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ORIGINAL ARTICLE

Brain white matter tract integrity as a neural foundation for general intelligence

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General intelligence is a robust predictor of important life outcomes, including educational and occupational attainment, successfully managing everyday life situations, good health and longevity. Some neuronal correlates of intelligence have been discovered, mainly indicating that larger cortices in widespread parieto-frontal brain networks and efficient neuronal information processing support higher intelligence. However, there is a lack of established associations between general intelligence and any basic structural brain parameters that have a clear functional meaning. Here, we provide evidence that lower brain-wide white matter tract integrity exerts a substantial negative effect on general intelligence through reduced information-processing speed. Structural brain magnetic resonance imaging scans were acquired from 420 older adults in their early 70s. Using quantitative tractography, we measured fractional anisotropy and two white matter integrity biomarkers that are novel to the study of intelligence: longitudinal relaxation time (T1) and magnetisation transfer ratio. Substantial correlations among 12 major white matter tracts studied allowed the extraction of three general factors of biomarker-specific brain-wide white matter tract integrity. Each was independently associated with general intelligence, together explaining 10% of the variance, and their effect was completely mediated by information-processing speed. Unlike most previously established neurostructural correlates of intelligence, these findings suggest a functionally plausible model of intelligence, where structurally intact axonal fibres across the brain provide the neuroanatomical infrastructure for fast information processing within widespread brain networks, supporting general intelligence.

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INTRODUCTION

Individual differences in cognitive domains are not independent; individuals who perform well on one type of cognitive test tend to do well on others. The construct of general intelligence (*g*) captures the common variance that is shared among diverse cognitive ability tests, such as measures of reasoning, memory, executive functions and spatial ability.[1–4] General intelligence is a robust predictor of important life outcomes, including educational and occupational attainment, successfully managing everyday life situations, good health and longevity.[1,5,6] Human intelligence is highly stable through the lifecourse and the origins of individual differences in intelligence include a substantial genetic component.[2,7] Some neuronal correlates of intelligence have been discovered, mainly indicating that larger cortices in widespread parieto-frontal brain networks and efficient neuronal information processing support higher intelligence.[2,8–11] However, there are few established associations between general intelligence and any basic structural brain parameters that have a clear functional meaning.

Cognitive information-processing speed, a well-replicated correlate of intelligence, has long been hypothesised as an intermediate phenotype between the brain and intelligence,[12] as well as being suggested as a leading indicator of age-related cognitive decline.[13] Efficient information processing between distal brain regions is thought to rely on the integrity of their interconnecting white matter tracts.[2,8,9] Unlike simple associations between global or regional brain size and intelligence, this suggests a mechanism by which neuroanatomical differences can translate to integral processes underlying intelligence. Well-connected white matter may allow for faster, more efficient information processing within widespread brain networks responsible for good cognitive functioning.[1,14] This functionally meaningful model of the neural underpinnings of intelligence differences awaits empirical testing.

Diffusion tensor magnetic resonance imaging (DT-MRI) is the method of choice for assessing brain white matter tract integrity *in vivo*. It quantifies the degree to which the diffusion of water molecules is directionally restricted in the environment of the highly structured axonal tracts that constitute intact white matter. Conceptually, the more directionally restricted the water movement, the more tightly aligned and closely related are the individual axons in the tracts, and hence the more efficient is the transmission of electrical signals along the tracts. Information-processing speed correlates with DT-MRI measures of white

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matter tract integrity, such as fractional anisotropy (FA).[15] Some studies have also reported positive associations between FA and intelligence.[16–18] Such associations are especially found in old age, where it has been hypothesised that cortical disconnection due to age-related declining white matter underpins cognitive ageing.[19] Measuring further neuroimaging indicators of white matter integrity *in vivo* is possible,[20,21] but their associations with cognitive abilities, such as information-processing speed and general intelligence, have not yet been studied.

We have previously shown that individual differences in DT-MRI measures of white matter tracts are, to a substantial degree, shared among different major tracts.[22] Therefore, white matter tract integrity, as measured by DT-MRI, is a global property of the brain, and it is this common variance in integrity that explains the association with processing speed. It is not known whether other indicators of white matter integrity also show these characteristics.

We examined the association between general intelligence and three quantitative biomarkers of brain white matter tract integrity, FA from DT-MRI alongside two others which are novel to the study of human intelligence differences; namely, longitudinal relaxation time (T1), and magnetisation transfer ratio (MTR). T1 is a fundamental nuclear magnetic resonance decay constant describing how rapidly the z component of the perturbed nuclear spin magnetisation returns to its thermal equilibrium value. It is related to tissue water content, with increased T1 being potentially associated with increased brain water, generally in the extracellular space.[20,21] MTR measures the efficiency of the magnetisation exchange between any relatively free water protons and those water protons that are bound to protein macromolecules in cellular membranes. MTR is reduced when there is pathological change in axonal structure, for example in areas affected by demyelination.[21]

MATERIALS AND METHODS

Participants

The participants were generally healthy, older individuals from the Lothian Birth Cohort 1936 (LBC1936).[23,24] All were Caucasian and living independently in the community. For this report, appropriate data was available for 453 individuals. A total of 33 subjects (7.3%) were excluded because they were not right-handed (29 participants) or had showed signs of dementia or mild cognitive impairment as indicated by self-reports and Mini-Mental State Examination scores below 24 (4 participants).[25] There is no indication that this dropout was systematic. The final sample used for all reported analyses consisted of 420 individuals (228 men, 192 women, age 71–73 years, Mean = 72.3, s.d. = 0.6 years). Written informed consent was obtained from all participants under protocols approved by the National Health Service Ethics Committees (Local Research Ethics Committee and Multi Centre Research Ethics Committee).

Our earlier report of an association between g_{FA} and g_{Speed}[22] was based on 132 individuals from the current sample. However, g_{FA} at that time was based on only 8 instead of 12 white matter tracts. Thus, here we extended the findings from Penke *et al.*[22] in a more comprehensive sample of tracts and a larger sample of individuals. The associations of g_{FA} with g and the discovery of g_{T1} and g_{MTR} as well as their associations with g_{Speed} and g are novel.

Image acquisition

As described in detail in the LBC1936 brain imaging protocol paper,[24] subjects underwent clinically optimised whole brain diffusion tensor (DT), magnetisation transfer (MT) and T1-mapping MRI protocols on a GE Signa HDxt 1.5T. scanner (General Electric, Milwaukee, WI, USA) using a self-shielding gradient set with maximum gradient strength of 33 mT m^{-1}, and an eight-channel phased-array head coil. The DT-MRI protocol consisted of 7 T2- ($b = 0$ s mm^{-2}) and 64 diffusion-weighted ($b = 1000$ s mm^{-2}) axial single-shot spin-echo echo-planar imaging volumes (imaging matrix 128×128), the latter acquired with diffusion gradients applied in 64 non-collinear directions. Each echo-planar imaging volume comprised 72 contiguous 2-mm-thick slices acquired with 2 mm in-plane resolution. MTR volumes were generated from two standard spin echo structural sequences acquired with and without a magnetisation transfer pulse applied 1 kHz from the water resonance frequency, whereas quantitative maps of T1 were obtained from two axial T1-weighted fast-spoiled gradient echo sequences with 2 and 12° flip angles.[26] The component structural volumes acquired in the MT- and T1-mapping MRI protocols shared the same field of view (256×256 mm), slice locations and thickness as the DT-MRI protocol, albeit with an in-plane resolution of 1×1 mm, allowing easier co-registration between the biomarker volumes.

Image analysis

For all three of these imaging biomarkers, which give complementary information on white matter integrity, tract-averaged values were derived from 12 major fibre pathways segmented using probabilistic neighbourhood tractography from DT-MRI data.[27] Data sets were preprocessed using FSL tools (FMRIB; http://www.fmrib.ox.ac.uk/) to extract the brain, remove bulk subject motion and eddy current-induced artifacts, and estimate water DT parameters.[28] MTR and T1 biomarker volumes were generated as previously described.[24,26] The BEDPOSTX/ProbTrackX tractography algorithm[29] with a two-fibre model and 5000 streamlines was used to reconstruct tracts of interest. An automatic tract selection method with good reproducibility,[30] based on a model of tract topology,[31] was used to generate equivalent tracts of interest in each subject. This technique, termed probabilistic neighbourhood tractography, optimises the choice of seed point for tractography by estimating the best matching tract from a series of candidates placed in a neighbourhood, for example, $7 \times 7 \times 7$ voxels, surrounding a seed point transferred from standard space against a reference tract derived from a digital human white matter atlas.[32,33] The topological tract model was also used to reject false-positive connections.[34] A total of 12 major white matter pathways in the brain thought to be related to cognitive functioning were segmented, namely genu and splenium of corpus callosum, and bilateral cingulum cingulate gyri, arcuate, uncinate and inferior longitudinal fasciculi and anterior thalamic radiations (see Figure 1). After affine registration to the structural scans, where appropriate, the resulting tractography masks were then applied to each subject's FA, MTR and T1 volumes to generate tract-averaged biomarker values for each fibre pathway.

Cognitive testing

General intelligence was assessed by six subtests from the Wechsler Adult Intelligence Scale III^{UK} Symbol Search, Digit Symbol, Matrix Reasoning, Letter–Number Sequencing, Digit Span Backwards and Block Design.[35] Cognitive information-processing speed was assessed with three well-established tasks. Reaction times were assessed using a stand-alone device.[36] Simple reaction time (averaged across 20 trials) required pressing a button as fast as possible when a '0' was displayed on an LCD screen. Four-choice reaction time (averaged across correct responses in 40 trials) required pressing the correct button out of the four as fast as possible when a number from 1 to 4 was displayed on an LCD screen. Inspection time (correct responses across 150 trials, stimulus exposure time = 6–200 ms) is a two-alternative, forced-choice, backward-masked visual discrimination task that requires indicating, without response time pressure, which of the two parallel, vertical lines of markedly different lengths was longer.[23] Descriptive statistics for all cognitive tests can be found in Supplementary Table S1.

Statistical analysis

Simple reaction times were natural log transformed to normality. Structural equation modelling (SEM) was used to model relationships among latent white matter tract integrity factors and associations with latent factors of general intelligence (g) and information-processing speed (g_{Speed}).[37] For the SEMs, we used standardized residuals from separate regressions of all variables in the models on sex and age in days at assessment. Sex and age were thus statistically controlled for in all SEMs. In addition, we tested all SEMs separately for men and women, but as the results were very similar

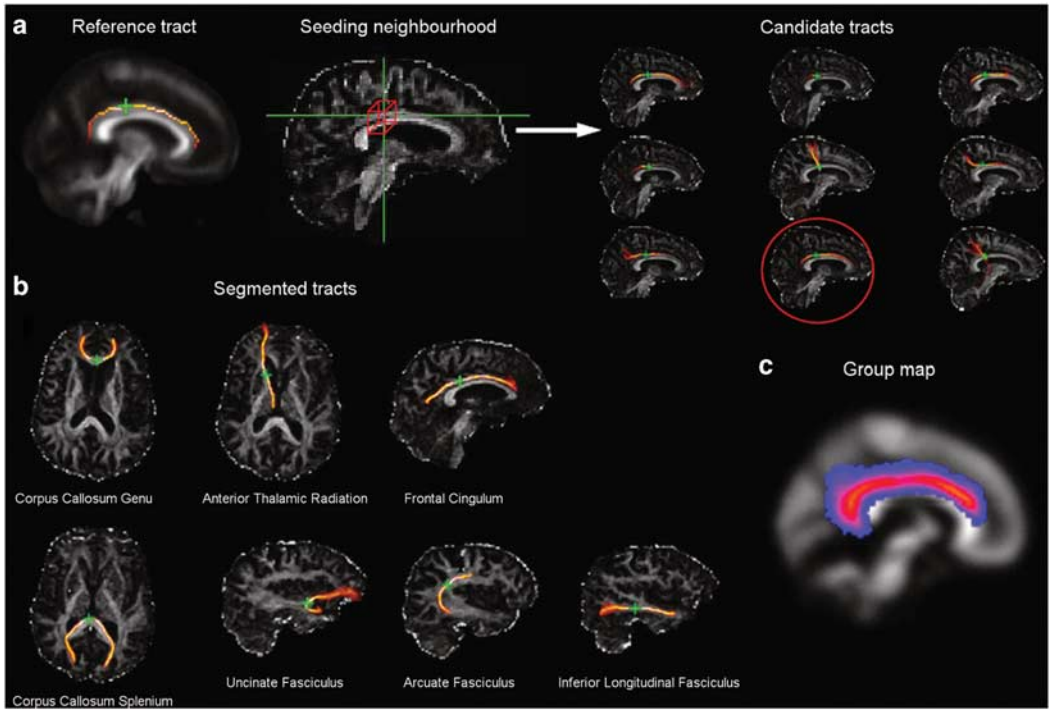

Figure 1. (**a**) Schematic diagram showing the probabilistic neighbourhood tractography processing pipeline for automatic tract segmentation. Given a pre-defined reference tract, in this case rostral cingulum, seed points are automatically placed in a neighbourhood surrounding a seed point transferred from standard space (red box). The tract that best matches the reference in terms of both length and shape (red circle) is chosen from this group of 'candidate' tracts. (**b**) Examples of the tracts segmented in this study for a representative subject. (**c**) A maximum intensity projection of a standard space group map of a segmented fasciculi-of-interest, in this case rostral cingulum, overlaid on an MNI white matter volume. Note the consistent segmentation of the tract across the cohort.

for both sexes, we only present results for the full sample covarying for sex here (see Supplementary Information for more details).

RESULTS

The tract-averaged FA values for the 12 studied tracts were all significantly positively correlated (r (range) = 0.13–0.60, P (all) < 0.01). This allowed the extraction of a general principal component, g_{FA}, that was positively loaded by all tracts and explained 38.35% of the variance shared among all tracts. Similarly, universally significant and positive correlations were found among the tract-averaged T1 (r (range) = 0.28–0.89, P (all) < 0.001) and MTR (r (range) = 0.18–0.87, P (all) < 0.001) values for the 12 tracts of interest. This allowed the extraction of a general principal component based on T1 (g_{T1}; explained variance = 66.76%) and one based on MTR (g_{MTR}; explained variance = 67.79%). Thus, for all three imaging biomarkers, white matter integrity is to a substantial degree shared among tracts across the brain. Individuals with lower integrity, as assessed by FA, MTR or T1, of one tract tend also to have lower integrity in all other tracts.

In structural equation models (Figure 2) the three latent biomarker-specific white matter tract integrity factors showed weak to moderate correlations with each other. They were all independently and significantly associated with general intelligence (g), a latent factor defined by the six subtests of the Wechsler Adult Intelligence Scale III^{UK} (Figure 2a).[35] Together, they explained 10.0% of the variance in g. g_{T1} showed the strongest association (standardized path coefficient $ß = -0.26$), suggesting that longer T1, potentially indicating increased water content, was detrimental to general intelligence in our sample.

Next, we tested whether a latent cognitive information-processing speed factor (g_{Speed}) explained the link between the three white matter tract integrity factors and g by acting as a mediating variable (Figure 2b). It is important to note that g_{Speed} was defined using experimental psychology tasks, and not psychometric (paper and pencil-type) tests. We used simple and four-choice reaction time tasks, as well as inspection time, which is a psychophysical test of the early stages of visual information processing.[23] All three white matter tract integrity factors showed independent significant associations with g_{Speed}, explaining 14.5% of its variance. g_{Speed} in turn was strongly associated with g, as has often been found.[12] With g_{Speed} in the model, the common white matter tract integrity factors were no longer significantly associated with g, and removing these paths slightly increased the model fit. Thus, we found full mediation of the link between the three different indicators of white matter tract integrity and g by g_{Speed}.

DISCUSSION

In a sample that is large among the studies including multiple complex imaging parameters, we identified three brain-wide white matter tract integrity biomarkers derived from quantitative MRI methods. Two of them (T1 and MTR) are new to the study of intelligence in non-clinical samples. These biomarkers explained a substantial proportion of individual differences in cognitive information-processing speed and general intelligence in this relatively large sample of generally healthy older people. The finding that all three indicators are only modestly correlated with each other and showed independent significant associations with cognitive ability (information-processing speed and general

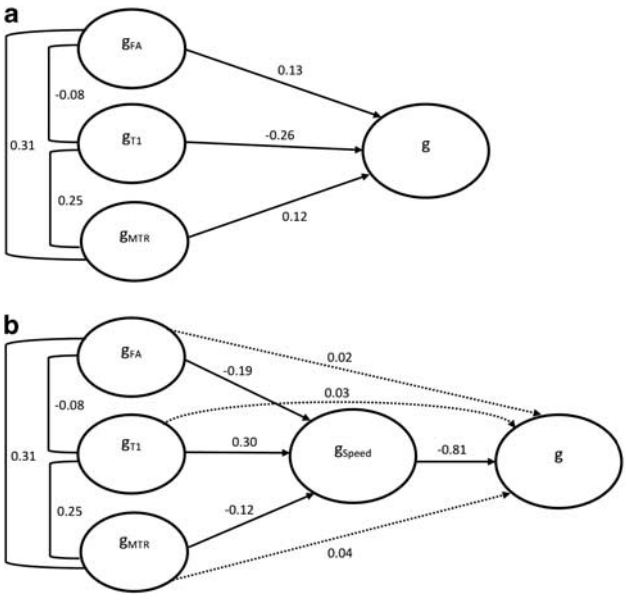

Figure 2. Results of SEM of the three white matter integrity factors, general intelligence, and information-processing speed. Only the latent variables are depicted. For full measurement models see Supporting Online Materials. All path estimates are standardised. (**a**) g_{FA}, g_{T1} and g_{MTR} (common latent factors each defined by their respective tractography estimate for all 12 tracts) are independently associated with general intelligence (*g*) ($\chi^2(755) = 1721.27$, CFI = 0.945, NNFI = 0.938, RMSEA = 0.055, SRMR = 0.054), explaining 10.0% of the variance. (**b**) Cognitive information-processing speed (g_{Speed}) mediates the association between the three latent white matter tract integrity factors and general intelligence. Note that higher values of g_{Speed} indicate slower (less favourable) information-processing speed. The model with solid lines fits the data well ($\chi^2(880) = 1900.894$, CFI = 0.943, NNFI = 0.936, RMSEA = 0.053, SRMR = 0.053, AIC = 36524.9, BIC = 37151.1). Additional direct paths from g_{FA}, g_{T1} and g_{MTR} to *g* (dotted lines) have negligible, non-significant path estimates and decrease model fit (AIC = 36530.1, BIC = 37168.5), indicating full mediation of the effect of the three white matter tract integrity indices on general intelligence by cognitive information-processing speed.

intelligence) suggests that they reflect complementary functional aspects of white matter integrity, possibly related to loss of axonal structural organisation (FA), increased interstitial water content (T1) and reduced macromolecular (MTR) integrity of axons.[15,20,21] Thus, T1 and MTR provide important novel additions to the more widely used neurostructural and DT-MRI-based biomarkers in clinical and cognitive neuroscience studies of white matter across the lifespan.

We replicated and extended our previous finding of substantial, uniformly positive correlations among tracts for FA,[22] and discovered similar correlation patterns for T1 and MTR. These correlations are reflected in the strong general factors found for all three parameters. Although these results do not preclude that specific tracts can stand out in their association with intelligence, as has, for example, been hypothesised for the arcuate fasciculus,[8] they imply that white matter integrity is to a substantial degree a brain-wide property, not something that differs markedly between individual tracts. Thus, if an otherwise healthy individual shows structural deficits in one tract, all other tracts will usually be affected to some degree.

Owing to the age-homogeneous and generally healthy nature of our sample, the results are not confounded by chronological age-related factors or pathological differences between individuals, which can exaggerate results from more heterogeneous samples. On the other hand, the average age of our sample, in their early 70s, makes it plausible that common accompaniments of ageing (for example, loss of microvascular integrity and increased interstitial brain water content) have already affected white matter integrity and cognitive ability,[38,39] possibly partly explaining the strength of our findings.[19] However, the extent to which age-related changes in brain structure and cognitive ability are causally linked remains unclear[40] and repeating our analyses while statistically controlling for self-reported medical histories of hypertension, cardiovascular disease and diabetes did not have noteworthy effects on the reported results. Additional analyses controlling for childhood cognitive ability, assessed at 11 years of age in this cohort,[23] give some indication that FA and T1 are more associated with intelligence later in life, whereas the association with MTR could have long-standing neurodevelopmental origins (see Supplementary Information). It will be interesting to explore how far the results can be generalised to different age groups, with and without overt white matter damage, and to patients with clinical conditions like stroke, dementia, neuroinflammatory or neurodegenerative disorders.

Combined, the three biomarkers of brain-wide white matter tract integrity explained 10% of the intelligence differences in our older sample and even more of the differences in information-processing speed. The large sample size implies that the effect estimates are likely to be robust. These effect sizes do compare with that of the best-replicated neuroanatomical correlate of intelligence, brain size.[2,41] However, the present study's results are based on a more tractable set of brain biomarkers; it is far from clear why brain size affects cognitive performance.[2,42] By contrast, white matter tracts constitute the neuroanatomical infrastructure for any brain network model of cognitive performance,[14] and tract integrity can be directly linked to cognitive information-processing speed and via this mediating path to general intelligence. Although there might be several heterogeneous neurostructural substrates underlying intelligence,[43,44] the current study provides empirical evidence for one mechanistically plausible neurostructural model of human intelligence differences.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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