Brain White Matter Tract Integrity and Cognitive Abilities in Community-dwelling Older People: The Lothian Birth Cohort 1936

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Abstract

Objective: The present study investigates associations between brain white matter tract integrity, and cognitive abilities in community-dwelling older people (N=655). We explore two potential confounds of white matter tract-cognition associations in later life: 1) whether the associations between tracts and specific cognitive abilities are accounted for by general cognitive ability (*g*); and 2) how the presence of atrophy and white matter lesions affect these associations.

Method: Tract integrity was determined using quantitative diffusion MRI tractography (tract-averaged fractional anisotropy, FA). Using confirmatory factor analysis, we compared 1st-Order and bi-factor models to investigate whether specific tract-ability associations were accounted for by g.

Results: Significant associations were found between *g* and FA in bilateral anterior thalamic radiations ($r=0.16$ to 0.18, $p<0.01$), uncinate ($r=0.19$ to 0.26, $p<0.001$) and arcuate fasciculi ($r=0.11$ to 0.12, $p<0.05$), and the splenium of corpus callosum ($r=0.14$, $p<0.01$). After controlling for *g* within the bi-factor model, some significant specific cognitive domain associations remained. Results also suggested that the primary effects of controlling for whole brain integrity were on g associations, not specific abilities.

Conclusions: Results suggest that *g* accounts for most of, but not all, the tract-cognition associations in the current data. When controlling for age-related overall brain structural changes, only minor attenuations of the tract-cognition associations were found and these were primarily with g. In totality, the results highlight the importance of controlling for g when investigating associations between cognitive specific abilities and neuropsychology variables.

Key Words: Cognitive ability; tractography; white matter integrity; bi-factor model.

Introduction

Cognitive ability is associated with many important life outcomes. Recent research suggests communicative white matter pathways are an important aspect of its neurostructural foundation (Deary, Penke and Johnson, 2010). The retention of cognitive functioning is of particular importance to successful ageing (Deary et al., 2009); with a growing body of research exploring the associations between cognitive ability and measures of white matter integrity in the brain (see Madden et al. 2012 for a recent review).

Diffusion tensor MRI (DTI) is a widely used technique for studying brain connectivity (Sullivan and Pfefferbaum, 2006), providing biomarkers of white matter integrity, in particular fractional anisotropy (FA) which measures the directional coherence of water molecule diffusion. In normal ageing, FA shows a gradual mean decrease, indicative of decreasing white matter tract integrity (Wozniak and Lim, 2006). Here we focus on studies which have utilised DTI tractography as this method is applied in the current study (see Methods).

DTI tractography studies of associations between white matter tract integrity and cognitive ability in older people have provided inconsistent findings (Madden et al., 2012). Higher FA in the genu of corpus callosum has been associated with working memory (Davis et al., 2009; Zahr, et al., 2009; Voineskos et al., 2012), while significant associations have been found between integrity of the right uncinate fasciculus and spatial working memory (Davis et al., 2009), and the left cingulum and performance on verbal paired associates (a test of verbal declarative memory) and executive function (Davis et al., 2009; Sasson et al., 2011). Penke et al. (2012), using a subsample of the participants from the current study (n=420), found that general factors of white matter integrity derived from three brain imaging biomarkers (FA, longitudinal relaxation time (T_1) and magnetisation transfer ratio) significantly predicted general intelligence, and that this prediction was fully mediated by

processing speed. Though Penke et al. (2012) provided strong support for the associations between white matter tract integrity and cognitive ability, specific tract associations were not considered.

Inconsistency in associations between white matter tracts and cognitive abilities make it difficult to provide substantive theoretical explanations for the associations. For example, the Parieto-Frontal Integration Theory (P-FIT) has been proposed as an integrative framework for understanding the associations between the brain and intelligence (Jung and Haier, 2007). P-FIT suggests that the arcuate fasciculus, which forms part of the superior longitudinal fasciculus, may be particularly important in understanding tract-cognitive ability associations (Jung and Haier, 2007; Colom et al., 2009; Turken et al., 2008). However, as can be seen from the above brief review of studies in ageing samples, the arcuate fasciculus has not been consistently associated with cognitive ability.

In the current study, we explore two possible methodological reasons for the inconsistent findings in ageing samples. First, the studies documented above assess both general and specific (e.g. verbal, spatial, memory) cognitive abilities. From such studies, it is not clear the extent to which correlations between white matter tract integrity and specific cognitive abilities are accounted for by general cognitive ability. This is of interest since each cognitive test score will comprise a proportion of variance which is attributable to specific ability, a proportion which is attributable to general ability, as well as a proportion of error variance (see Deary, et al., 2010 for discussion in the context of neuroscience). The importance of partitioning this variance in neuroimaging studies of cognitive ability has been previously noted by a number of authors (e.g. Colom & Thompson, 2011; see also Chen, West & Sousa, 2006 for a more general discussion), but no studies to date have been able to do so using highly robust methods.

Figures 1 and 2 graphically depict how test score variance is decomposed based on the methods applied to study the associations of cognitive ability and neuroimaging measures. Figure 1 panel A depicts perhaps the most common situation, in which a single cognitive test score is associated with a neuroimaging measure (e.g. Davis et al., 2009; Sasson et al., 2009; Zahr et al., 2009). The test score comprises general ability variance, specific ability variance, and error variance. In such circumstances, it is not possible to know which aspect of score variance is driving the correlation with the external measure. It is also important to note that, if researchers choose to sum a number of standardized scores (z-scores) from individual tests into a single composite, the same effect as is depicted in Figure 1 panel A occurs, and variance cannot be separated.

(Insert Figure 1 about here)

In order to try and estimate the extent to which specific ability variance associates with neuroimaging measures, some authors (e.g. Colom et al., 2009; Haier et al., 2009; Tang et al., 2010), regress a general cognitive ability score (e.g. a sum score or factor score), on individual test scores, and associate the resultant residual with neuroimaging measures (Figure 1, panel B). Although such methods partial out general ability variance, the residual term still consists of both specific ability and error variance, thus the association remains muddied.

Both situations described above are based on analyses of single variables, be they individual test scores or summed composites. In recent years, it has become increasingly common to apply exploratory and confirmatory factor analytic methods (EFA and CFA), and the more general structural equation modelling (SEM) framework to investigate associations between cognitive ability and neuroimaging measures (see Kievet et al., 2012; and Penke and Deary, 2010, for discussions). In SEM, a measurement model is specified in which multiple cognitive tests are used to estimate latent cognitive ability factors based on the common

variance across test scores. Simultaneously, the estimated latent factors can be associated with the neuroimaging measures of interest. A primary advantage of SEM approaches is that latent variables are error free (Bollen, 1989), as they are estimated from only common variance between tests. Error variance is explicitly modelled in SEM as a residual term on observed variables (test scores).

SEM is, therefore, highly useful in accounting for one source of variance, error variance, which may confound associations between cognitive and neuroimaging measures. However, some specifications of measurement models fail to separate general cognitive ability variance from specific ability variance. For example, in a 1st -order factor model (Figure 2, Panel A), common variance associated with both the specific ability and general cognitive ability is conflated in the latent variable. Once again, it is not clear whether the association with neuroimaging variables is driven by general or specific abilities. Figure 2 panel A depicts only a single latent variable; however, the above statement remains true when multiple 1st -order latent variables are modelled.

(Insert Figure 2 about here)

A possible solution to this problem is the application of bi-factor models. Bi-factor modelling has been advocated as the best method for simultaneously measuring both specific and general cognitive abilities (Gignac, 2008; Schmiedek and Li, 2004; Brunner, *In Press;* for technical details on the estimation of bi-factor models see Reise, Moore & Haviland, 2010; Yung, Thissen & McLeod, 1999). Figure 2 panel B depicts the decomposition of test score variance within a bi-factor model. Here, a latent general cognitive ability factor is estimated based on all test scores, whilst specific ability latent factors are estimated from a subset of test scores hypothesized to measure a specific ability. In Figure 2 panel B for example, tests 1 to 3 may be arithmetic tests, whereas tests 4 and 5 may be verbal tests. Thus, bi-factor modelling provides a framework within which test score variance can be

decomposed into its constituent parts, which can then be associated with external variables. To the authors' knowledge, no studies of white matter tract integrity have applied a bi-factor modelling approach.

In the current study we seek to compare the results of 1st -order and bi-factor models within the SEM framework, in order to help understand the extent to which brain white matter tract associations with specific cognitive abilities are caused by cognitive variation unique to that ability or general cognitive ability. The reliable identification of specific and general cognitive ability factors, and their associations with neuroimaging biomarkers, may be of particular importance in ageing samples (Schmiedek and Li, 2004), given that specific abilities such as processing speed, memory, reasoning and spatial skills start to decline much earlier than experience-based specific abilities such as vocabulary and knowledge (Salthouse, 2011).

A second potential methodological issue the current study seeks to explore is to what extent are any cognitive associations with specific white matter tracts owed to more general aspects of age-related brain degeneration. In general, the ageing brain displays both grey and white matter atrophy, and white matter lesions (Anderton, 2002) as well as accumulating microstructural changes that are not sufficient to show as overt lesions on conventional imaging. These features of the ageing brain have been suggested to cause disconnections in cognitive networks (Bullmore and Sporns, 2009), and to be predictive of cognitive ability in later life (Deary et al., 2003). Here we investigate whether these general aspects of brain integrity impact upon tract-cognitive ability associations, and whether these attenuations are stronger for general or specific cognitive abilities.

Methodology

Participants

Participants were drawn from the Lothian Birth Cohort 1936 (LBC1936), a longitudinal study of cognitive ageing. Most of the participants took part in the Scottish Mental Survey 1947 (SMS1947) at about age 11 years, and were resident in Edinburgh and its surrounding area (the Lothians) at recruitment to Wave 1 of the study at about age 70 years. Protocols for recruitment, testing and brain MRI are reported in detail elsewhere (Deary et al., 2007; Deary et al., 2011; Wardlaw et al., 2011).

From the original 1091 participants in Wave 1 (mean age = 69.5 years, s.d = 0.8), 866 participants returned in Wave 2 (mean age = 72.5 years, s.d = 0.7), of which 700 provided some usable data from structural and diffusion MRI. In the present study, a cut-off of 25% was applied for missing data, which resulted in 39 subjects being removed for missing MRI data, and one for missing cognitive ability data. Further, subjects were removed from analysis if they scored below 24 on the Mini Mental State Exam (Folstein et al., 1975), as this is often considered an indicator of possible pathological cognitive impairment. Five subjects were removed based on this criterion. A total sample of 655 was used in the current study.

Ethical Approval

Ethical permission for the LBC1936 study protocol was obtained from the Multi-Centre Research Ethics Committee for Scotland and the Lothian Research Ethics Committee. All research was carried out in compliance with the Helsinki Declaration.

Cognitive Ability Measures

The current analyses used 18 cognitive ability subtest scores. Full details of the cognitive tests have been published previously (Deary, et al. 2007; also Supplementary Material A).

Briefly, we used seven subtest scores from the Wechsler Memory Scale III (WMS-III^{UK}: Wechsler, 1998a; Logical Memory Immediate and Delayed recall, Verbal Paired Associates Immediate and Delayed recall, Digit Span Backward, and Spatial Span forward and backward); five subtests from the Wechsler Adult Intelligence Scale III (WAIS-III^{UK}:

Wechsler, 1998b; Block Design, Matrix Reasoning, Digit Symbol Coding, Symbol Search, Letter-Number Sequencing); the National Adult Reading Test (NART: Nelson and Wilson, 1991), the Wechsler Test of Adult Reading (WTAR: Holdnack, 2001), verbal fluency (Lezak, 2004), an inspection time task of visual information processing (Deary et al., 2004), and simple and 4-choice reaction time tasks (Deary, Der and Ford, 2001).

Image Acquisition

Full details of the image acquisition can be found in Wardlaw et al. (2011). In brief, participants underwent whole brain structural and high angular resolution 2 mm isotropic voxel diffusion MRI (7 T2- and 64 diffusion-weighted (b = 1000 s/mm2) axial single-shot spin-echo echo-planar imaging volumes) on a GE Signa Horizon HDxt 1.5T clinical scanner (General Electric, Milwaukee, USA) using a shelf-shielding gradient set (maximum gradient 33 mT/m), and an 8-channel phased-array head coil. The structural MRI included T2-, T2*- and FLAIR-weighted scans, and a high resolution T1-weighted volume scan.

Tract segmentation

The diffusion MRI data were preprocessed using FSL tools (FMRIB, Oxford, UK; http://www.fmrib.ox.ac.uk) to extract the brain, remove bulk patient motion and eddy current induced artefacts, and generate parametric maps of FA. Underlying connectivity data were generated using BedpostX/ProbTrackX with the default settings of a two-fibre model per voxel, and 5000 probabilistic streamlines with a fixed separation of 0.5 mm between successive points (Behrens et al., 2007).

Twelve tracts of interest were identified using probabilistic neighbourhood tractography, a novel approach for automatic and reproducible tract segmentation (Clayden, Storkey and Bastin, 2007), as implemented in the TractoR package for fibre tracking analysis (Clayden et al., 2011; http://www.tractor-mri.org.uk). Briefly, this method works by segmenting the same fasciculus-of-interest across a group of subjects from single seed point

tractography output by modelling how individual tracts compare to a predefined reference tract in terms of their length and shape (Clayden et al., 2007). In practice, multiple native space seed points are placed in a cubic neighbourhood of voxels (typically 7 × 7 × 7) surrounding a seed point transferred from the centre of the reference tract, which is defined in standard space, with the tract that best matches the reference chosen from this group of 'candidate tracts'. Tracts assessed were the genu and splenium of corpus callosum, and bilateral anterior thalamic radiations, rostral cingulum bundles, arcuate, uncinate and inferior longitudinal fasciculi. Tract masks generated by probabilistic neighbourhood tractography were overlaid on the FA parametric maps and tract-averaged values of these biomarkers, weighted by the connection probability, determined for each tract in every subject.

To ensure that the segmented tracts were anatomically plausible representations of the fasciculi of interest, a researcher (SMM) visually inspected all masks blind to the other study variables and excluded tracts with aberrant or truncated pathways. In general, probabilistic neighbourhood tractography was able to segment the 12 tracts of interest reliably (See Clayden et al, 2009) in the majority of subjects, with tracts that did not meet quality criteria, such as truncation or failing to follow the expected path, ranging from 0.3% for the splenium of corpus callosum to 16% for the left anterior thalamic radiation, with a mean of 5%. (Failures in tract segmentation are typically caused by underlying tractography errors in BedpostX/ProbTrackX resulting from finite image resolution, small registration mismatches in the component diffusion MRI volumes and measurement noise.) From the point of view of substantive investigations, the 12 tracts represent a good balance between projection, commissural and association fibres which connect a wide variety of brain regions.

Structural MRI volumetric analysis

Brain tissue volumes were measured blind to participant information using a validated multispectral segmentation tool, MCMxxxVI (Wardlaw et al., 2011; Valdés Hernández et al.,

2010; http://sourceforge.net/projects/bric1936), from the co-registered structural MRI data. The tissue compartments measured were intracranial volume (ICV; all soft tissue structures inside the cranial cavity including brain, dura, cerebrospinal fluid (CSF) and venous sinuses); total brain tissue volume (brain tissue volume without the superficial or ventricular CSF); CSF (all CSF inside the cranial cavity including the ventricles and superficial subarachnoid space); and white matter lesion volumes. Since MCMxxxVI does not distinguish hyperintense and hypointense areas of cerebromalacea due to old cortical/subcortical infarcts or lacunes from white matter lesions and CSF respectively, these areas were masked out from the respective binary masks by thresholding the FLAIR sequence using a region-growing algorithm from Analyze 10.0 (http://www.analyzedirect.com/Analyze). Where stroke lesions were confluent with white matter lesions, the boundary between the two was determined by comparison with the contralateral hemisphere and neuroradiological knowledge.

Visual white matter lesion rating

White matter lesion burden was also rated from T2- and FLAIR-weighted sequences using the Fazekas scale by an expert neuroradiologist. Lesions were coded depending on whether they were located in subcortical or periventricular white matter and the individual scores summed to give an overall lesion rating (Wardlaw et al., 2011).

Statistical Analysis

We performed two primary analyses. Firstly, associations between tract integrity and specific cognitive abilities were compared, with and without controlling for *g*, using 1st-order and confirmatory bi-factor models. In the second, we considered whether atrophy and white matter lesion load, the latter assessed using both volume measurements and visual rating scores, accounted for the associations between tract integrity and cognitive ability. The input data for all models were standardized residuals after regressing age, sex and handedness on tract integrity measures, and age in days and sex on each cognitive test.

1st-Order versus Bi-factor Models

In the first set of analyses, EFA was initially applied to identify the appropriate number of first-order cognitive ability factors (cognitive abilities) from our battery of 18 tests. Next, confirmatory factor analysis was used to estimate both 1st-order and bi-factor structural models for the cognitive tests, based on the results of the exploratory analysis. Here, a 1st-order model is defined as containing only specific cognitive abilities as factors. The bi-factor model contains both a general cognitive ability factor and specific cognitive ability factors. Structural equation models were estimated in which FA from each of the 12 segmented tracts was correlated with the cognitive ability factors in both models.

Exploratory Factor Analysis: EFA was conducted using maximum likelihood estimation and oblique Equamax rotation. The number of factors to extract was determined using parallel analysis (PA:Horn, 1965) and Minimum Average Partial (MAP:Velicer, 1976), using the 'psych' package in R.2.13.2 (Revelle, 2011; http://www.r-project.org).

Confirmatory Factor Models: The exploratory factor solution was tested in both 1st-Order (Figure 3) and bi-factor (Figure 4) models. In the 1st-order model, specific cognitive abilities are modelled by factor loadings on specific subtest scores. The specific cognitive ability factors are allowed to correlate, but no general cognitive factor is included. In the bi-factor model, each specific subtest score is loaded on both its specific factor, and a general cognitive ability factor, thereby accounting for the variance in performance on that test which is general, not due to specific cognitive factors.

In both the 1st-order and bi-factor models, a number of correlated residuals were included. In a confirmatory factor model, residuals contain the proportion of variance not accounted for by the latent construct, namely unique and error variance. The battery of cognitive tests used in the current study includes subtests for which two scores have been retained, e.g., immediate and delayed recall on Verbal Paired Associates. Such scores will

share test-specific variance which would not be expected to be explained by the latent construct. See Results for full details of the residual correlations included.

Structural Equation Models: In the structural models, the 12 tract-averaged FA values were included and allowed to correlate with each cognitive ability factor. The tract-averaged FA values were allowed to correlate, following the empirical findings of a general integrity factor using a subsample of the LBC1936 data (Penke et al., 2012).

Covarying for total brain atrophy and white matter lesion load.

In the second set of analyses, the 1st-order and bi-factor models were re-estimated including total white matter lesion rating score (Fazekas), white matter lesion volume as a percentage of ICV, and brain atrophy (calculated as: Atrophy = (1 – (Total Brain Tissue Volume/ICV))*100)as covariates in the model. The aim of the second analysis was to ask whether specific white matter tract- cognitive ability associations were attenuated by controlling for more general measures of brain integrity.

Structural Equation Model Estimation and Evaluation

All models were estimated using Full Information Maximum Likelihood (FIML) estimation in Mplus 6.0 (Muthen and Muthen, 2010). FIML was used because the present study's data set contained a small proportion of missing data (see Results for details). FIML is considered to be one of the most robust missing data techniques (Enders and Bandalos, 2001).

Model fit was evaluated based on recommendations from the Monte Carlo simulation studies of Hu and Bentler (1998, 1999), and a review by Schermelleh-Engel, Moosbrugger, and Muller (2003). We adopted cut-off points of ≤0.05 for the standardised root mean square residual (SRMR), ≤0.06 for the root mean square error of approximation (RMSEA), and ≥0.95 for the Tucker-Lewis Index (TLI) and Comparative Fit Index (CFI). If a model displays appropriate levels of fit, it is considered to be a good representation of the data and the researcher can consider substantive interpretations of parameter estimates.

Results

Descriptive Statistics

Descriptive statistics for the cognitive test results, tract-averaged FA values and covariates are presented in Table 1. The greatest proportion of variance missing from any individual variable is 16.0 % (n=105) for the left anterior thalamic radiation. Across all variables, the proportion of missing data was low. Simple Reaction Time and Inspection Time Total score displayed the greatest levels of skew or kurtosis (4.09 and 3.82 respectively). However, on inspection of the histograms, these deviations from normality were considered small. All other variables displayed close to normal distributions.

(Insert Table 1 about here)

1st-Order versus Bi-factor

Results of MAP analysis suggested that 2 factors should be retained from the analysis of the 18 cognitive tests, whereas PA suggested 7 factors should be retained. All factor solutions with between 2 and 7 factors were considered. The 7, 6 and 5-factor solutions all contained under-identified factors (fewer than 3 indicators), and/or Heywood cases (implausible loadings > 1.00). Therefore, these solutions were rejected. The 4-factor solution (see Supplementary Material Table B1) was retained as it represented the most psychologically-interpretable solution retaining the greatest number of specific cognitive factors. The four factor solution also remained stable across different forms (Geomin, FC-Parsimax and Oblimin) of oblique rotations. Factor consistency across rotational methods is generally considered as a marker of a robust solution (Sass and Schmitt, 2010). The four factors were labelled Knowledge, Verbal Declarative Memory, Processing Speed, and Non-Verbal Reasoning.

Next, we tested the EFA solution as a 1st-order confirmatory factor analytic (CFA) model (Figure 3) and a bi-factor CFA model (Figure 4). Across both models, three correlated

residuals were included between Logical Memory Immediate and Delayed Recall, Simple and Choice Reaction Time, and Digit Span Backward and Letter-Number Sequencing. Though the inclusion of a greater number of correlated residuals would have improved model fit, it also would have resulted in identification problems in the bi-factor model.

Both 1st-order (Figure 3) and bi-factor (Figure 4) confirmatory models showed acceptable to excellent levels of fit across all indices. The specific cognitive ability factors in the first 1st-order model correlated significantly and positively (0.43 to 0.76; mean = 0.56).

(Insert Figure 3 about here)

In the bi-factor model, retaining all correlated residuals from the previous model (Figure 4), the factor loadings of each subtest on *g* were generally moderate to large (>0.40), with the exception of Simple Reaction Time (-0.27), Spatial Span Forward (0.32) and Backward (0.38), and Inspection Time (0.38). The average general factor loading was 0.51.

(Insert Figure 4 about here)

Table 2 presents the results when all 12 tract-averaged FA measurements are included in each of the models. In the discussion that follows we focus on the raw associations. Given the current sample size, a significance level of $p<0.05$ and 80% power, the current study is powered to identify associations of approximately ±0.11 and greater. Further, applying a Bonferroni correction to the 1st-order and bi-factor models resulted in corrected *p*-values of 0.0011 and 0.0008 respectively. As a result, we consider all associations significant to $p<0.001$ to be robust to multiple comparisons, and values at $p<0.01$ to be highly indicative given the conservative nature of Bonferroni corrections.

In the 1st-order factor model (Figure 3), which contains only specific cognitive abilities, a large number of significant tract associations are found between posterior-frontal tracts, especially with Processing Speed and Non-Verbal Reasoning (Table 2). A number of

smaller significant associations (<0.11) are also seen, again in posterior-frontal tracts, with Knowledge and Verbal Declarative Memory.

In the bi-factor model (Figure 4), in which *g* is controlled for, most of the significant associations with specific cognitive ability factors are markedly attenuated, and become non-significant (Table 2). These results suggest that, in the current battery of tests, the associations between specific factors of cognitive ability and white matter tract integrity are largely driven by *g*, and not by separable specific cognitive ability variance.

(Insert Table 2 about here)

As can be seen in Table 2, the strongest associations with *g* are found for bilateral uncinate fasciculi (Left = 0.19; Right = 0.26; $p<0.001$) and anterior thalamic radiations (Left = 0.16, $p<0.01$; Right = 0.19, $p<0.001$). A small number of associations with specific cognitive abilities remain significant after controlling for g. In the bi-factor model, the right uncinate fasciculus is significantly associated with Knowledge (-0.16, $p<0.01$). The left inferior longitudinal fasciculus (0.16, $p<0.001$) and right anterior thalamic radiation (0.14, $p<0.05$) are both associated with Processing Speed. The right uncinate fasciculus (-0.14, $p<0.05$) is associated with Non-Verbal Reasoning. The left arcuate fasciculus (-0.10, $p<0.05$) is associated with Verbal Declarative Memory.

Covarying for atrophy and white matter lesion load

Next, we re-estimated both the 1st-order and bi-factor models using input data residualised for whole brain integrity variables (Table 2, columns 4 and 7 labelled Residuals). The results for the bi-factor model suggest most attenuation of associations were small, with all parameter changes at the second decimal place, and the greatest change in estimate being 0.08. For a number of associations, particularly with g, this resulted in estimates becoming non-significant. However, the strongest associations between specific tracts and g across

models remained significant, namely the right anterior thalamic radiation (0.12, $p<0.05$), and the left (0.13, $p<0.05$) and right (0.22, $p<0.001$) uncinate fasciculus.

Further, it is also of interest that the residual attenuations on specific ability associations are generally greater in the 1st-order model than in the bi-factor model. This suggest that much of the attenuation in tract-cognitive associations is attributable to g, as when this variance is separated in the bi-factor model, the greatest attenuations are seen in g, not specific factor associations.

Discussion

The results of the current study lead to three main conclusions. Firstly, we provide further evidence that failure to control for *g* when investigating the associations between specific cognitive abilities and neuroimaging biomarkers could result in misleading, spurious or inflated associations with the specific cognitive factors. Second, integrity in a large number of white matter tracts, primarily the uncinate fasciculus and anterior thalamic radiation, were associated with general cognitive ability, *g*, in our ageing sample. However, a small number of associations with specific tracts remained, suggesting further robust analyses of specific associations would be beneficial. Thirdly, the results suggest that, despite loss of brain structural integrity, i.e., increased atrophy and white matter lesion load, associations between white matter tract integrity and cognitive ability are independent of these general indicators of brain structural decline.

In the current sample, higher general cognitive ability was significantly associated with greater white matter tract integrity in both right and left uncinate fasciculi and anterior thalamic radiations. In the limited research published to date on individual tract-cognitive ability associations in ageing samples, neither of these two tracts has commonly been associated with *g*. However, Zahr et al. (2009) found significant age effects for the uncinate

fasciculus when comparing small samples of young (mean age 25.5 years; n=12) and older (mean age 77.7 years; n=12) participants.

Across all individual tracts, the right uncinate fasciculus showed the greatest number of significant associations with both specific and general cognitive ability, supporting previous findings in younger samples (Yu et al., 2008). The right uncinate fasciculus is larger than the left leading some to suggest greater connectivity and information flow between the right fronto-temporal regions it connects (Highley et al. 2002). The number of significant associations found in the current study may therefore be a reflection of the greater connectivity of the right uncinate fasciculus.

Outside of the associations with *g*, the strongest bilateral association between any tract and cognitive ability was seen for the inferior longitudinal fasciculus and processing speed. This in part confirms prior findings of Davis et al. (2009), yet there remains much uncertainty as to the functional role of the inferior longitudinal fasciculus (Ashtari, 2012). Clearly the current finding of a specific association requires replication, but the large sample and association after controlling for general cognitive ability suggest that further studies on speed of processing may be fruitful.

The importance of estimating specific cognitive abilities, controlling for g, was demonstrated in comparing the results from the 1st-order and bi-factor models. In the 1st-order model, a large number of the significant associations were found for processing speed and non-verbal reasoning, but were attenuated and became non-significant when *g* was controlled for in the estimation of specific ability factors using a bi-factor model. Clearly the associations of the specific abilities with white matter tract integrity were driven, at least in part, by the variance in test scores associated with general cognitive ability, not specific abilities.

The current study demonstrates the utility of bi-factor modelling in ageing samples (Brunner, *In Press*; Schmiedek and Li, 2004), to control for general cognitive ability in the associations between narrow level specific abilities and neuroimaging variables (Colom and Thompson, 2011; Gignac, 2008; Chen, Sousa and West, 2006). This is an important extension to past studies which have generally taken one of two approaches to controlling for g, either regressing out a sum score for g from sum scores for specific abilities (e.g. Colom et al., 2009), or by using a hierarchical factor analytic procedure, such as the Schmid-Lieman transformation, to extract factor scores for both g and specific abilities (e.g. Glascher et al., 2010). The bi-factor approach has a number of distinct advantages, most notably the ability to simultaneously estimate associations between criterion variables and specific and general cognitive ability factors, and the robust nature of the estimates based on latent constructs free from measurement error. Further, the bi-factor models has a number of methodological advantages such as being free from the proportionality constraints present in higher-order models and methods such as the Schmid-Lieman transformation (Schmiedek and Li, 2004).

Our findings are in conformity with previous suggestions from the literature (e.g. Colom and Thompson, 2011), and may go some way to explaining the variability of tract-cognitive ability associations found across studies. Commonly in neuroimaging studies of cognitive ability, researchers use single sub-tests or small batteries of sub-tests either to measure *g,* or to measure specific abilities. These batteries are often sum scored, and not measured as latent constructs using SEM (see Figure 1). When single tests are measured, it is not possible to determine the extent to which associations are driven by *g,* or specific abilities, as any individual tests vary in the level to which they measure *g* and specific abilities (Major, Johnson and Bouchard, 2011). Thus, in any individual study, it may not be immediately apparent exactly what cognitive ability factor is being measured, and how much effect *g*, when not explicitly measured, is exerting on the associations found. If researchers

are interested in associations of specific abilities and external constructs, we recommend gathering data on multiple sub-tests.

Consideration of the results of the models controlling for whole brain integrity (global atrophy and white matter lesion load) further emphasizes the importance of controlling for g. In the 1st-order model, attenuation in associations between tracts and specific cognitive ability factors was present for all specific ability factors, suggesting whole brain integrity is significantly associated with each of these factors. However, when controlling for g in the bi-factor model, especially in the case of Verbal Declarative Memory, Processing Speed, and Fluid Ability, the attenuations became much smaller, and the larger effects were seen in the g associations with specific tracts, suggesting that whole brain integrity more strongly influences g, not specific abilities.

There are a number of limitations to the current study. Firstly, the specific cognitive ability factors within the bi-factor model were identified by a limited number of individual test scores. In an ideal case, more individual tests would have been included in the battery to ensure over identification of these factors. Secondly, a number of studies (e.g. Haier et al., 2005; Tang et al., 2010) have suggested sex differences in tract-cognitive ability associations. In the current study, we chose not to investigate sex differences, and to control for variance in tests due to sex. Future research may consider if the patterns of association found here are consistent across the sexes. Thirdly, the observed lack of attenuation of the tract cognition associations by whole brain integrity variables, may result from the measure of global atrophy being relatively insensitive to ageing related white matter damage which typically affects subcortical structures and leads to ventricular enlargement. Finally, the present cohort was relatively healthy and the results should not be taken to represent advanced stages of ageing related brain atrophy or white matter lesions.

However, the current study also has a number of major strengths. Firstly, the availability of a large sample from a narrow range age cohort eliminates many of the potential confounds of age in cross-sectional studies. Secondly, by applying probabilistic neighbourhood tractography, we were able to segment a large number of major white matter tracts, and measure tract-averaged FA in these pathways both reliably and automatically. Thirdly, we extend the previous work of Penke et al. (2012) by focussing on specific tract associations using a larger sample. Forth, we used both visual and computational measures of white matter lesion load as they provide different, but complementary, information on disease burden. Finally, we applied a broad battery of psychometric tests which, in part due to our large sample size, allowed us to model latent cognitive ability factors within a structural equation model framework. The current study is, to the authors' knowledge, the only study to combine bi-factor modelling of general and specific cognitive abilities with tractography estimates of tract integrity. Collectively, we provide highly robust estimates of tract-cognitive ability associations.

In summary, the current study reports associations between white matter tract integrity and cognitive abilities in a large, age-homogeneous sample of relatively healthy older people. It finds that the associations of specific cognitive abilities with external variables may be biased if researchers fail to account for *g*; that is, significant associations may not be due to a specific, but general cognitive ability. However, once variance associated with *g* was controlled for, a number of specific ability –specific tract associations remained. Importantly, this finding suggests the potential fruitfulness of further research based on robust methodologies in the investigation of specific cognitive abilities. Lastly, the results demonstrate that, in the current sample, controlling for atrophy and white matter lesion load does not alter tract-cognitive ability associations.

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There are no actual or potential conflicts of interest with regard to this manuscript and any of its authors.

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Figure Captions

Figure 1: Diagrammatic representations of variance decomposition in two methods for estimating the association between cognitive ability and neuroimaging variables. Panel A depicts a simple correlation between an individual cognitive test or sum score. Panel B depicts controlling for a total g or IQ score on a single test or sum score. Rectangles = observed variables; Circles = latent or residual variables; Single headed arrows = direct paths; Double headed arrows = correlations; WM FA = white matter fractional anisoptropy; g_v = general cognitive ability variance; s_v = specific cognitive ability variance; e_v= error variance.

Figure 2: Diagrammatic representations of variance decomposition in two structural equation models for estimating the association between cognitive ability and neuroimaging variables. Panel A depicts a 1st –order factor model. Panel B depicts a bi-factor model, including separate general and specific ability latent factors. Rectangles = observed variables; Circles = latent or residual variables; Single headed arrows = direct paths; Double headed arrows = correlations; WM FA = white matter fractional anisotropy; g_v = general cognitive ability variance; s_v = specific cognitive ability variance; e_v= error variance.

Figure 3: Measurement model for the 1st -order model. VDM = Verbal Declarative Memory. Model Fit: χ^2 = 417.99(126), p<0.001; CFI = 0.95; TLI = 0.93; RMSEA = 0.059 (95% Conf. 0.053 to 0.066); SRMR = 0.058.

Figure 4: Measurement model for the bi-factor model. VDM = Verbal Declarative Memory. Model Fit: χ^2 = 315.68(114), p<0.001; CFI = 0.96; TLI = 0.95; RMSEA = 0.052 (95% Conf. 0.045 to 0.059); SRMR = 0.044.

Table 1: Descriptive statistics of cognitive ability tests, tractography FA measures and covariates.

Variable	No. Missing	Mean	SD	Skew	Kurtosis
Cognitive Ability					
Logical Memory Immediate Recall WMS-III	1	45.88	10.18	-0.48	0.30
Logical Memory Delayed Recall WMS-III	1	28.89	8.08	-0.56	0.26
Verbal Paired Associates 1st Recall WMS-III	12	2.80	2.30	0.62	-0.66
Verbal Paired Associates 2nd Recall WMS-III	15	6.39	2.09	-1.26	0.57
Spatial Span Forward WMS-III	1	7.66	1.65	-0.09	-0.39
Spatial Span Backward WMS-III	2	7.08	1.60	-0.06	-0.10
Verbal Fluency Total Score	1	43.47	12.68	0.23	0.14
National Adult Reading Test	1	34.57	7.86	-0.54	-0.10
Wechsler Test of Adult Reading	1	41.26	6.70	-0.93	0.61
Simple Reaction Time Mean Score	0	0.27	0.05	1.66	4.09
Choice reaction Time Mean Score	0	0.65	0.08	0.89	1.77
Inspection Time Total Correct Responses	11	111.45	11.64	-1.16	3.82
Digit Symbol WAIS-III^{UK}	1	56.43	12.22	0.11	-0.20
Digit Span Backward WAIS-III^{UK}	0	7.90	2.30	0.28	-0.20
Block Design WAIS-III^{UK}	2	34.26	9.98	0.47	0.13
Letter-Number Sequencing WAIS-III^{UK}	0	11.01	2.99	0.28	0.41
Matrix Reasoning WAIS-III^{UK}	1	13.46	4.86	-0.10	-0.93
Symbol Search WAIS-III^{UK}	1	24.74	6.09	-0.32	0.78
FA Tractography					
Genu of corpus callosum	17	0.41	0.05	-0.07	-0.12
Splenium of corpus callosum	4	0.49	0.07	-0.30	0.61
Left Arcuate Fasciculus	27	0.45	0.04	-0.42	0.50
Right Arcuate Fasciculus	87	0.43	0.04	-0.29	0.72
Left Anterior Thalamic Radiation	105	0.32	0.03	-0.10	0.25
Right Anterior Thalamic Radiation	20	0.33	0.03	-0.31	0.54
Left Rostral Cingulum	23	0.44	0.05	-0.53	0.76
Right Rostral Cingulum	13	0.39	0.04	-0.61	1.84
Left Uncinate fasciculus	93	0.33	0.03	-0.13	0.39
Right Uncinate fasciculus	33	0.33	0.03	-0.25	0.47
Left Inf. Longitudinal Fasciculus	4	0.40	0.05	-0.28	0.08
Right Inf. Longitudinal Fasciculus	3	0.38	0.05	-0.40	0.18
Covariates					
Age	0	72.6	0.70	-0.00	-0.87
Atrophy (Percent Decline)	13	22.39	3.84	0.16	0.10
White mater lesion volume in ICV (%)	13	0.83	0.91	2.52	10.24
Fazekas Total Lesion Rating Score	6	2.45	1.14	0.83	0.83

		Male	Female	
Sex	0	345	310	
		Right	Left	Ambidextrous
Handedness	0	614	38	3

Table 2: White matter tract integrity and cognitive ability correlations in the 1st-Order and bi-factor models.

			Knowledge			
	1st-Order	95% CI	Residual (Δ)	Bi-F	95%CI	Residual (Δ)
Genu Corpus Callosum	0.01	-0.07 to 0.09	0.01 (0.00)	-0.03	-0.13 to 0.08	0.00 (0.03)
Splenium Corpus Callosum	0.08	0.00 to 0.16	0.06 (0.02)	-0.03	-0.14 to 0.07	-0.03 (0.00)
Left Arcuate fasciculus	0.02	-0.06 to 0.10	0.00 (0.02)	-0.08	-0.18 to 0.02	-0.07 (0.01)
Right Arcuate fasciculus	0.02	-0.06 to 0.11	0.01 (0.01)	-0.06	-0.17 to 0.04	-0.06 (0.00)
Left. Anterior Thalamic Radiation	0.09*	0.01 to 0.18	0.09* (0.00)	-0.03	-0.14 to 0.08	0.00 (0.03)
Right Anterior Thalamic Radiation	0.10*	0.02 to 0.18	0.08* (0.02)	-0.04	-0.14 to 0.07	0.00 (0.04)
Left Rostral Cingulum	0.05	-0.03 to 0.13	0.05 (0.00)	-0.01	-0.12 to 0.09	0.01 (0.00)
Right Rostral Cingulum	0.08*	0.00 to 0.16	0.07 (0.01)	0.03	-0.07 to 0.14	0.06 (0.03)
Left Uncinate fasciculus	0.09*	0.01 to 0.17	0.08 (0.01)	-0.05	-0.15 to 0.06	-0.02 (0.03)
Right Uncinate fasciculus	0.08	0.00 to 0.16	0.08 (0.00)	-0.16**	-0.26 to -0.06	-0.14** (0.02)
Left Inferior. Longitudinal Fasciculus	0.07	-0.01 to 0.15	0.05 (0.02)	0.03	-0.07 to 0.13	0.05 (0.02)
Right Inferior Longitudinal Fasciculus	0.04	-0.04 to 0.11	0.02 (0.02)	-0.01	-0.12 to 0.09	0.00 (0.01)
			Verbal Declarative Memory			
	1st-Order	95% CI	Residual (Δ)	Bi-F	95%CI	Residual (Δ)
Genu Corpus Callosum	0.03	-0.06 to 0.12	-0.01 (0.04)	0.04	-0.05 to 0.13	0.04 (0.00)
Splenium Corpus Callosum	0.10*	0.01 to 0.18	0.07 (0.03)	-0.01	-0.10 to 0.08	-0.01 (0.00)
L. Arcuate fasciculus	0.00	-0.09 to 0.09	-0.07 (0.07)	-0.10*	-0.19 to -0.01	-0.10* (0.00)
R. Arcuate fasciculus	0.02	-0.07 to 0.12	-0.03 (0.05)	-0.09	-0.18 to 0.00	-0.09 (0.00)
L. Ant. Thalamic Radiation	0.05	-0.05 to 0.14	-0.01 (0.06)	-0.06	-0.16 to 0.04	-0.06 (0.00)
R. Ant. Thalamic Radiation	0.11*	0.02 to 0.20	0.07 (0.04)	-0.02	-0.10 to 0.10	0.02 (0.04)
L. Rostral Cingulum	0.01	-0.08 to 0.10	-0.03 (0.04)	-0.07	-0.16 to 0.02	-0.07 (0.00)
R. Rostral Cingulum	0.07	-0.02 to 0.16	0.04 (0.03)	-0.07	-0.16 to 0.02	-0.07 (0.00)
L. Uncinate fasciculus	0.11*	0.01 to 0.20	0.06 (0.05)	0.00	-0.09 to 0.10	0.01 (0.01)
R. Uncinate fasciculus	0.11*	0.02 to 0.20	0.06 (0.05)	-0.05	-0.14 to 0.05	-0.05 (0.00)
L. Inf. Longitudinal Fasciculus	0.02	-0.07 to 0.10	-0.03 (0.05)	-0.03	-0.12 to 0.06	-0.01 (0.02)
R. Inf. Longitudinal Fasciculus	0.02	-0.07 to 0.11	-0.01 (0.03)	-0.07	-0.16 to 0.02	-0.06 (0.01)

Table 2 cont.			**Processing Speed**			
	1st-Order	95% CI	Residual (Δ)	Bi-F	95%CI	Residual (Δ)
Genu Corpus Callosum	0.04	-0.05 to 0.13	-0.01 (0.05)	0.04	-0.08 to 0.17	0.02 (0.02)
Splenium Corpus Callosum	0.13**	0.05 to 0.21	0.07 (0.06)	0.05	-0.08 to 0.17	0.01 (0.04)
L. Arcuate fasciculus	**0.15*** **	**0.07 to 0.24**	0.05 (0.10)	0.10	-0.02 to 0.22	0.03 (0.07)
R. Arcuate fasciculus	0.13**	0.04 to 0.22	0.04 (0.09)	0.07	-0.06 to 0.20	0.01 (0.06)
L. Ant. Thalamic Radiation	**0.16*** **	**0.07 to 0.25**	0.06 (0.10)	0.07	-0.06 to 0.20	0.01 (0.06)
R. Ant. Thalamic Radiation	**0.23*** **	**0.15 to 0.31**	**0.15*** (0.08)**	0.14*	0.01 to 0.26	0.10 (0.04)
L. Rostral Cingulum	0.13**	0.05 to 0.22	0.08 (0.05)	0.09	-0.03 to 0.22	0.07 (0.02)
R. Rostral Cingulum	0.08	-0.01 to 0.16	0.02 (0.06)	0.00	-0.12 to 0.13	-0.03 (0.03)
L. Uncinate fasciculus	0.13**	0.04 to 0.22	0.03 (0.10)	-0.02	-0.14 to 0.11	-0.08 (0.06)
R. Uncinate fasciculus	0.13**	0.04 to 0.21	0.06 (0.07)	-0.10	-0.23 to 0.02	-0.13* (0.03)
L. Inf. Longitudinal Fasciculus	**0.19*** **	**0.10 to 0.27**	0.08 (0.11)	0.16**	0.04 to 0.28	0.08 (0.08)
R. Inf. Longitudinal Fasciculus	0.15**	0.06 to 0.23	0.08 (0.07)	0.11	-0.02 to 0.23	0.06 (0.05)
			Fluid Ability			
	1st-Order	95% CI	Residual (Δ)	Bi-F	95%CI	Residual (Δ)
Genu Corpus Callosum	-0.01	-0.09 to 0.08	-0.05 (0.04)	-0.08	-0.21 to 0.05	-0.08 (0.00)
Splenium Corpus Callosum	0.09	0.00 to 0.17	0.04 (0.05)	-0.12	-0.25 to 0.01	-0.13 (0.01)
L. Arcuate fasciculus	0.07	-0.02 to 0.16	0.00 (0.07)	-0.10	-0.23 to 0.02	-0.10 (0.00)
R. Arcuate fasciculus	0.04	-0.05 to 0.14	-0.02 (0.06)	-0.11	-0.25 to 0.02	-0.12 (0.01)
L. Ant. Thalamic Radiation	0.12*	0.03 to 0.21	0.05 (0.07)	-0.09	-0.23 to 0.05	-0.08 (0.01)
R. Ant. Thalamic Radiation	**0.19*** **	**0.10 to 0.27**	0.14** (0.05)	-0.03	-0.17 to 0.12	0.02 (0.05)
L. Rostral Cingulum	0.09*	0.00 to 0.18	0.05 (0.04)	-0.03	-0.16 to 0.10	-0.03 (0.00)
R. Rostral Cingulum	0.10*	0.01 to 0.19	0.06 (0.04)	-0.00	-0.13 to 0.13	0.01 (0.01)
L. Uncinate fasciculus	**0.16*** **	**0.07 to 0.25**	0.10* (0.06)	-0.05	-0.18 to 0.09	-0.04 (0.01)
R. Uncinate fasciculus	**0.18*** **	**0.09 to 0.26**	0.13** (0.05)	-0.14*	-0.27 to-0.01	-0.13 (0.01)
L. Inf. Longitudinal Fasciculus	0.15**	0.06 to 0.23	0.09 (0.06)	0.05	-0.07 to 0.18	0.07 (0.02)
R. Inf. Longitudinal Fasciculus	0.11**	0.02 to 0.20	0.07 (0.04)	0.01	-0.13 to 0.16	0.04 (0.03)

Table 2 cont.				**g**		
	1st-Order[a]	95% CI	Residual (Δ)	Bi-F	95%CI	Residual (Δ)
Genu Corpus Callosum	-	-	-	0.03	-0.07 to 0.13	-0.01 (0.04)
Splenium Corpus Callosum	-	-	-	0.14**	0.04 to 0.24	0.11 (0.03)
L. Arcuate fasciculus	-	-	-	0.12*	0.02 to 0.22	0.05 (0.07)
R. Arcuate fasciculus	-	-	-	0.11*	0.00 to 0.21	0.06 (0.05)
L. Ant. Thalamic Radiation	-	-	-	0.16**	0.06 to 0.27	0.09 (0.07)
R. Ant. Thalamic Radiation	-	-	-	**0.19*** **	**0.09 to 0.29**	0.12* (0.07)
L. Rostral Cingulum	-	-	-	0.10	0.00 to 0.20	0.06 (0.04)
R. Rostral Cingulum	-	-	-	0.10	0.00 to 0.20	0.06 (0.04)
L. Uncinate fasciculus	-	-	-	**0.19*** **	**0.09 to 0.29**	0.13* (0.06)
R. Uncinate fasciculus	-	-	-	**0.26*** **	**0.16 to 0.35**	**0.22*** (0.04)**
L. Inf. Longitudinal Fasciculus	-	-	-	0.10*	0.00 to 0.20	0.03 (0.07)
R. Inf. Longitudinal Fasciculus	-	-	-	0.09	-0.01 to 0.20	0.04 (0.05)

Note: Bi-F = Bi-Factor; Residual = Correlations based on standardized residuals controlling for sex, age, handedness (tracts only), white matter lesion as a percentage of ICV, Fazekas ratings of white matter lesions, and atrophy; (Δ) = the difference between raw and residualized associations; [a]The 1st -order model contains no g associations as *g* is not included in this model. All estimates are standardized with confidence intervals presented in parentheses below.
$p<0.05$*; $p<0.01$**; $p<0.001$***. Values in in bold are significant after Bonferroni correction.

Figure 1:

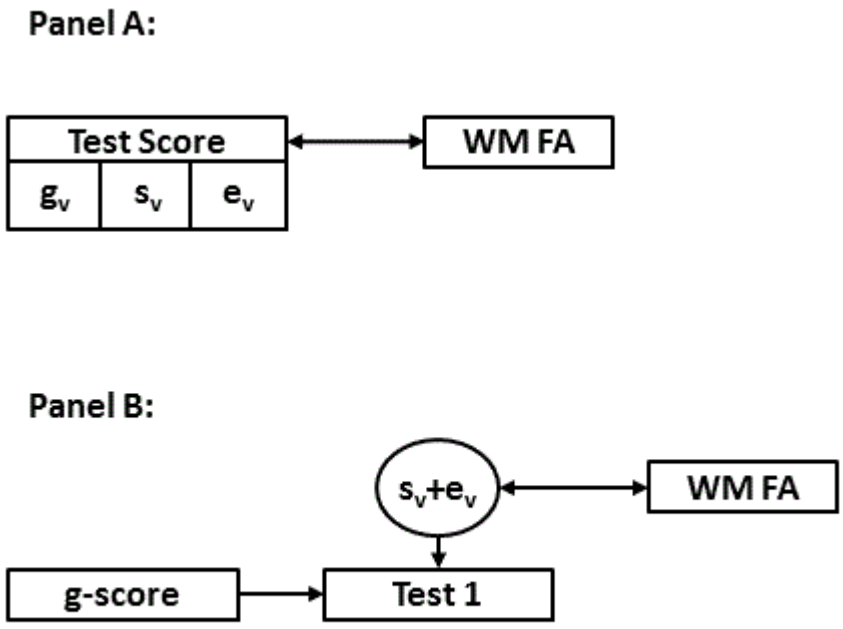

Panel A:
Test Score
g_v
s_v
e_v
WM FA
Panel B:
s_v+e_v
WM FA
g-score
Test 1

Figure 2

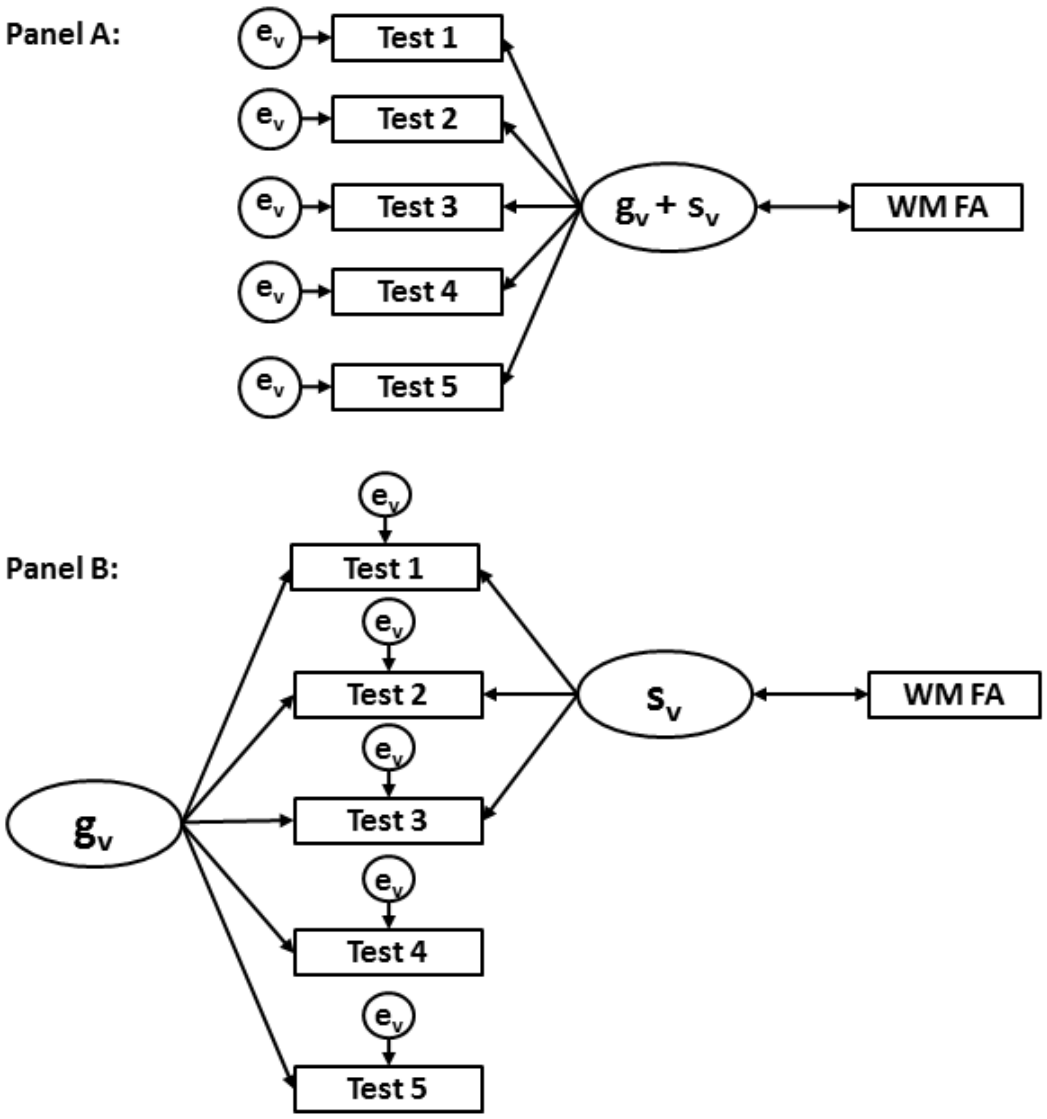

Panel A:
e_v
Test 1
Test 2
Test 3
Test 4
Test 5
$g_v + s_v$
WM FA
Panel B:
e_v
Test 1
Test 2
Test 3
Test 4
Test 5
g_v
s_v
WM FA

Figure 3

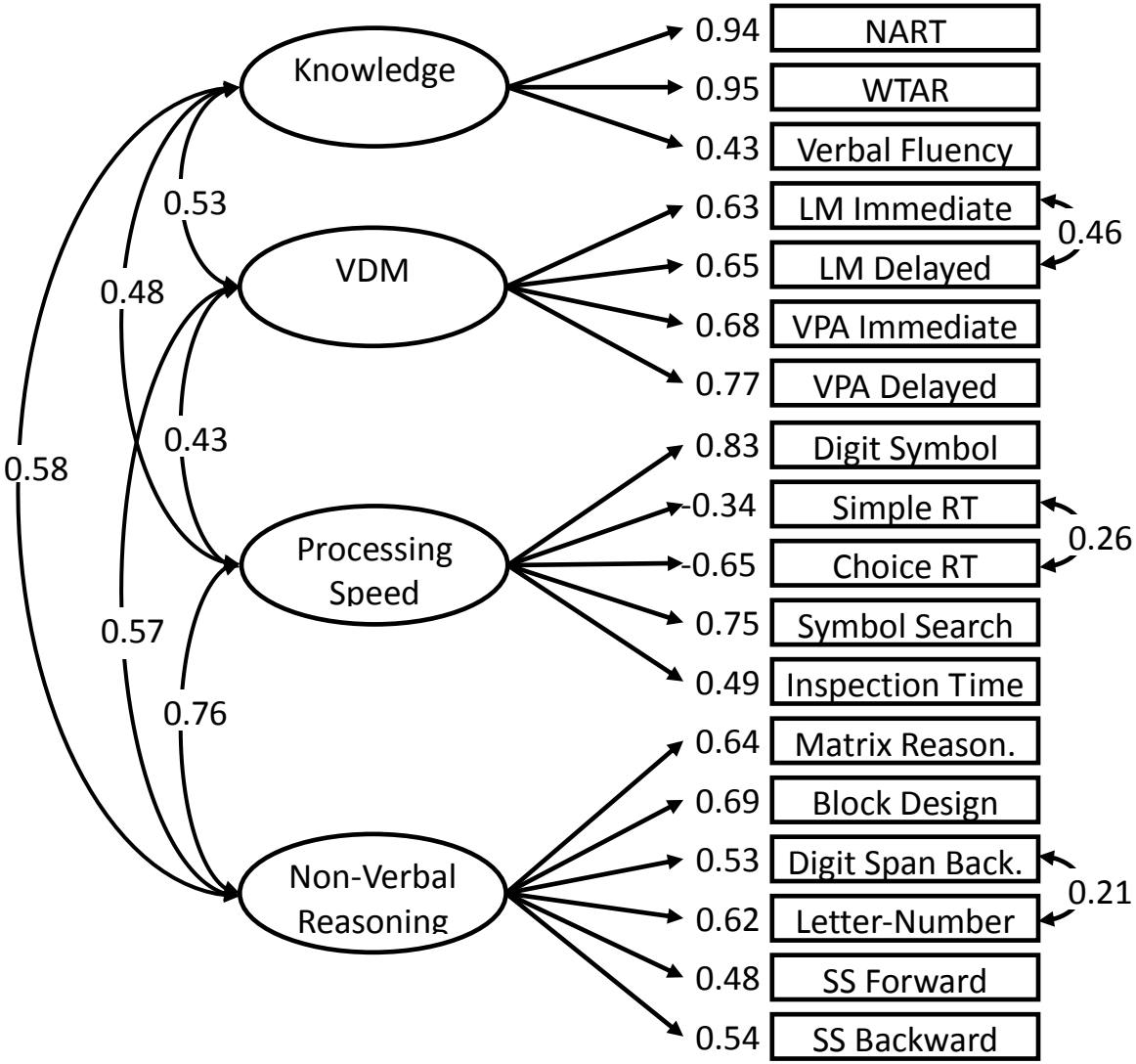
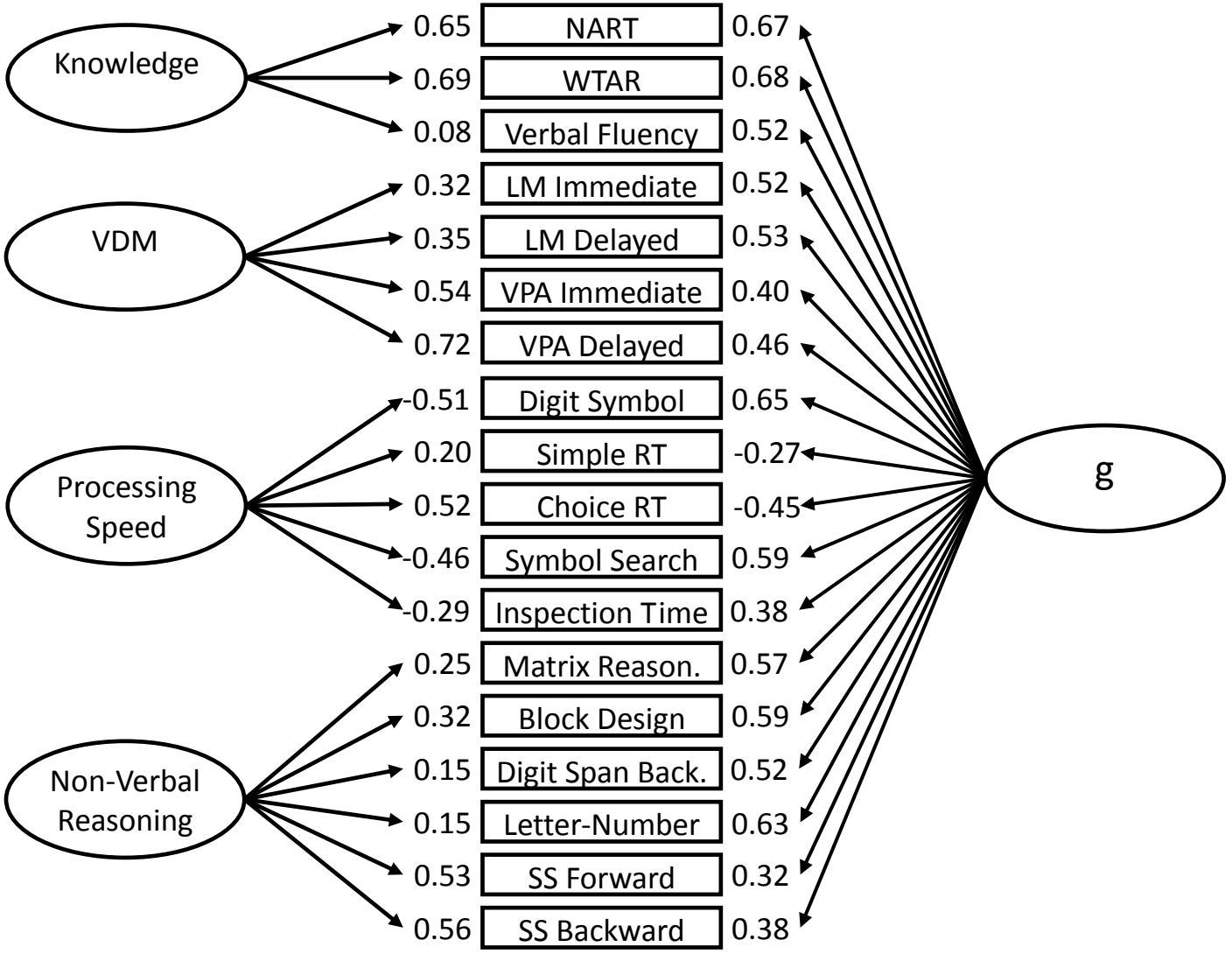

Knowledge
VDM
Processing Speed
Non-Verbal Reasoning
0.53
0.48
0.58
0.43
0.57
0.76
0.94
NART
0.95
WTAR
0.43
Verbal Fluency
0.63
LM Immediate
0.46
0.65
LM Delayed
0.68
VPA Immediate
0.77
VPA Delayed
0.83
Digit Symbol
-0.34
Simple RT
0.26
-0.65
Choice RT
0.75
Symbol Search
0.49
Inspection Time
0.64
Matrix Reason.
0.69
Block Design
0.53
Digit Span Back.
0.21
0.62
Letter-Number
0.48
SS Forward
0.54
SS Backward

Figure 4


Knowledge
VDM
Processing Speed
Non-Verbal Reasoning
g
0.65 NART 0.67
0.69 WTAR 0.68
0.08 Verbal Fluency 0.52
0.32 LM Immediate 0.52
0.35 LM Delayed 0.53
0.54 VPA Immediate 0.40
0.72 VPA Delayed 0.46
-0.51 Digit Symbol 0.65
0.20 Simple RT -0.27
0.52 Choice RT -0.45
-0.46 Symbol Search 0.59
-0.29 Inspection Time 0.38
0.25 Matrix Reason. 0.57
0.32 Block Design 0.59
0.15 Digit Span Back. 0.52
0.15 Letter-Number 0.63
0.53 SS Forward 0.32
0.56 SS Backward 0.38

Online Supplementary Material

Brain White Matter Tract Integrity and Cognitive Abilities in Community-dwelling Older People: The Lothian Birth Cohort 1936

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Supplementary Material A

Further details of the cognitive ability tests used in the current analyses are provided below.

1. *Logical Memory (WMS-III^{UK})* tests verbal declarative memory and provides immediate and delayed recall scores. Participants are asked to recall two 25 item stories which are read aloud by the examiner. Immediate (3 recalls total possible score 75) and delayed (2 recalls total possible score 50) scores were used.
2. *Verbal Paired Associates (WMS-III^{UK})* tests learning and memory. Participants are read lists of unrelated word pairs and are asked to recall the second of the pair when given the first. Immediate and delayed scores were used.
3. *Digit Span Backward (WMS-III^{UK})* tests working memory, with participants asked to recall increasingly long strings of numbers backwards.
4. *Spatial Span (WMS-III^{UK})* tests non-verbal/spatial learning and memory. The participant observes a series of blocks being touched and then has to touch the blocks in the correct order. The procedure is repeated with participants required to touch the blocks in reverse order. Forward and backwards recall scores were used.
5. *Block Design (WAIS-III^{UK})* participants are asked to use blocks to reproduce a diagram of a specific design.
6. *Matrix Reasoning (WAIS-III^{UK})* tests abstract reasoning. Participants view an incomplete pattern within a matrix, and are required to select from a number of options which piece completes the matrix.
7. *Digit Symbol Coding (WAIS-III^{UK})* tests speed of information processing. The participant is required to enter a symbol according to a particular number-symbol code. Participants are given 2 minutes to complete as many items as possible.
8. *Symbol Search (WAIS-III^{UK})* tests speed of information processing. Participants are given two target symbols and have to decide (yes or no) whether either symbol

appears in a row of symbols. Participants are given 2 minutes to complete as many items as possible.

9. *Letter-Number Sequencing (WAIS-III^{UK})* is conducted by testers reading increasingly long lists of letters and numbers, with participants asked to recall the list immediately afterwards by stating the numbers in numerical order and then the letters in alphabetical order.
10. *NART and WTAR* are often used to estimate 'prior cognitive ability level' since they tap word recognition and pronunciation, a cognitive ability very robust against age- and trauma- related cognitive decline. Each requires the pronunciation of 50 irregular words.
11. *Verbal Fluency* tests executive function. Participants are asked to list as many words as they beginning with C, and then F, and then L, with 1 minute for each letter. Here we used a total score across letters.
12. *Reaction Time* tests speed of processing. Here we use both simple and 4-choice mean reaction time scores. In the simple task which had 20 trials, participants had to press a 0 key as quickly as possible when presented with a 0 on screen. In the 4-choice task, which had 40 trials, participants are presented with a 1, 2, 3 or 4 on screen, and have to press the corresponding button (labelled 1, 2, 3 and 4) as quickly as possible.
13. *Inspection Time* tests efficiency of visual discrimination. It is a forced-choice, two-alternative psychophysical task using the method of constant stimuli. In each of the 150 trials, participants are presented with two parallel vertical lines of very different lengths and, without time pressure, are asked to select which of the lines is longer. Stimulus durations range from 6 ms to 200 ms and stimuli were backward masked immediately after presentation.

Supplementary Material B

Table B1: Factor loading matrix for exploratory factor analysis of the 18 cognitive tests.

	Knowledge	**Verbal Declarative Memory**	**Processing Speed**	**Non-Verbal Reasoning**
Eigenvalue	6.19	1.95	1.26	1.23
Wechsler Test of Adult Reading	**0.94**	0.03	0.01	0.03
National Adult Reading Tests	**0.89**	0.08	0.03	0.01
Verbal Fluency Total Score	**0.31**	0.00	0.29	0.07
Logical Memory Delayed Recall	0.02	**0.92**	0.02	0.03
Logical Memory Immediate Recall	0.05	**0.91**	0.02	0.00
Verbal Paired Associates 2nd Recall	0.11	**0.42**	0.08	0.11
Verbal Paired Associates 1st Recall	0.14	**0.34**	0.01	0.12
Choice Reaction Time	0.04	-0.05	**-0.80**	0.01
Digit Symbol	0.17	0.06	**0.58**	0.16
Simple Reaction Time	0.02	-0.02	**-0.52**	0.05
Symbol Search	0.12	-0.01	**0.50**	0.26
Inspection Time Total Score	0.01	0.01	**0.40**	0.17
Spatial Span Backwards	-0.11	0.03	0.09	**0.60**
Block Design	0.16	-0.02	0.06	**0.60**
Spatial Span Forwards	-0.12	0.03	0.09	**0.55**
Matrix Reasoning	0.16	0.11	-0.02	**0.53**
Digit Span Backwards	0.19	0.10	0.04	**0.39**
Letter-Number Sequencing	0.18	0.13	0.21	**0.35**

Note: All values >0.30 are displayed in bold as this was used as the cut-off for salience of factor loadings