing and in studies of psychiatric and neurological disorders. Here, we examined associations between the FD of white matter and cognitive changes across the life course in the absence of detectable brain disease. The FD was calculated from segmented cerebral white matter MR images in 217 subjects aged about 68 years, in whom archived intelligence scores from age 11 years were available. Cognitive test scores of fluid and crystallised intelligence were obtained at the time of MR imaging. Significant differences were found (intracranial volume, brain volume, white matter volume and Raven’s Progressive Matrices score) between men and women at age 68 years and novel associations were found between FD and measures of cognitive change over the life course from age 11 to 68 years. Those with greater FD were found to have greater than expected fluid abilities at age 68 years than predicted by their childhood intelligence and less cognitive decline from age 11 to 68 years. These results are consistent with other reports that FD measures of cortical structural complexity increase across the early life course during maturation of the cerebral cortex and add new data to support an association between FD and cognitive ageing.

Introduction

The neurobiological basis of cognition and age-related changes in cognitive abilities (‘cognitive ageing’) is uncertain. Development of effective interventions to delay cognitive ageing will almost certainly rely on, at least in part, careful scientific analysis of structural changes in the ageing brain. For years the notion has prevailed that more is better, in terms of neuro-development and in terms of reserve or protection against ageing and disease in late life. Testing the ‘more is better’ hypothesis has produced mixed results, although an extensive meta-analysis (McDaniel, 2005) concluded that brain size correlated with fluid intelligence measures. The size of this correlation indicates that size is not everything. It would be rash to assume that cognition could be entirely explained by brain volume measures, but there is evidence to suggest that having more in particular regions is seen in individuals with superior cognitive abilities (Haier et al., 2004; Staff et al., 2006).

The cerebral cortex is a fractal structure made up of parts that are in some ways similar to the whole. The cortical fractal structure can be characterised by a single numerical value (the fractal dimension, FD) that summarises the irregularity of the external cortical surface and the boundary between subcortical grey and white matter (Bullmore et al., 1994). As shown below, FD measures are used in neuroscience to reveal gender and age structural differences in the cerebral cortex in the absence of disease and to investigate psychiatric and neurological disorders. Development and ageing of the human brain can be studied with FD and have shown increasing cortical complexity from early foetal life (Garelli et al., 2001; Kedzia et al., 2002; Rybaczk et al., 1996; Shyu et al., 2010; Wu et al., 2009) through childhood (Blanton et al., 2001) and into adulthood (Annunts et al., 1997; Free et al., 1996; Takahashi et al., 2004) until decreasing complexity is seen in late life and in Alzheimer’s disease (King et al., 2009, 2010; Zhang et al., 2007). There is also a growing literature on the cortical FD in many psychiatric disorders including schizophrenia and manic depression (Bullmore et al., 1994; Ha et al., 2005; Narr et al., 2001, 2004), obsessive compulsive disorder (Ha et al., 2005), autism (Raznahan et al., 2010) and neurological disorders including stroke (Zhang et al., 2008), Williams syndrome (Thompson et al., 2005; Van Essen et al., 2006) and multiple sclerosis (Esteban et al., 2007, 2009).

Cognitive abilities increase across the life course from childhood to mid-life and then decline; slowly at first, accelerating through late middle age into old age. ‘Crystallised intelligence’ remains relatively stable and ‘fluid intelligence’ tends to decline in late life. ‘Crystallised
intelligence’ is considered a reliable estimate of an individual’s ‘best ever’ ability before the onset of disease and ageing (Crawford et al., 2001). The ‘fluid intelligence’ measures speed of thought and some aspects of current problem solving ability. The difference between fluid and crystallised intelligence in late life is often considered a reliable estimate of overall life course decline from pre-morbid ability (ΔL). Similarly, the difference between an estimate of childhood intelligence and adult crystallised intelligence measures cognitive maturation from early life to the ‘best ever’ level of adult ability (ΔE). The difference between an early life measure of ability and a late life measure of fluid ability is an estimate of lifelong change in fluid ability (ΔF). The hypothesised cognitive life course changes and the estimates of maturation (ΔE), fluid ability change (ΔF) and decline (ΔL) are schematically shown in Fig. 1.

There are reports that human intelligence is related to the total volume of grey and white matter in frontal, temporal and parietal areas (Haier et al., 2004). Im et al. (2006) examined 44 volunteers of mean (SD) age, 26.4 (±5.5) years to investigate: (1) how structural properties of the cerebral cortex affected the value of FD; (2) the relationships between FD of the cortical surface and intelligence (mean IQ of 116.27 (range between 89 and 134)) and the duration of education (mean of 15.7 years (range between 12 and 21 years)). They found that FD increased with intelligence and years of education. Their findings were interpreted as support for a contribution to cortical structural complexity by education and intelligence and are consistent with the view that learning and training through education can change and reorganise cortical structure (Draganski et al., 2004; Mechelli et al., 2004). Sex differences in cortical structure and cognitive performance are major potential confounders of correlative studies of cortical structure variations with specific cognitive abilities. Women are better at many tests of verbal ability whereas men have better spatial ability. Comparisons between sexes show men have larger brains and a thicker cortex, but women have greater gyrification (Luders et al., 2004, 2006; Staff et al., 2006; Thompson et al., 2005). In 176 individuals, Sowell et al. (2007) found that women on average have thicker grey matter in temporal and parietal cortices and these differences are independent of brain and body size.

Brain size reduces with age in late adulthood. This is predominately due to a loss of grey matter with white matter volume remaining relatively stable (Good et al., 2002). When considering the influence of brain structure (measured in later life) on the change in cognitive measures across the life course, it is reasonable to expect that white matter would remain relatively stable when compared to grey matter, which loses volume faster and is susceptible to disease such as Alzheimer’s disease.

FD has the potential to contribute in understanding how differences in structural complexity might explain individual differences in cognitive ageing. Therefore, we decided to analyse our structural MRI database to explore how differences in cognitive variables might be accounted for by variance in the FD measures and how these could be related to changes in mental performance across the life course. We hypothesised that fractal descriptors of white matter would be associated with childhood IQ, suggesting early cognitive maturation, better cognitive performance, less decline in late life and that in general, more complex structures are associated with better cognitive outcomes.

Methods and materials

Subjects

Aberdeen 1936 Birth Cohort (ABC36) project has been described in detail elsewhere (Deary et al., 2004b; Whalley et al., 2011). Briefly, the data used in the analyses reported here were taken from the ABC36 brain imaging database held in the Aberdeen Biomedical Imaging Centre. The primary goal of ABC36 is to identify brain imaging, biomedical and neuropsychological predictors of progress to dementia with onset after age 68 years in a volunteer sample without dementia all born in 1936 and recruited to the project between the years 2000 and 2002. A subset of 248 subjects from 506 recruited to ABC36 volunteered for brain MRI examination at age about 68 years. ABC36 volunteers were drawn from an original sample of Aberdeen school children who were born in 1936 and in 1947 took part in the Scottish Mental Survey of the general intelligence of Scottish school children (Deary et al., 2004a). Intelligence scores from age 11 were archived by the Scottish Council for Research in Education which gave the University of Aberdeen access to these IQ scores. The volunteers have been assessed on four occasions since age 64 years when comprehensive clinical, sociodemographic, nutritional and neuropsychological data have been collected. MRI data were first obtained at age about 68 years and are reported here. Cognitive tests have included non-verbal abstract reasoning using Raven’s Progressive Matrices (RPM: Raven, 1960) and the National Adult Reasoning Test (NART; Nelson and Willison, 1982) which tests the ability to pronounce...
irregular words and is associated with educational level and general intelligence. For this study, 217 subjects who have a complete data set have been used in this analysis.

**MR acquisition**

The MR imaging study was performed on a 1.5 Tesla GE NVi system. The 3 dimensional (3D) images of 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 between 100 and 124, effective slice thickness 1.6 mm and matrix 256×256 in-plane resolution 1 mm×1 mm.

**Segmentation**

White matter structure was obtained from the T1W MR image using Freesurfer (FS) software (Fischl et al., 2002). FS is a free software package used as a set of semi automated tools for creating computerised model of the brain from MR imaging data and measuring the brain’s morphometric properties. Details of the segmentation procedures are described elsewhere (Fischl et al., 2002, 2004; Han and Fischl 2007).

The first steps in FS processing concern motion correction, affine transformation to Talairach image space, non-uniform intensity normalisation for intensity inhomogeneity correction and removal of non-brain tissues. Intensity normalisation was then applied to the brain volume to match the FS atlas image intensity histogram and continued with a non-linear warping of the atlas brain image to subject brain image. The warped atlas brain image space was utilised in atlas-based tissue segmentation to label the subcortical structural, brain stem, cerebellum and cerebral cortex. The second step involves cortical parcellation of the white matter surface. The main components in surface mapping are surface inflation, projection to spherical coordinates, topology correction and surface based warping to align anatomically homologous points. After processing was completed, the left and right cerebral white matters were extracted from the subcortical structure to form a whole white matter mask (256×256×256 mm³). The 3D white matter mask generated by FS was used for the fractal dimension calculation. The mask was not altered in any way (e.g. trimming). The total brain size and total intracranial volume (TICV) were extracted from the FS statistical output file and the total white matter volume (WMV) was counted using a program written in the Interactive Data Language (IDL, Boulder, CO, USA).

**Fractal measure**

The fractal dimension (FD) of the cerebral white matter was estimated using a box-counting method (voxel based). The box-counting method was chosen because of its simplicity, robustness (Jiang et al., 2008) and ability to evaluate the fractal with and without self-similarity (Esteban et al., 2007; Zhang et al., 2006). A program to calculate and analyse white matter’s fractal measures was written in the Interactive Data Language (IDL, Boulder, CO, USA).

FD was computed by altering the scale of the image and counting the number of white matter voxels at each scale. This was done by starting at the original resolution and removing a part of the border to give a 240×240×240 matrix and counting the white matter voxels. The original 240×240×240 image was then rescaled to give matrix sizes of 120×120×120, 80×80×80, 60×60×60, 40×40×40 and 20×20×20. At each scale (rFD = 1, 2, 3, 4, 6, 12 respectively), the number of white matter voxels (N) was counted (observed data). The white matter structures with three different scales are shown in Fig. 2 (the images are represented in 2D for illustration only).

FD of the white matter structure from one subject was computed by performing a linear regression analysis using N at each scale in logarithmic to find a line (expected) that best fits the data (the least amount of difference between the ln(N) and the line). The line of best fit is given by: ln(Nexp) = M ln(1/rFD) + C where C is a constant and the M (gradient) corresponds to an estimation of the FD. Fig. 3 shows that when any line is fitted to a set of experimental data, there will be small differences between the values predicted by the fit and the observed data. To establish how well FD was estimated using box counting method and summarise the discrepancy between the ln(N) and the ln(Nexp), the fractal fit (χ²) was calculated using the following equation (Lemeshow and Hosmer, 1982):

\[
\chi^2 = \sum \left(\frac{\ln(N) - \ln(N_{exp})}{\ln(N)}\right)^2
\]

**Statistical analysis**

Statistical analysis was performed using SPSS 19.0 (Statistical Package for Social Sciences 19.0; Chicago, IL, USA). Data were grouped as men, women and both sexes combined. A student’s t-test was used to test for differences between men and women. Relationships between the fractal measures (FD and χ²) and the other variables (cognitive measures and structural volumes) were examined using Pearson’s correlation (r).

We chose a univariate general linear model (GLM) analysis to test the association between fractal measures and cognitive measures separately. Using the same analysis, the association between the life course changes was tested with the fractal measures modelled separately and together.

**Results**

Data are summarised in Table 1. A plot of ln(N) versus ln(1/rFD) taken from one subject is shown in Fig. 4. Examples of white matter structures of low and high FD are shown in Fig. 5. First, we tested the differences between men (n = 116) and women (n = 101) using

![Fig. 2. Example of FD estimation for cerebral white matter using box-counting method. Each scale represents different numbers of voxel in one box. A: rFD = 4; B: rFD = 6; C: rFD = 12.](Image)
an independent t-test. There were expected differences between the sexes in total intracranial volume (TICV), brain volume, white matter volume (WMV) and RPM.

We next examined the relationships (Table 2) between the fractal measures and the other variables for each gender and for the group as a whole and found a significant positive correlation between the FD and TICV, brain volume and WMV for the whole sample and for each gender with the exception of men TICV. The additional analyses showed that there were no differences between genders when the correlation values were compared with the exception of the TICV-FD correlation where women were more strongly correlated than men. When gender was examined separately none of the cognitive measures was associated with FD. RPM was significantly correlated with FD when the sample was analysed as a whole.

$\chi^2$ was found to be significantly correlated with brain volume in men, with WMV in both men and women and with childhood intelligence in men. The additional analyses found no differences between men and women in terms of their correlation between $\chi^2$ and each volumetric and cognitive measure. $\chi^2$ was found to be significantly associated with brain volume, WMV and MHT when the sample was analysed as a whole.

Tables 1 and 2 show that TICV, brain volume, WMV and gender are associated with the fractal measures. This may confound any association between fractal measures and cognition. In a univariate GLM, we tested for associations between FD and cognitive scores using gender as a fixed factor and WMV as a covariate. The same analysis was repeated for the $\chi^2$. The results can be seen in Table 3 and show a significant association between MHT for both FD and $\chi^2$.

NART is a measure of crystallised ability and provides an estimate of an individual’s ‘best ever’ pre-morbid ability. We calculated: (1) the standardised difference between the MHT and NART as an estimation of cognitive maturation from age 11 years to adulthood ($\Delta E$); (2) the standardised difference between the NART and RPM to estimate a decline in cognition in late life ($\Delta L$) and; (3) the estimation lifelong fluid change ($\Delta F$) using the standardised difference between the MHT and RPM. We correlated these three standardised difference scores with FD and found a significant positive correlation ($r=0.235$ with $\Delta F$ ($p<0.001$) and a significant negative $r$ of $-0.201$ with $\Delta L$ ($p<0.005$). The opposite pattern was seen with $\chi^2$ with an $r$ of $-0.224$ with $\Delta F$ and $0.198$ with $\Delta L$ ($p<0.005$). No significant correlations were found between $\Delta E$ and FD or $\chi^2$. A scatter-gram of these data is shown in Fig. 6. No differences were found between cognitive change measures and FD or $\chi^2$ when the data were split by sex and testing for differences in terms of the correlation ($p<0.05$).

Using a GLM approach, we tested the association between the two fractal measures and the estimated changes in cognitive ability, after adjusting for sex modelled as a fixed factor and WMV modelled as a covariate. We first modelled the data with the fractal measures separately (models 1 and 2) and then together (model 3). The results are shown in Table 4. They show significant associations between the fractal measures and the cognitive change scores when modelled separately with the exception of $\Delta E$. After modelling the fractal measures together, only the FD association with $\Delta F$ was retained. The influence of WMV on the cognitive change scores was not significant in any models. Gender was found to significantly influence $\Delta F$ in models 1 and 3 only ($p<0.05$). Similar analyses were done after adjustment for TICV and brain volume instead of WMV and yielded an identical pattern of significant associations with similar effect sizes.

**Table 1** Fractal measures, demographic and intelligence scores in men, women and both sexes combined. Values are means ± standard deviation.

|                     | Men (n = 116) | Women (n = 101) | Both sexes (n = 217) |
|---------------------|--------------|-----------------|---------------------|
| FD                  | 2.5028 ± 0.0270 | 2.4988 ± 0.0244 | 2.501 ± 0.0258      |
| $\chi^2$            | (384.52)     | (398.81)        | (391.17)            |
| TICV (mm$^3$)       | ± 72.46 x 10^{-6} | ± 68.24 x 10^{-6} | ± 70.72 x 10^{-6}   |
| Brain volume (mm$^3$)$^\dagger$ | (1.61 ± 0.12) x 10$^6$ | (1.40 ± 0.11) x 10$^6$ | (1.51 ± 0.16) x 10$^5$ |
| WMV (mm$^3$)$^\dagger$ | ± 51.48 x 10$^3$ | ± 45.29 x 10$^3$ | ± 56.64 x 10$^3$    |
| MHT                 | 44.58 ± 10.05 | 44.88 ± 10.56 | 45.18 ± 10.60       |
| RPM                 | 38.47 ± 7.34 | 36.27 ± 8.35 | 37.45 ± 7.88        |
| NART                | 34.03 ± 6.84 | 33.96 ± 7.34 | 34.00 ± 7.06        |

FD: fractal dimension; $\chi^2$: fractal fit; TICV: total intracranial volume; WMV: white matter volume; MHT: Moray House Test; RPM: Raven’s Standard Progressive Matrices Test; NART: National Adult Reading Test.

$^\dagger$ Indicates a significant difference between men and women, $p<0.005$. 

**Fig. 3.** Illustration of plot ln(N) versus ln(1/rFD). This graph shows a few observed data (marked as crosshair) and a linear regression line. The right brace represents the difference between ln(N) and ln(Nexp) (a point on expected line) at a specific scale. The $\chi^2$ is calculated by adding the squared differences between ln(N) and ln(Nexp) at each scale.

**Fig. 4.** Example of plot of ln(N) versus ln(1/rFD) taken from one subject. The expected line is shown by straight line and the observed data are marked as crosshair. No gaps can be seen between ln(N) and ln(Nexp) as the difference between ln(N) and ln(Nexp) is very small (giving a small value of $\chi^2$).
those with a more complex white matter surface and those whose complexity is regular across scales do better.

Brain size is almost entirely genetically determined (Bartley et al., 1997). However, structure is predominately environmentally determined (Bartley et al., 1997). These results suggest that subtle structural differences measured using FD and χ² are associated with successful cognitive ageing. Moreover, these structural complexity measures appear to be associated with differences in decline.

Fractal measures of brain structure provide novel information about morphology not entirely captured by other MR structural measures such as volume or surface area. Reports of morphological studies are limited. Studies based on conventional MRI have focused on measuring volumes (size) as correlates of cognitive ageing (Kaup et al., 2011; Salthouse 2011; Staff et al., 2006). Reports using fractal measures are infrequent. Studies by Zhang et al. (2007) using a range of FD measures have shown larger FD in a group of young adults (17 to 35 years) when compared with an elderly group (72 to 80 years) and between genders. It is unclear if this reduced FD value in the old is brought about by ageing or it represents differential early structural development between individuals raised in the late twentieth century and those raised in the third decade. Similarly, in this study we have assumed that the fractal measures are estimates of structural maturity but the value maybe brought about, at least in part, by individual differences in pathological ageing. Further investigation may consider using different and perhaps more sophisticated measures such as discussed by Thompson et al. (1996, 2005) and Ashburner et al. (2003) may reveal additional and structural subtleties associated with cognitive ageing.

Lifelong cognitive changes may also be influenced by other life experiences such as education level and occupation (Staff et al., 2004). A higher education level and a more cognitively complex education

**Table 3**

| Model | FD | p value | Partial χ² | p value | Partial χ² |
|-------|----|---------|-----------|---------|-----------|
| WMV, gender | 0.118* | 0.626 | 0.042 | 0.019 |
| RPM  | 0.252 | 0.006 | 0.577 | 0.001 |
| NART | 0.385 | 0.004 | 0.080 | 0.014 |

FD: fractal dimension; χ²: fractal fit; WMV: white matter volume; MHT: Moray House Test; RPM: Raven’s Standard Progressive Matrices Test; NART: National Adult Reading Test.

* Indicates a significant association between the fractal measures and the cognitive scores, p<0.05.
Fig. 6. Relationship between life course cognitive changes and fractal measures. A larger increases in $\Delta E$ and $\Delta F$ is associated with greater FD (A and B) and smaller $\chi^2$ (D and E). A less decline in $\Delta L$ at age 68 years is associated with greater FD (C) and smaller $\chi^2$ (F).
obtained across the life course predict higher cognitive ability in old age than would be expected from a person's childhood ability and accumulated brain burden. In addition to these intellectual activities, genetics, lifestyle, diet and nutrition can also influence cognitive abilities (Deary et al., 2009). Therefore, the roles of the other variables should be investigated in the future as the underlying source of variance in the models.

Conclusion

To the best of our knowledge, this is the first use of fractal measures to estimate life course changes in cognitive ability. This study demonstrates the potential of complexity measures as an estimate of structural maturation. The results indicate that those with greater white matter complexity have a superior cognitive life course trajectory. A better understanding of structural brain maturation and its impact on life course decline and disease could prove essential to development of new therapies aimed at maintaining cognitive ability in late life.

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