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

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 Abstract

Brain morphology and cognitive ability change with age. Grey 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 purpose of this study is 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 modelling 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.

1. 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, grey 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 characterises 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, Hashemi-Golpayegani, Ashburner 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 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 the 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, Hashemi-Golpayegani, Ashburner 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 cortical complexity changes and how this is 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 modelling 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.

2. Methods

2.1 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).

2.2 Cognitive tests

All participants took Raven's Standard progressive Matrices (RPM) measuring nonverbal reasoning (Raven, Court, Raven 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.

2.3 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.

2.4 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 normalisation 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 neighbouring 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).

2.5 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/the 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.

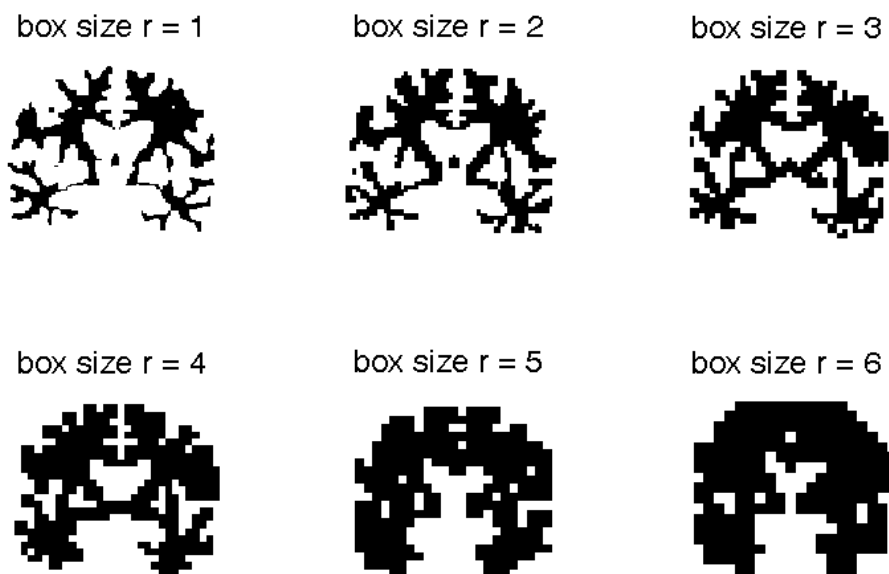| box size r = 1 | box size r = 2 | box size r = 3 |
| box size r = 4 | box size r = 5 | box size r = 6 |

Fig. 1 Legend: In an illustration of the box-counting method, the mid-coronal slice is covered with boxes of increasing size. The section is extracted after the construction of boxes on three-dimensional white matter 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 per iteration, within the range from *r = 3* to *r = 30* voxels for whole brain WM. The absolute value of the slope of a linear regression line provides the fractal dimension of the WM volume (see Fig 2).
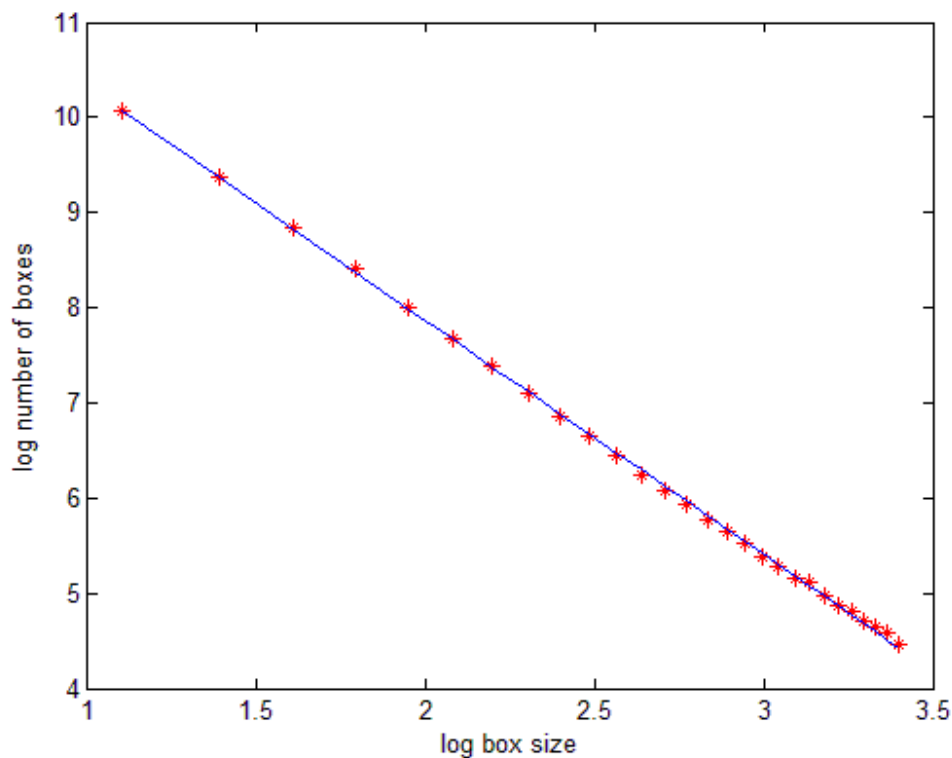

Fig. 2 Legend: Logarithmic plot of the number of boxes containing white matter versus box radius. The fractal dimension given by the slope is 2.4507

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The algorithm and a validation procedure of the method were presented in a previous study (Sandu et al., 2008b). This was done using digital phantoms with known fractal dimension and the reliability of the method was measured through an intraclass correlation coefficient (ICC>0.9) between data acquired from two different scanners. The analyses were based on in-house developed software written in Matlab R2012a (Mathworks, Natick, MA, USA).

2.6 Statistical analysis

Statistical analysis was performed using SPSS 21 (Statistical Package for Social Sciences 21; IBM, Chicago, IL, USA). Data collected from healthy subjects in two waves (at 68 and 73 years old) were compared using paired two samples t-test. Relationships between cortical complexity and cognitive scores were examined using Pearson's correlation. The correlation was also used to test the association between the precise scan interval and changes in WM volumes.

To test the hypothesized association between the structural complexity of WM and cognitive abilities in late life, we used a multilevel linear modelling approach and the software MLwiN (Rasbash et al., 2009). We assumed that on each occasion cognitive ability is explained by a linear combination of age, brain volume and structural complexity summarized by equation 1. Each variable and the intercept were modelled as a fixed effect. Here, each cognitive test was standardized as an IQ-type score (*aIQ*, mean 100, standard deviation 15). Age was expressed as years past their sixtieth birthday (Age$_{+60}$). The WM fractal dimension and brain volume were also standardized (FDWM, mean = 0, standard deviation =1), using all of the data in our sample. Whole brain volumes and white matter volumes were also standardized (*Vol*, mean =0, standard deviation = 1). The participants are identified by the subscript *i* and the occasion of testing by the subscript *j*. $\beta_{0,j}$ is the intercept and represents the estimated cognitive ability at the age of 60

years, $e_{i,j}$ represents the residual.   Preliminary analysis of our data suggested FD differed between men and women, but after adjusting for brain volumes this relationship was not maintained.

$$aIQ_{i,j} = \beta_{0,j} + \beta_{1,j}Age_{+60} + \beta_{2,j}FDWM + \beta_{3,j}Vol + e_{i,j} \qquad (1)$$

In order to test a hypothesized association between complexity and life-long cognitive change, we extended our model to include childhood ability. As with adult ability, we standardized the MHT (Moray House Test) score into an IQ –type score (cIQ, mean = 100. standard deviation = 15).

$$aIQ_{i,j} = \beta_{0,j} + \beta_{1,j}Age_{+60} + \beta_{2,j}FDWM + \beta_{3,j}Vol + \beta_{4,j}cIQ + e_{i,j} \quad (2)$$

3. Results

243 participants (128 male) were imaged aged around 68 years and of this original sample, 148 participants, (80 male) were imaged at follow-up, aged around 73 years. FD values for WM and brain volumes were compared within subjects between ages 68 and 73 years using paired two samples t-test (Table 1). All comparisons showed significant decreases. FD values and brain volumes were significantly lower at wave 2 when compared to wave 1 and those participants who did not return for image at wave 2 had significantly smaller baseline FD and brain volumes. Decreased brain complexity with age is illustrated in the Figure 3. The decline of complexity with age was further tested using a multilevel linear model which included volume as a covariable Equation 3. Here, the relationship with age was maintained after adjustment for volume (WM or whole brain).

$$FDWM_{i,j} = \beta_{0,j} + \beta_{1,j}Age_{+60} + \beta_{2,j}Vol + e_{i,j} \quad (3)$$
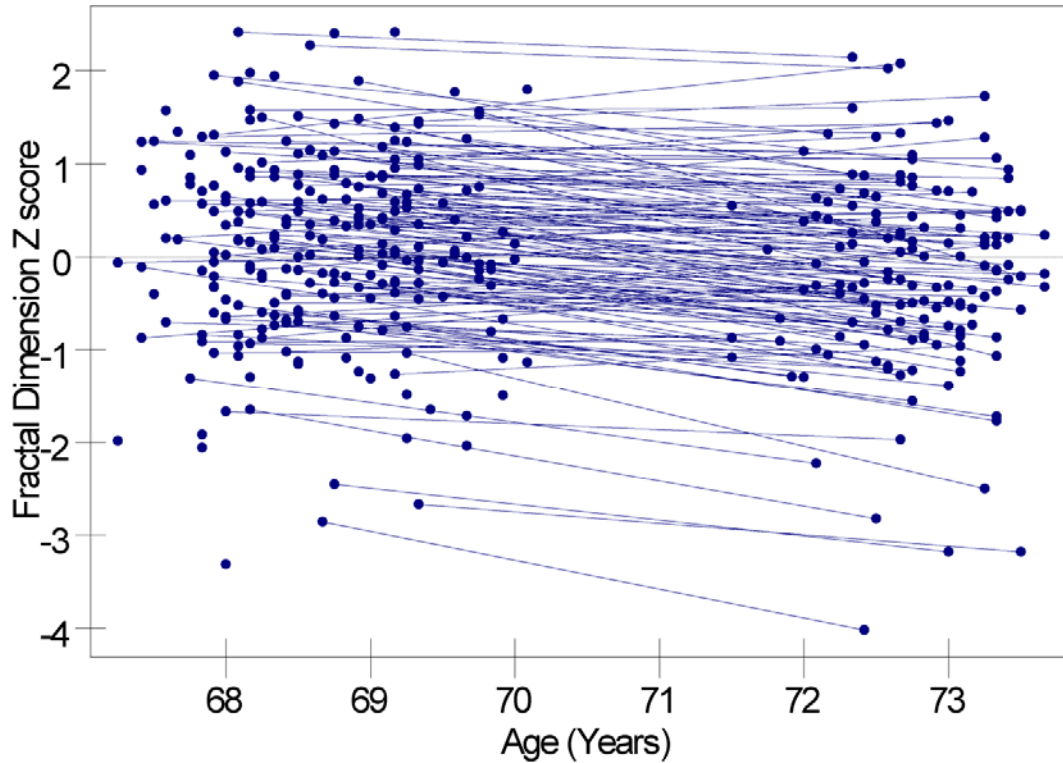

Fig. 3 Legend: Complexity decline with age- plotting the changes in standardized white matter Fractal Dimension vs age past 60 years

Table 1 compares raw cognitive rest test scores between test occasions. All cognitive test scores were expected to be positively correlated. To examine whether the hypothesized associations between FD and cognitive test scores are specific to particular cognitive domains or have general associations with all domains, we reduced data using principal component analysis. From cognitive test scores, we extracted the first un-rotated principal component, also known as the general factor (g), which explained 46% of the observed variance. Individual factor loadings were: - RPM: 0.80 DS: 0.65, AVLT: 0.65, BLK: 0.69, UFO: 0.59. DS, AVLT, g and BLK all showed significant decline over the testing period. RPM remained unchanged and UFO showed

some improvement. RPM and UFO results are probably attributable to practice effects. Those of higher ability on RPM, UFO, g and BLK were more likely to provide wave 2 samples, age ~73. Those individuals who returned for wave 2 imaging were slightly younger at wave 1, age ~68.

Imaging			
ID	W1 Completed	W1+2 Completed	W1 Only
Measurement Wave	Wave 1	Wave 2	Wave 1
Participation	Completed Wave 1 and 2	Completed Wave 1 and 2	Completed Wave 1 only
N	148	148	94
FDWM	2.47 (.019)	2.46 (.021)***	2.46 (.023)[#]
Volume WM (cm^3)	447.2 (54.3)	431.6 (54.2)***	432.3 (60.5)[#]
Brain Volume (cm^3)	912.6 (91.2)	881.2 (90.2)***	886.9 (100.4)[#]
Cognition			
N	132-151	132-151	72-138
RPM	39.1 (6.9) N=151	38.3 (7.2)	35.1 (6.6)[###] N=82
DS	47.5 (10.2) N=132	41.3 (10.0)***	43.6 (10.8) N=94
UFO	13.6 (6.1) N=154	15.0 (5.2)***	12.3 (4.9)[###] N=72
AVLT	63.4 (14.4) N=148	59.7 (16.9)***	60.1 (15.7) N=83
BLK	27.2 (8.6) N=150	25.0 (9.6)***	23.4 (8.7)[#] N=74
MHT	46.0 (10.1) N=148		43.8 (11.1) N=94
g	.29 (.96) N=87	-.07 (1.03)***	-.22 (.96)[###] N=138
Age (years)	68.6 (.6) N=148	72.7 (.5)***	68.8 (.72)[#] N=94

Table 1 Legend: Means and standard deviations for the fractal dimension (FD) measurements of white matter (WM), brain volumes and the cognitive test scores: Raven's standard progressive matrices test (RPM), digit symbol scores (DS), use of objects (UFO), auditory verbal learning test (AVLT), Block Design (BLK), general intelligence factor (g) using paired and unpaired t-tests between the different groups and measurement waves. Moray House Test (MHT) is childhood intelligence test at age 11. *** = p<.001 by paired t-test; 'W1 Completed vs W1+2 Completed'. [###] = p<.001, [#]= p<.05, t-test 'W1 Completed vs W1 only'.

The multilevel linear model shown in equation 1 is seen in Table 2. It shows that, after adjustment for age, FD and WM volume, there is a significant association between processing

speed (DS) and memory (AVLT) and WM complexity (FD). For DS and AVLT, a FD difference of 1 standard deviation represents an IQ difference of between 2.5 and 3 points. Table 2 shows intercepts significantly greater than zero as expected. The results used whole brain volume estimates as the *Vol* variable, repeating the results of an analysis using WM volume produced an almost identical set of results.

	RPM	DS	AVLT	BLK	UFO	*g*
β_0 intercept	95.8 (4.0)*	109.4 (4.1)*	104.3 (3.9)*	96.6 (3.9)*	92.8 (4.0)*	99.1 (4.3)*
β_1 Age	.41 (.39)	-.95 (.41)*	-.42 (.38)	.32 (.38)	.71 (.39)	.07 (.43)
β_2 FD	1.78 (1.21)	2.44 (1.24)*	2.92 (1.14)*	-.71 (1.18)	1.26 (1.18)	1.93 (1.28)
β_3 Volume	.085 (1.17)	-1.35 (1.19)	-1.15 (1.13)	4.91 (1.13)*	.06 (1.16)	-.08 (1.24)
σ^2	220.8 (16.5)	217.6 (16.1)	210.8 (15.7)	204.9 (15.4)	221.2 (16.4)	221.1 (17.5)
*-2*loglikelihood*	2931.7	2786	2931.7	2880.7	2981.9	2619.2

Table 2 Legend: The multilevel linear model results (equation 1) for each of cognitive tests: Raven's standard progressive matrices test (RPM), digit symbol scores (DS), auditory verbal learning test (AVLT), Block Design (BLK), use of objects (UFO), general intelligence factor (*g*) was standardized into an IQ-like score. Age was expressed as the number of years past their sixtieth birthday. The FD is the fractal dimension for white matter; the volume is brain volume. β_0 is the intercept and represents the estimated cognitive ability at the age of 60 years. β_1, β_2 and β_3 are the coefficients for corresponding measures. σ^2 represents the residual or error and *-2*loglikelihood* represents the goodness of fit, the smaller the value the better fit. The standard errors are in brackets. The significant association is marked with * where p<.05

After introduction of childhood ability into the model -MHT (Equation 2), the effect of FD on cognition was maintained for DS and AVLT. In addition a significant association between the general factor *g* and RPM and FD was also seen (Table 3). As in model 1, replacing brain volume with WM volume produced an almost identical set of results. The intercepts were

significantly greater than zero as expected as was the association between childhood ability and

late life cognition.

	RPM	DS	AVLT	BLK	UFO	g
β_0 intercept	72.6(5.6)*	74.4 (6.1)*	71.6 (6.0)*	61.0 (5.8)*	67.4 (6.3)*	48.1 (5.8)*
β_1 Age	.26 (.34)	-1.07 (.34)*	-.51 (.36)	.18 (.35)	.64 (.37)	-.16 (.36)
β_2 Volume	-.42 (1.01)	-1.53 (1.10)	-1.29 (1.06)	4.67 (1.05) *	-.13 (1.11)	-.43 (1.04)
β_3 FD	2.72 (1.05)*	3.00 (1.15)*	3.30 (1.07)*	-.14 (1.10)	1.60 (1.14)	2.75 (1.08)*
β_4 IQ MHT	.50 (.05)*	.36 (.05)*	.33 (.05)*	.37 (.05)*	.26 (.05)*	.53 (.05)*
σ^2	164.9 (12.4)	188.0 (14.4)	186.3 (13.9)	175.1 (13.2)	206.3 (15.3)	156.5 (12.4)
-2*loglilkelihood	2827.7	2737.2	2887.3	2825.1	2956.6	2509.4

Table 3 Legend: The multilevel linear model results (equation 2) for each of the cognitive tests: Raven's standard progressive matrices test (RPM), digit symbol scores (DS), auditory verbal learning test (AVLT), Block Design (BLK), use of objects (UFO), general intelligence factor (*g*) was standardized into an IQ-like score. Age was expressed as the number of years past their sixtieth birthday. The FD is the fractal dimension for white matter and the Volume is its volume. Moray House Test (MHT) is childhood intelligence test at age 11. β_0 is the intercept and represents the estimated cognitive ability at the age of 60 years. $\beta_1, \beta_2, \beta_3$ and β_4 are the coefficients for corresponding measures. σ^2 represents the residual or error and *-2*loglikelihood* represents the goodness of fit, the smaller the value the better fit. The standard errors are in brackets. The significant association is marked with * where p<.05.

All significant FD beta values are significant after correction for multiple comparisons, for each cognitive test, using a False Discovery Rate (FDR) procedure (Benjamini and Hochberg 1995) and an acceptable FDR of 0.05. The value for g was not included in the multiple comparison correction since it is a summary measure of the other variables.

Tables 2 and 3 suggest an inter-individual association between cognition and FD. However, it is unclear if cognition and FD show intra-individual variation, in other words that a change in FD is associated with a change in cognition in that participant. When correlations are examined between changes in cortical complexity and change in cognition, a significant correlation was found between FD and DS and g (Table 4).

	ΔRPM	ΔDS	ΔAVLT	ΔBLK	ΔUFO	Δg
ΔFD	.018	.208*	.120	.177	.103	.270*
N	117	104	118	119	123	87

Table 4 Legend: Pearson correlation between the change in the fractal dimension (ΔFD) and the changes in cognitive variables: Raven's standard progressive matrices test (ΔRPM), digit symbol scores (ΔDS), auditory verbal learning test (ΔAVLT), Block Design (ΔBLK), use of objects (ΔUFO), general intelligence factor *(*Δg*)* with age, where N is the number tested participants and * means p<.05.

Using linear regression, we investigated whether correlations remained significant after adjustment for confounding by age, change in brain volume and WM volume. We found no significant association.

4. Discussion

Here, using longitudinal measures of brain structural complexity and cognition, we observe inter-individual associations between WM structural complexity and cognition, specifically with processing speed (DS) and verbal memory (AVLT) in late life. After adjustment for childhood cognitive ability, we find further associations between reasoning (RPM) and general cognitive ability (*g*). We also find some evidence of an intra-individual association, but this was not

maintained after adjustment for confounding by age and brain volume. In conclusion, structural brain complexity is associated with higher cognitive ability and appears to decline in late life.

Decline of brain volume with age is well established (Sowell, Thompson, Toga 2004; Staff 2012) and there are also studies measuring specific volumes as correlates of cognitive aging (Salthouse 2011; Staff et al., 2006). Differences in the FD value between adults and elderly people are reported by Zhang et al. (2006; 2007) and by Lee et al. (2004). Cortical fractal complexity is reduced with increasing age as the surface of the brain becomes smoother and the sulci become wider and less curved. Our results indicate that this reduction is not entirely explained by a concurrent reduction in volume. It is not established whether the FD effects seen in elderly people described by Zhang et al. (2007) and Lee et al. (2004) are a continuation of the reduction of FD which begins in adolescent/young adult brain. These results suggest that reduction in cortical complexity occurs in late life; however, it remains unclear whether there is a stable period before our period of observation in late adulthood.

The initial multilevel linear model (1) indicated an association with processing speed and memory. It is unclear why this relationship is domain specific. Cortical sulcal variability was investigated in correlation with cognitive performance from five cognitive domains including attention/processing speed, memory, language and executive function by Liu et al. (2011). They found that processing speed performance was correlated with spans of most sulci in elderly. This finding helps consolidate our results, stressing once more that the speed of information processing decreases with age in late adulthood and is correlated with the structural brain complexity. The greater the WM complexity, the greater the information processing speeds in healthy participants.

Cognitive tests may differ in the effect of practice on performance and our model is less sensitive in those domains most subject to practice effects. When we introduced childhood ability into our model, RPM and the general factor (*g*) became significant. This result is essentially a confirmation of a previous work (Mustafa et al., 2012) but with additional longitudinal data. That is, that structural complexity is associated with lifelong cognitive differences. Here, we also show that this is a general effect and not limited to a specific domain.

The correlation between change in FD and change in DS and *g* would indicate that intra-individual structural change is an estimate of brain aging associated with cognitive decline. However, this relationship was not maintained after adjustment for volume and, therefore, we have not showed it to be independent predictor of decline.

Taking the results of these two analyses together, we have demonstrated that greater WM complexity is associated with retention of cognitive ability across the life course and individual differences in ability in late life. It may well be that FD is a measure of resilience to cognitive decline and those with less structural complexity may be more vulnerable to cognitive decline, mild cognitive impairment and dementia. It is conjecture to attribute a causal relationship between structural complexity and intelligence. An alternative explanation would be that complexity and intelligence share a common causal origin. However, systems theory suggests that more complex systems are more robust to perturbation and insult. Lipsitz (2004) has suggested that with ageing and disease, there is a loss of complexity in many integrated physiological processes. Normal physiological function requires the integration of intricate networks of control systems, feedback loops, and other regulatory mechanisms to enable a system to simultaneously perform the many necessary and varied activities. Here, we suggest

that more complex structure may well be better able to maintain this intricate networks and therefore outputs (cognitive performance).

The strengths of this study are the novelty of longitudinal analysis of change in brain structural complexity in well-characterized normal people. A weakness of our study is similar to those examining cognitive decline in late life; namely, drop out and practice effects. It is clear from Table 1 that those retained in the study have larger and more complex brains and had superior cognitive abilities. It is generally true that aging is kinder to the more gifted (Bourne et al., 2007) and our results may well be skewed because of this differential retention. However, demonstration of FD differences in this relatively healthy sample makes our results more generalizable to the general older population. Future work could investigate whether localized measurements of brain structural complexity are informative in decline in specific cognitive abilities and dementia risk.

Understanding development, maturation and decline of the brain will inform the development of strategies to maximize resilience in the face of decline or reserve. Identifying those at risk of decline and the factors that endow us with the ability to overcome brain change brought about by aging and disease will inform policy and health care.

Declaration of interests:

None

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