Abstract

Objectives: to evaluate the role of childhood intelligence and white matter hyperintensities (WMH) in the prediction of the trajectory of fluid intelligence in healthy old people from age 78 to 81.


Received 23 December 2009; accepted in revised form 28 March 2011
Design: observational follow-up study from 1999 to 2002.
Setting: a university teaching hospital in Aberdeen, UK.
Participants: a total of 106 volunteers born in 1921, with childhood intelligence records at 11, recruited 1997–98 to a follow-up study.
Measurements: participants underwent brain MRI in 1999–2000, to obtain measurements of brain WMH using Scheltens’ scale and a test of fluid intelligence (Raven’s Progressive Matrices) on three occasions between 1999 and 2002.
Results: in a latent growth model, we found a significant association between childhood intelligence and the intercept, but not the slope, of fluid cognitive ability. Similarly, baseline WMH score was associated with the intercept of late life cognitive ability, but not the slope. Age at imaging was associated with slope but not intercept. There was no significant association between sex and intercept or slope of late life cognitive ability.
Conclusions: results suggest that brain MRI measures of WMH (attributed to cerebrovascular disease) and childhood intelligence significantly contribute to late life fluid cognitive ability but not to the trajectory of age-related change in fluid intelligence. We also show that age is associated with the cognitive trajectory from 78 to 81 years, even within our narrow age range sample. This may be a consequence of the recruitment pattern, with those having greater WMH burden, and who subsequently declined, being recruited later in the study.

Keywords: childhood intelligence, fluid intelligence, brain MRI, white matter hyperintensities, healthy old people, elderly

Introduction
Ageing has deleterious effects on both brain structure and cognition. Brain white matter hyperintensities (WMH) are common in old people without any apparent disease [1] and the association with vascular risk factors in non-demented elderly people is well established [2]. WMH are detected on MRI as parenchymal areas of increased signal intensity on T2-weighted images compared with brain tissue.

WMH become visible on MRI in subcortical, deep white matter and posterior fossa structures as focal areas of high signal and in the periventricular regions as bright caps and bands around the ventriciles. Hyperintensities are also seen in the basal ganglia. Here, the term WMH includes white matter, basal ganglia, posterior fossa and periventricular hyperintensities. Severity of WMH at baseline has been shown to be a predictor of WMH progression in late life, after accounting for age and blood pressure [3].

Fluid intelligence, which generally refers to reasoning and novel problem solving ability, is susceptible to age-related decline [4] and concerned with processes and assessed with tests that require on the spot processing [5]. The influence of education on fluid ability is unclear; Horn and Cattel 1967 have shown its influence is not significant [6], whereas Kaufman et al. 2009 have shown a significant positive effect with years of education [7]. The issue is further complicated by the causal direction of fluid ability and education with gifted individuals generally achieving more at school and receiving more education.

Age-related decline in ‘fluid intelligence’ arises in step with general slowing of information processing, frontal decline and other unidentified factors [8], begins in the third and fourth decades and possibly accelerates around age 50, but significant decline in longitudinal cognitive performance is seldom evident until adults are in their 60s or older [9].

Many studies demonstrate associations between the presence and severity of WMH and deficits in global and specific cognitive performance [10]. Our group has shown the negative influence of WMH on cognitive ability across most of the human life span [11]. However, in spite of numerous studies in ageing, the relationship between WMH and cognition has not yet been established clearly and little is known about this association in old age, especially in the ninth decade. Furthermore, it is unclear whether WMH is as important a predictor of cognitive decline in people aged 78–81 compared with earlier stages of late life.

Age-related cognitive decline is an aetiological heterogeneous phenomenon comprising the effects of incipient Alzheimer Disease, vascular dementia and other related conditions. However, it is also established that the main determinant of cognitive ability in late life is cognitive ability in childhood [12].

Here, we study the combined effects of MRI detected WMH at baseline and childhood intelligence on cognitive decline in normal old people, who were free from dementia using latent growth modelling (LGM). In this study, we are in the fortunate position of being able to account for pre-morbid ability in order to examine the effect of WMH on cognition without this significant confounding influence in old age.

We tested the effects of WMH and childhood intelligence on the level (intercept) and trajectory (slope) of fluid intelligence in a birth cohort for whom childhood intelligence was known. Longitudinal studies of predictors of cognitive change in the eighth and ninth decades are rare, but crucial to our understanding of cognitive ageing.

Methods
Participants
The Scottish Mental Survey of 1932 (SMS32) collected valid IQ-type test scores using the Moray House Test
have changed significantly during this period. We would not expect the WMH load to have changed significantly during this period.

MRI and image analysis

MRI was performed using a 1.0-T unit (Magnetom Impact; Siemens, Erlangen, Germany) in a teaching hospital setting. A T2-weighted fast spin-echo sequence (4,000/96 repetition time/echo time milliseconds; section thickness 5 mm; acquisition time 1 min 53 s; intersection gap, 1.5 mm) was acquired and used for assessment of WMH. WMH were identified and assessed on axial slices of the T2-W images using Scheltens' method [15]. Scores of different brain regions were added to obtain total scores of WMH.

Neuropsychological assessment

Our studies of brain imaging and cognition in the elderly take advantage of childhood mental ability archives maintained by the Scottish Council for Research in Education. The University of Aberdeen was given access to their archives in 1998 [16]. These data provide scores on a reliable test of general mental ability (MHT) comprising items that include language comprehension, verbal and non-verbal reasoning, spatial ability and simple calculations. In a subset of 1,000 children drawn from the SMS32, the MHT scores were highly correlated with Stanford–Binet scores \( r = 0.8 \) (0.81 in boys, 0.78 in girls) [17].

Raven's Progressive Matrices (RPM) [18] is a test of non-verbal reasoning in which progressively more complex series of abstract figures are completed by the participant choosing the next figure in the series from a group. Successful completion requires the participant to identify from the presented series the rule governing the series and then to apply that rule to the choice of next figure in the series. RPM was administered on successive occasions: on recruitment at age about 78 years, and then at intervals of about 15 months until age about 81 years.

Statistical analysis and data modelling

Latent growth modelling

Individual differences in the level and slope of RPM were analysed using LGM [19]. Analyses were conducted with the AMOS software package [20] using the Full Information Maximum Likelihood (FIML) approach to missing data [21]. Latent growth models are similar to random coefficient or mixed effect models for repeated-measure data, with random effects re-conceptualised as latent variables. Latent growth models have one latent variable capturing initial status (intercept) and one or more additional variables capturing change over time (slope). An overview of the model used for this cognitive measure can be seen in Figure 1. ‘LGM’ is sensitive and appropriate for longitudinal studies, allows for missing data, and is appropriate for studies of cognitive ageing.

In each case, we hypothesised that the longitudinal trajectory can be described by two latent variables, the intercept \( I \) and the slope \( S \) and that these latent variables have a causal association with the longitudinal cognitive measures, \( W1, W2 \) and \( W3 \) (RPM test in three waves). The variance in each, not explained by the latent variables (I and S) is accounted for by the error terms \( e1, e2 \) and \( e3 \), respectively. In addition, we hypothesised that the WMH, \( \text{SEX} \), age at recruitment at age about 78 years, and then at intervals of about 15 months until age about 81 years.

![Figure 1. The latent growth model. W1, W2 and W3 represent the RPM scores at 3 waves, respectively. I and S represent the intercept and slope. MHT is the Moray House Test score. Age is the age of the participant when first imaged.](http://ageing.oxfordjournals.org/)

S. Salarirad et al.
imaging (AGE) and a previous estimate of cognitive ability (MHT) all have a direct causal effect on I and S. The variance in I and S not explained by MHT, WMH, AGE and SEX is accounted for by error terms e4 and e5, respectively.

For each wave of RPM, the model was used to estimate the missing data using a FIML approach. The full data sets were then used to estimate the goodness of fit of the data to the model and the significance of the relationships between the variables.

The model was assessed using conventional estimates of goodness of fit. The model was considered to be a reasonable fit to the data if the following criteria were met: χ²/df < 2 [22], Normed Fit Index (NFI) > 0.9 [23]; Comparative Fit Index (CFI) > 0.9 [24] and root mean square error of approximation (RMSEA) <0.08 [25].

**Results**

Summary statistics and correlations are shown in Table 1. There is generally significant correlation between the repeated estimates of fluid cognitive ability in late life and childhood ability. An initial analysis of the model using the AMOS modification indices indicated that a superior model would be obtained if e1 and e2, e2 and e3, and e1 and the age at imaging, were correlated. These modifications were introduced.

The goodness of fit measures indicated a reasonable fit to the model with the following measures obtained: χ²/df = 1.00, NFI = 0.975, CFI = 0.999, RMSEA = 0.06. The estimated slope did not significantly differ from zero (mean = −0.051, SD = 2.6).

The standardised regression weights for each association are shown in Table 2. Childhood ability was associated with the intercept of late life cognitive ability, but not with the slope. WMH score was also associated with the intercept of late life cognitive ability, but not with the slope. Age at imaging was associated with the slope but not the intercept. However, the regression weights for the latter association approached significance (P = 0.063). There was no significant association between sex and either intercept or slope.

**Table 1.** The means, standard deviations (SD), and Pearson correlations between variables used in the models

<table>
<thead>
<tr>
<th></th>
<th>MHT</th>
<th>WMH</th>
<th>AGE (months)</th>
<th>RPM W1</th>
<th>RPM W2</th>
<th>RPM W3</th>
</tr>
</thead>
<tbody>
<tr>
<td>MHT</td>
<td>0.046</td>
<td>−0.080</td>
<td>0.317*</td>
<td>0.425*</td>
<td>0.367*</td>
<td></td>
</tr>
<tr>
<td>WMH</td>
<td>0.290*</td>
<td>−0.214*</td>
<td>−0.164*</td>
<td>−0.124*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGE</td>
<td>−0.104</td>
<td>−0.039</td>
<td>−0.121*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPM W1</td>
<td>0.811*</td>
<td>0.823*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPM W2</td>
<td>0.860*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>41.7</td>
<td>24.7</td>
<td>942.0</td>
<td>28.5</td>
<td>29.7</td>
<td>29.7</td>
</tr>
<tr>
<td>SD</td>
<td>11.1</td>
<td>8.9</td>
<td>4.5</td>
<td>8.7</td>
<td>8.4</td>
<td>8.7</td>
</tr>
<tr>
<td>n</td>
<td>106</td>
<td>106</td>
<td>106</td>
<td>103</td>
<td>81</td>
<td>76</td>
</tr>
</tbody>
</table>

WMH, white matter hyperintensities; MHT, Moray House Test; RPM, Raven progressive matrices in three waves: W1, W2 and W3.

**Table 2.** Regression weights (β) for each model, *P < 0.01

<table>
<thead>
<tr>
<th></th>
<th>RPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>I ← WMH</td>
<td>−0.254 (0.10)*</td>
</tr>
<tr>
<td>S ← WMH</td>
<td>−0.054 (0.07)</td>
</tr>
<tr>
<td>I ← MHT</td>
<td>0.28 (0.07)*</td>
</tr>
<tr>
<td>S ← MHT</td>
<td>−0.01 (0.05)</td>
</tr>
<tr>
<td>I ← SEX</td>
<td>−1.41 (1.61)</td>
</tr>
<tr>
<td>S ← SEX</td>
<td>0.58 (1.20)</td>
</tr>
<tr>
<td>I ← AGE</td>
<td>0.46 (0.25)</td>
</tr>
<tr>
<td>S ← AGE</td>
<td>−0.61 (0.22)*</td>
</tr>
</tbody>
</table>

The regression weights for the association between the variables of interest, (RPM, Raven progressive matrices; WMH, white matter hyperintensities; MHT, Moray House Test; I, intercept; S, slope).

**Missing data**

Assessing cognition in this longitudinal manner is vulnerable to biased withdrawal, with those who are failing more likely to withdraw from wave 2 or wave 3 testing. We found that those who did not return for wave 2 testing had mean RPM of 27.40 (SD = 8.85) and those who did not return for wave 3 testing had mean RPM 25.85 (SD = 8.64) confirming that those who were declining were more likely to withdraw. Comparing those that did not provide data with those that did at W2 and W3 in terms of WMH at baseline we found no significant difference, indicating that WMH did not predict withdrawal.

**Discussion**

These data support the proposal that brain MRI measures of cerebrovascular disease and childhood intelligence have a significant impact on level of fluid cognitive ability in late life, but not on the trajectory of decline of fluid intelligence. We have demonstrated that the main association with cognitive trajectory age 78–81 years is age, even within a sample all born in the same year. However, contrary to our hypothesis, we found no association between WMH and the trajectory of decline over a 3-year period.

Lack of a significant association with longitudinal change could be explained by the limitations of our study. Measuring longitudinal cognitive decline is difficult and confounded by learning or practice effects [26]. The absence of a significant group change in RPM can be attributed to practice effects cancelling out any ‘real’ decline. It may well be that with observation over a longer time period; decline would outweigh any practice effect and may reveal such an association. An alternative explanation is that, while WMH are associated with cognitive impairment, they are not the principal cause of cognitive decline in normal old people age 78–81.

It may be expected those with low current cognitive scores would decline faster due to an inability to compensate for age-related cerebral pathologies, that is WMH level or burden would affect cognitive decline. Introducing a direct effect of level on decline we found a regression...
weight of $-0.97$ ($P > 0.05$). This would imply that the variance in decline is not significantly explained by level of WMH when sex, age and MHT are accounted for.

These results are in keeping with the ‘cognitive reserve hypothesis’ of cognitive ageing, which proposes that adults with higher initial cognitive ability are better able to withstand the consequences of ageing and dementia [27] and will experience less cognitive decline in later life [28]. Such reserve may result from increased neural plasticity in those with higher childhood ability, allowing compensation for the neuropathological effects of ageing [29].

The association between childhood intelligence and late life cognitive abilities is well documented [30]. Their results based on more traditional statistical methods suggested that higher pre-morbid cognitive ability is protective of decline in later life. Our results indicate that after adjusting for age-related changes in the brain, the trajectory of decline was not influenced by childhood intelligence.

These results demonstrate for the first time, using an advanced modelling approach and a uniquely defined cohort, that the presence of WMH does not predict the trajectory of decline in fluid intelligence. It may well be that WMH can be considered as a record of cerebral stress brought about by vascular risk factors including lifestyle, experience and genetic susceptibility, and that the accumulation of more WMH and their subsequent influence on cognition are predominantly determined by these ongoing factors.

The present study adds to these findings by demonstrating that WMH are associated with a poorer level of cognitive ability, but not with its decline from age 78 to 81. Age at imaging was found to have a significant negative association with the RPM slope. That is, the older participants were at baseline MRI, even though this was within 12 months of younger participants, the faster they declined. This can be partly explained by those people with poorer ability volunteering later. Comparing the first 25 participants imaged with the last 25 in terms of their childhood intelligence showed that the first to volunteer had significantly better MHT scores ($P < 0.005$ t-test).

The association between age and slope demonstrated in our model came as a surprise given the narrow age range of recruitment and may be explained by an unintended bias in the order that they were initially recruited to the parent study. All participants were approach via their GP at the same time. The more affluent citizens came forward first. The age effect on trajectory observed may well represent socio-economic inequalities in health and subsequently cognition.

The strengths of this study include the narrow age range of the participants, minimising the confounding effect of age, comprehensive longitudinal cognitive data and, importantly availability of childhood intelligence as a uniquely valuable cognitive baseline. Participants in this MRI study were more intelligent at age 11 than those who did not consent to MRI. Characteristics of the cohort otherwise reflect those of the general population making relationships demonstrated here generalisable.

In previous studies that have measured cognitive performance in old age at two time points, it was difficult to sufficiently distinguish baseline performance from change in cognitive performance due to practice effects [29]. However, this study benefits from a new statistical model with more complex method of analysis which included three waves of cognitive testing in old age and provides better insights into the link between childhood cognitive ability and change in cognitive ability in old age. However, our data are further complicated by practice effects within each participant. These may mask the true decline and would imply that the effect sizes calculated are underestimates, although, the individual differences in decline may still be included in means, despite being masked by practice effects. Other potential weaknesses are the MRI acquisition and analysis methods, which, while no longer state of the art, remain valid for demonstration and semi-quantitative assessment of WMH. In addition the size of the sample and the duration of observation have restricted our study. The size of the sample limits the magnitude of the individual differences we are able to detect, although its size is comparable with similar studies in this age range. Extending the observation period would improve our study. However, this must be played off against attrition of this sample through death, illness and refusal, which is considerable in this age range and would compromise any findings.

Future work should determine whether the longitudinal WMH progression rate in a younger healthy cohort is a better predictor of cognitive decline than baseline in healthy elderly people. Using a voxel-based method of WMH measurement and modelling other brain image variables, such as volumes, would give a more complete picture of the ageing brain.

**Key points**

- Demonstrating that WMH are associated with poorer cognitive ability, but not decline from age 78 to 81.
- Childhood intelligence significantly contribute to late life fluid cognitive ability not to the trajectory of age-related change.
- Age is the main association with cognitive trajectory age 78–81 years, even within a sample all born in the same year.

**Acknowledgments**

S.S., R.T.S. and A.D.M. are part of the Scottish Imaging Network SINAPSE www.sinapse.ac.uk.

**Conflicts of interest**

None declared.
Funding

This work was supported by grants from the Chief Scientist Office of the Scottish Government Health Directorates (C2785) and The Millar McKenzie Trust.

Supplementary data

Supplementary data mentioned in the text is available to subscribers in Age and Aging online.

References


Received 23 August 2010; accepted in revised form 28 March 2011