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. 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.

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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 et al., 2014).
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 a 1.5 Tesla GE NVi system. Three dimensional (3D) images of the brain were acquired with a T1 SPGR (TIW) 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 acquisition

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 × 256 × 256 mm³). 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 \( N = r^{-D} \), 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 (R² = 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 matter 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).

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 a known fractal dimension and the reliability of the method was measured through an intraclass correlation coefficient (ICC) between data acquired from two different scanners. The analyses were based on in-house developed software written in Matlab R2012a (Mathworks, Natick, MA, USA).

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 modeling 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 Eq. (1). Each variable and the intercept were modeled as a fixed effect. Here, each cognitive test was standardized as an IQ-type score ($aIQ_{ij}$, 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 $j$. $\beta_0$ is the intercept and represents the estimated cognitive ability at the age of 60 years, $e_{ij}$ 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.

$$aIQ_{ij} = \beta_0 + \beta_1 Age_{60} + \beta_2 FDWM + \beta_3 Vol + e_{ij}. \quad (1)$$

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).

$$aIQ_{ij} = \beta_0 + \beta_1 Age_{60} + \beta_2 FDWM + \beta_3 Vol + \beta_4 cIQ + e_{ij}. \quad (2)$$

Results

243 participants (128 males) were imaged aged around 68 years and of this original sample, 148 participants, (80 males) 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 sample 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 Fig. 3. The decline of complexity with age was further tested using a multilevel linear model which included volume as a covariate (Eq. (3)). Here, the relationship with age was maintained after adjustment for volume (WM or whole brain).

\[ FDWM_{i,j} = f_{0,j} + f_{1,j} \times \text{Age}_{i} + f_{2,j} \times \text{Vol}_{i} + e_{i,j}. \]  

Table 1 compares raw cognitive 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 a 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.

The multilevel linear model shown in Eq. (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.

After introduction of childhood ability into the model — MHT (Eq. (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. 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).

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.

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 et al., 2004; Staff, 2012) and there are also studies measuring specific volumes as correlates of cognitive aging (Saltheuse, 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 adolescence/young adulthood. 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 with age and 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 our model is less sensitive in those domains most subject to practice 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 have 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.

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 an 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 aging 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).

Table 2
The multilevel linear model results (Eq. (1)) 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), and general intelligence factor (g) were 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. \( \beta_0 \) is the intercept and represents the estimated cognitive ability at the age of 60 years. \( \beta_1, \beta_2, \beta_3, \beta_4 \) and \( \beta_5 \) are the coefficients for corresponding measures. \( \sigma^2 \) represents the residual or error and \( -2\log\text{likelihood} \) 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 \( p < .05 \).

<table>
<thead>
<tr>
<th>RPM</th>
<th>DS</th>
<th>AVLT</th>
<th>BLK</th>
<th>UFO</th>
<th>g</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta_0 ) intercept</td>
<td>95.8 (4.0)*</td>
<td>109.4 (4.1)*</td>
<td>104.3 (3.9)*</td>
<td>96.6 (3.9)*</td>
<td>92.8 (4.0)*</td>
</tr>
<tr>
<td>( \beta_1 ) Age</td>
<td>.41 (.39)</td>
<td>-.05 (4.1)*</td>
<td>-.42 (3.8)</td>
<td>.32 (.38)</td>
<td>.71 (.39)</td>
</tr>
<tr>
<td>( \beta_2 ) FD</td>
<td>1.78 (1.21)</td>
<td>2.44 (1.24)*</td>
<td>2.92 (1.14)*</td>
<td>-.71 (1.18)</td>
<td>1.26 (1.18)</td>
</tr>
<tr>
<td>( \beta_3 ) Volume</td>
<td>.085 (1.17)</td>
<td>-.135 (1.19)</td>
<td>-.115 (1.13)</td>
<td>4.91 (1.13)*</td>
<td>.06 (1.16)</td>
</tr>
<tr>
<td>( \sigma^2 )</td>
<td>220.8 (16.5)</td>
<td>217.6 (16.1)</td>
<td>210.8 (15.7)</td>
<td>204.9 (15.4)</td>
<td>221.2 (16.4)</td>
</tr>
<tr>
<td>( -2\log\text{likelihood} )</td>
<td>2931.7</td>
<td>2786</td>
<td>2931.7</td>
<td>2880.7</td>
<td>2981.9</td>
</tr>
</tbody>
</table>

Table 3
The multilevel linear model results (Eq. (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), and general intelligence factor (g) were 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; \( \beta_0 \) is the intercept and represents the estimated cognitive ability at the age of 60 years. \( \beta_1, \beta_2, \beta_3, \beta_4 \) and \( \beta_5 \) are the coefficients for corresponding measures. \( \sigma^2 \) represents the residual or error and \( -2\log\text{likelihood} \) 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 \( p < .05 \).

<table>
<thead>
<tr>
<th>RPM</th>
<th>DS</th>
<th>AVLT</th>
<th>BLK</th>
<th>UFO</th>
<th>g</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta_0 ) intercept</td>
<td>72.6 (5.6)*</td>
<td>74.4 (6.1)*</td>
<td>71.6 (6.0)*</td>
<td>61.0 (5.8)*</td>
<td>67.4 (6.3)*</td>
</tr>
<tr>
<td>( \beta_1 ) Age</td>
<td>.26 (.34)</td>
<td>-.017 (3.4)*</td>
<td>-.51 (3.6)</td>
<td>.18 (.35)</td>
<td>.64 (.37)</td>
</tr>
<tr>
<td>( \beta_2 ) Volume</td>
<td>-.42 (1.01)</td>
<td>-.153 (1.10)</td>
<td>-.129 (1.06)</td>
<td>4.67 (1.05)*</td>
<td>-.13 (1.11)</td>
</tr>
<tr>
<td>( \beta_3 ) FD</td>
<td>2.72 (1.05)*</td>
<td>3.00 (1.15)*</td>
<td>3.30 (1.07)*</td>
<td>-.14 (1.10)</td>
<td>1.60 (1.14)</td>
</tr>
<tr>
<td>( \beta_4 ) IQ MHT</td>
<td>.50 (0.05)*</td>
<td>.36 (0.05)</td>
<td>.33 (0.05)</td>
<td>.37 (0.05)</td>
<td>.36 (0.05)</td>
</tr>
<tr>
<td>( \sigma^2 )</td>
<td>104.9 (12.4)</td>
<td>188.0 (14.4)</td>
<td>186.3 (13.9)</td>
<td>175.1 (13.2)</td>
<td>206.3 (15.3)</td>
</tr>
<tr>
<td>( -2\log\text{likelihood} )</td>
<td>2827.7</td>
<td>2737.2</td>
<td>2887.3</td>
<td>2825.1</td>
<td>2956.6</td>
</tr>
</tbody>
</table>
Table 4
Pearson correlation between 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), and general intelligence factor (Δg) with age, where N is the number tested participants and * means p < 0.05.

<table>
<thead>
<tr>
<th></th>
<th>ΔRPM</th>
<th>ΔDS</th>
<th>ΔAVLT</th>
<th>ΔBLK</th>
<th>Δ UFO</th>
<th>Δg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔFD</td>
<td>0.18</td>
<td>0.20</td>
<td>-0.12</td>
<td>0.17</td>
<td>0.10</td>
<td>0.27</td>
</tr>
<tr>
<td>N</td>
<td>117</td>
<td>104</td>
<td>118</td>
<td>119</td>
<td>123</td>
<td>87</td>
</tr>
</tbody>
</table>

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.

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Declaration of interests
None.

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