A watershed model of individual differences in fluid intelligence

Rogier A. Kievit[1*]

Simon W. Davis[2,3]

John Griffiths[2,4]

Marta Correia[1]

Cam-CAN[5]

Richard N. Henson[1]

*Corresponding author. Rogier.Kievit@mrc-cbu.cam.ac.uk

[1]MRC Cognition and Brain Sciences Unit, 15 Chaucer Rd, Cambridge, CB2 7EF, United Kingdom
[2]Department of Psychology, University of Cambridge, Downing Street, Cambridge, CB2 3EB, United Kingdom
[3]Center for Cognitive Neuroscience, Duke University, Durham, North Carolina 27708
[4]Rotman Research Institute, Baycrest, Toronto, Ontario M6A 2E1, Canada
[5]Cambridge Centre for Ageing and Neuroscience (Cam-CAN), University of Cambridge and MRC Cognition and Brain Sciences Unit, Cambridge, UK, www.cam-can.com

Abstract

Fluid intelligence is a crucial cognitive ability that predicts key life outcomes across the lifespan. Strong empirical links exist between fluid intelligence and processing speed on the one hand, and white matter integrity and processing speed on the other hand. We propose a watershed model that integrates these three explanatory levels in a principled manner in a single statistical model, with processing speed and white matter figuring as intermediate endophenotypes. We fit this model in a large (N=562) adult lifespan cohort of the Cambridge Centre for Ageing and Neuroscience study (Cam-CAN) using multiple measures of processing speed, white matter health and fluid intelligence. The model fit the data well, outperforming competing models, providing evidence for a many-to-one mapping between white matter integrity, processing speed and fluid intelligence, and can be naturally extended to integrate other cognitive domains, endophenotypes and genotypes.

Keywords

Cognitive ageing, White matter, Processing speed, Fluid intelligence, Structural Equation Modelling, Watershed model

1.1 Introduction

Fluid intelligence, or fluid reasoning, is a core feature of human cognition. It refers to the ability to solve novel, abstract problems that do not depend on task-specific knowledge (Blair, 2006; Carroll, 1993; Deary, 2012; Horn and Cattell, 1966). In contrast to crystallized intelligence, which continues to improve across most of the lifespan, fluid intelligence shows strong age-related declines (Horn and Cattell, 1966; Salthouse, 2009). Understanding the causes of this decline is important for healthy ageing, as preserved fluid intelligence is strongly associated with independent day-to-day functioning (Tucker-Drob, 2011; Willis and Schaie, 1986), and is inversely related to mortality risk (Aichele et al., 2015). At the other end of the lifespan, low fluid intelligence in adolescence predicts poor outcome in later life (e.g. Huepe et al., 2011) and is a risk factor for psychopathologies such as schizophrenia (Blair, 2006; Snitz et al., 2006). However, our understanding of how this crucial cognitive ability relates to broader, mechanistic frameworks of cognition and the brain is limited. The most promising clues come from the relationships consistently observed between fluid intelligence, processing speed and white matter integrity (e.g. Bennett & Madden, 2013; Fry & Hale, 1996; Jackson, Balota, Duchek, & Head, 2012; Kail, 2007; Penke et al., 2010; Robitaille et al., 2013; Salthouse, 1996a). Although intriguing, these empirical relationships are often interpreted in isolation (e.g. relating fluid reasoning to processing speed, or processing speed to white matter). One unresolved question is whether fluid intelligence, processing speed and brain physiology are independent predictors of age-related decline, or whether they are emergent properties of a single, hierarchical system.

Here, we propose a statistical framework to examine this question, developed by formalizing a conceptual model taken from the literature on psychopathological constructs and their causes. This so-called 'watershed model' (Cannon and Keller, 2006) uses the metaphor of a river system to illustrate how complex behavioural traits can be seen as the downstream consequence of many small upstream (e.g., neural/genetic) contributions. From this perspective, the relationship between fluid intelligence (hereafter FI), processing speed (PS) and white matter (WM) is hierarchical, such that WM

integrity affects PS, which in turn affects FI. We show that this model naturally accommodates a wide and disparate range of empirical findings, integrates a series of relatively well-established mechanistic proposals into a single larger model, and, most importantly, can be formally tested using Structural Equation Modelling (SEM). Based on this model, we derive a variety of statistical predictions that follow from it, and use SEM to test them empirically in a large (N=562), population-based sample of ageing adults (18-87 years, Cam-CAN). First, we examine the empirical evidence concerning FI, PS and WM integrity.

1.2 Processing speed, fluid intelligence and white matter

Processing speed refers to the general speed with which mental computations are performed. It has been considered a central feature of higher cognitive functioning since the development of the first formalized models of (fluid) intelligence (Salthouse, 1982; Spearman, 1927). It shows comparatively steep age-related declines, similar to or even stronger than FI (Horn & Cattell, 1966; Salthouse, 2000; Schaie, 1994). It has been operationalized in a variety of ways, ranging from reaction times (RTs) on speeded cognitive tasks to estimation of neural response latencies via electroencephalography (EEG) (Schubert et al., 2015). The empirical association between PS and FI is one of the most robust findings in psychology (Sheppard and Vernon, 2008). This association holds across the lifespan (Salthouse, 1994), in both healthy elderly (Ritchie et al., 2014), in the extremes of mental retardation (e.g. Kail, 1992) and in longitudinal data (Ghisletta et al., 2012). A common metric of PS is the central tendency, such as the mean or median, of RTs on a simple reaction time task. However, individual differences in the *variability* of RTs also relate to fluid reasoning ability (Rabbitt, 1993), such that less variable responses are associated with higher scores on fluid reasoning tasks. This 'cognitive consistency' in RTs has been shown to predict cognitive performance in elderly subjects beyond mean RT (MacDonald, Li, & Bäckman, 2009). Both central tendency and variability of PS predict all-cause mortality (Batterham et al., 2014; Hagger-Johnson et al., 2014), supporting the idea that both are important and independent components of PS. The role of variability can be observed even on the purely neural level: A study using EEG in young adults (Euler et al., 2015) found

evidence for the role of variability of neural responses, such that individuals with more stable (less variable) responses to novel stimuli tended to have higher fluid reasoning ability.

Recent work suggests that the proper conceptualisation of the relation between PS and FI is as a causal factor (e.g.,Kail, 2000; Rindermann and Neubauer, 2004; Robitaille et al., 2013). The most influential causal account comes from Salthouse (1996), who suggested at least two mechanisms by which PS affects cognitive performance, namely the *limited time mechanism* and the *simultaneity mechanism.* The former suggests that in any timed task, slower speed of processing simply precludes the timely finishing of cognitive operations, leading to poorer scores; the latter suggests that high PS is necessary to juggle mental representations in sufficient detail for complex cognitive operations to be performed on them (see Burzynska et al., 2013, for neuroimaging evidence for this claim). More recent work (Schubert et al., 2015) used drift-diffusion and EEG modelling to show that there are multiple components to processing speed, and that these components play a different causal roles in different cognitive tasks. Moreover, they showed that neurophysiological indicators (ERP's) of speed were spatially specific in the cortex (the largest effects found in the central parietal electrodes), and that the relative importance of various neural speed measures (e.g. the P200 and P300) differed across levels of task difficulty. In summary, nearly all of the papers reviewed above, either explicitly or implicitly, consider PS to be a 'lower', or more fundamental, mental process that is not identical to FI itself (see also Schubert et al., 2015). We can go even further down this presumed causal hierarchy to understand the possible determinants of PS. One such candidate is white matter integrity. In summary, nearly all of the papers reviewed above, either explicitly or implicitly, consider PS to be a 'lower', or more fundamental, mental process that is not identical to FI itself (see also Schubert et al., 2015). We can go even further down this presumed causal hierarchy to understand the possible determinants of PS. One such candidate is white matter integrity.

Multiple investigations support a tight relationship between WM and PS. Among the most influential studies showing the importance of white matter integrity are two papers by Penke and colleagues, who showed that the first principal component of white matter integrity predicted both

information processing speed (Penke et al., 2010) as well as general intelligence (Penke et al., 2012). Further work has shown that decreased WM integrity has been associated with decreased PS both in healthy adults (Tuch et al., 2005) and in individuals suffering from clinical conditions associated with WM loss such as Multiple Sclerosis (Kail, 1997, 1998; Roosendaal et al., 2009; Segura et al., 2010; see Bennett & Madden, 2013, for a review). WM health has also been associated with the variability of RTs in children (Tamnes et al., 2012), in healthy controls and preclinical Alzheimer's dementia (Jackson et al. 2012), and decline in WM has been proposed as a key cause of age-related changes in cognition (O'Sullivan et al., 2001). This relationship between WM and performance variability has been found to strengthen with age (Fjell et al., 2011; Laukka et al., 2013; Lövdén et al., 2013b). Other studies have found direct relationships between WM measures and FI (Haász et al., 2013; Kievit et al., 2014; Ritchie et al., 2015a) and specific neural (including white matter) structural correlates of intra-individual variability (MacDonald et al., 2009, 2006). Similarly, lesions in WM predict age-related declines in mental speed (Rabbitt et al., 2007b; but see Yang et al., 2014). Assessing a broad set of cognitive and neural markers in a large, age-heterogeneous cohort, Hedden et al. (2014, p. 1) conclude that 'The largest relationships linked FA and striatum volume to processing speed and executive function'. In a longitudinal cohort investigating reasoning ability, white matter maturation and processing speed in children (6-18) (Ferrer et al., 2013) concluded that 'structure of the relations among processing speed, reasoning, and whole-brain FA are best captured as unidirectional, with WMO predicting processing speed, and processing speed in turn predicting reasoning.' (pp. 948).

A critical link in our model is the behavioural consequence of the microstructural properties evident in the large white matter structures critical for signal transmission between disparate regions of cortex. Various mechanisms (although none demonstrated definitively) have been proposed to explain the relation between WM and PS. One hypothesis is that greater noise in the nervous system due to inefficient signal transmission leads to a lower signal to noise ratio, which in turn affects signal strength by either weakening the signal, increasing the background noise, or both - ultimately leading to slower responses (Kail, 1997; Rolls and Deco, 2015). This is consistent with the fact that the

principal age-related change in white matter tissue with advanced ageing is a reduction in axonal density (Peters, 2009), which would be expected to result in a reduced effective synaptic gain. A related hypothesis that is gaining support is the proposal that age-related demyelination affects propagation of action potentials (Bartzokis et al., 2010), an explanation consistent with slowing in patients with MS (Turken et al., 2008). Unlike MS, however, observations of an age-related increase in dystrophic myelin are relatively rare in macaque microscopy studies, leading (Peters, 2009)to propose remyelination with shorter internodes as the cause of age-related slowing observed in neurophysiological data. Whilst much further research is needed, these mechanistic accounts help to explain the strong and consistent neurocognitive relationship between PS and WM (Bennett and Madden, 2013; Penke et al., 2010; Turken et al., 2008). Together this suggests a hierarchical relationship, where WM affects PS, which in turn affects FI. Below, we describe a model that can integrate these diverse findings.

1.3 Watershed Model

Our goal is to integrate the three explanatory levels (FI, PS and WM) into a single model that captures both the empirical findings and the hypothesized mechanistic links. This a general challenge in cognitive neuroscience, namely that of *reductionism* (Kievit et al., 2011a): How do we best relate the phenotype observed at the 'higher' level of measurement (e.g., scores on a test of fluid intelligence) to possible underlying mechanisms in the brain (e.g., WM integrity)? We show how a theoretical model from the field of psychopathology can be translated into a testable psychometric model to achieve this goal.

In psychopathology, single cause models for mental disorders such as schizophrenia were initially popular, but have not been successful: Despite being highly heritable and having various structural brain correlates, the search for single (or even a limited set of) genetic loci has not yielded candidates that explain more than a trivial percentage of the variance of the phenotypes of interest. One possible avenue of explanation is the 'watershed model', proposed by Cannon and Keller (2006)

has provided a conceptual framework to help understand the potential multiple determinacy between various explanatory levels in the study of mental disorders (see also Penke et al., 2007).

A simplified representation of this model is shown in *Figure 1*. The central idea is that an observable phenotype, such as schizophrenia, can be thought of as the mouth of a river (denoted by "1" in the Figure), and is the end product of a wide range of small, causal, genetic influences (genotypes) that exert their influence through a series of intermediate endophenotypes (such as neural and cognitive variables). A crucial assumption in this model is that genetic influences do not directly cause the phenotype of schizophrenia, but do so indirectly via the endophenotypes.

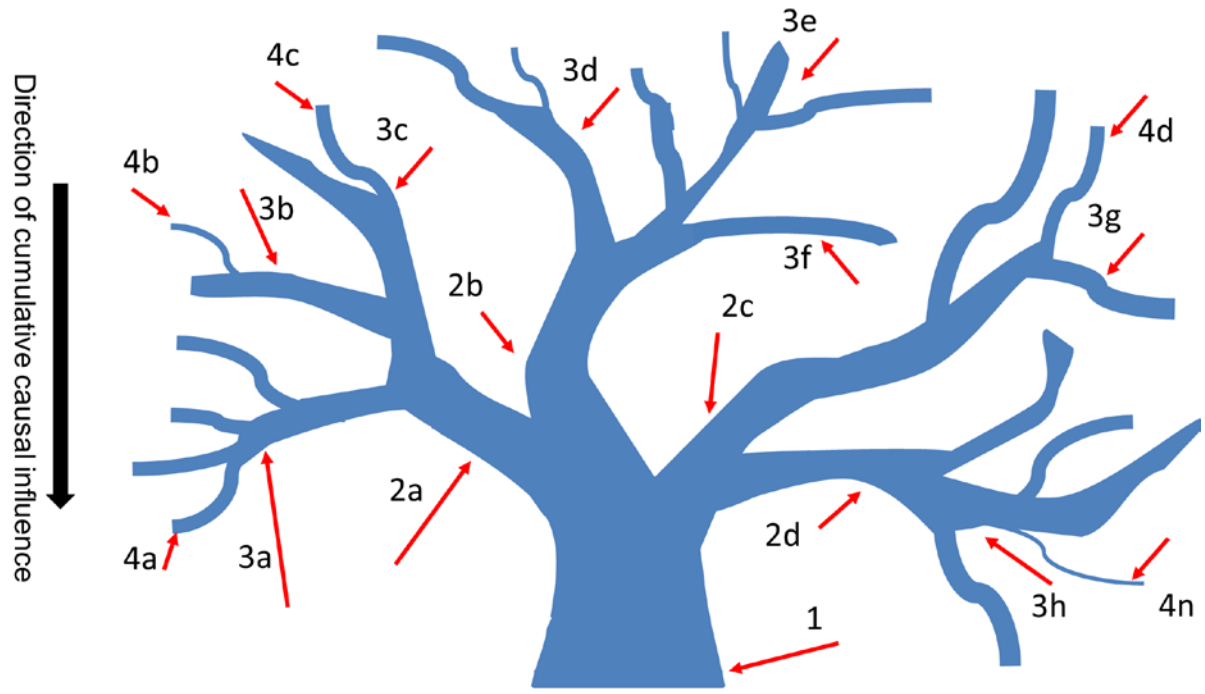

Figure 1: *The watershed model of psychopathology (adapted from Cannon & Keller, 2006). Point "1" represents the most complex phenotype, e.g. schizophrenia; points "2a-2d" represent endophenotypes, such as lower-level behavioural consequences; points "3a-3g" represent the neural antecedents of those behavioural phenotypes. Points 4a-4d represent hypothetical genetic influences (not measured here)*

These endophenotypes are the intermediate mechanistic steps between many small genetic influences that together exert considerable influence (the idea of many small genetic effects has been referred to as the Fourth Law of behavioural genetics, c.f. C. F. Chabris, Lee, Cesarini, Benjamin, & Laibson, 2015). Such a model allows us to integrate the disparate known endophenotypes of schizophrenia, such as working memory deficits, letter fluency, and auditory learning (Snitz et al., 2006) as potentially independent upstream 'tributaries' (denoted by "2a"-"2d") that all contribute to the distal consequence (1).

This model has a variety of conceptual benefits, including the fact that it naturally accommodates the heterogeneity of psychopathological constructs. For example, based on a strict interpretation of the DSM-V criteria, there are approximately 1500 ways (constellations of symptoms) to receive the same diagnosis of 'Major Depressive Disorder' (Ostergaard et al., 2011; see also Fried and Nesse, 2015). In other words, many constellations of antecedent causes can contribute, independently, to some aggregate behavioural phenotype. This proposed causal heterogeneity explains the relative lack of success of directly mapping phenotypes such as schizophrenia, depression or fluid intelligence onto genetic markers: Given that there is inherent multiplicity in the phenotype (the same simplifying label, e.g. 'schizophrenia', is used for distinct phenotypical profiles), the mapping of the phenotype to genetic causes will be noisy, so large samples will be needed. Recent empirical findings seem to support this perspective: Where an earlier, much smaller (N=3000) study explained 3% of the variance in schizophrenia (Purcell et al., 2009), an extremely large-scale (N= 150,064) GWAS study (Ripke et al., 2014) found a constellation of genes that together explained 18.4% of the variance, illustrating how many small effects can together have considerable downstream consequences.

Cannon and Keller (2006, p. 274) derive from their model various empirical and conceptual predictions. These include that endophenotypes (intermediate causes) should be heritable, they should be associated with causes rather than effects, and numerous endophenotypes should affect a given construct. The model therefore predicts that a more efficient way of studying genetic causes is

to focus on the endophenotypes of a disorder first, and then examine the genetic antecedents of those endophenotypes located further 'upstream'. Moreover, endophenotypes are expected to vary continuously in the population and they should affect multiple disorders. We here adopt the watershed model to explain the relationship between fluid intelligence, processing speed and white matter by translating the watershed model from conceptual tool into a testable statistical model.

In our representation, FI is the 'mouth' of the river, influenced by upstream endophenotypes of PS and WM. This implies a hierarchical relationship, such that greater WM integrity (3a-3h) affects PS (2a-2d), which in turn affects fluid intelligence (1). If we examine the predictions by Cannon and Keller described above, we can see that all are supported for our three explanatory levels. Firstly, both the phenotype and the proposed endophenotypes are highly heritable: FI (Deary et al., 2010), PS (e.g. Vernon, 1989) and WM integrity (Chiang et al., 2009). However, there has been a notable lack of success in establishing replicable genetic markers for FI (Chabris et al., 2012). Finding statistical support for a watershed model would represent an important step towards a mechanistic understanding of the myriad influences on the cognitive construct of fluid intelligence, which in turn may facilitate better understanding of why this key cognitive ability changes so rapidly across the lifespan. First we examine what statistical predictions follow from the model. Recent work has shown how, under certain circumstances, reductionist hypotheses can be translated to formal statistical models, such as structural equation models of covariance patterns (Kievit, 2014; Kievit et al., 2011a, 2011b; Salthouse, 2011). The watershed model makes multiple predictions that can be translated into testable models.

1.3.1 *Greater upstream statistical dimensionality*

As one can see in *Figure 1,* upstream 'tributaries' represent partially independent influences on the phenotype. This means that if we move up the tributaries of the river and examine the statistical dimensionality of the variables at each level, we would expect this dimensionality of the covariance pattern between all variables at that level to increase. Although they likely share some environmental

or genetic influences and so will be correlated to some degree, we expect that the upstream effects cannot be fully captured by a single summary statistic.

1.3.2 *Unidimensional constructs*

Complementary to the greater upstream dimensionality is the prediction that scores on the ultimate phenotype, whatever it may be, will be both continuous and approximately normally distributed. Although the individual component processes may have all kinds of distributions, these lower level endophenotypes will have additive effects such that they will together, due to the central limit theorem, lead to an approximately normal distribution of individual differences (Bartholomew, 2004, pp.99).

1.3.3 *Multiple realizability*

As we have seen above, the watershed model suggests that seemingly unitary phenotypes such as 'being depressed' or 'being schizophrenic' are nonetheless likely to have multidimensional antecedent causes. In other words, a single behavioural dimension such as intelligence map onto multiple neural determinants; a type of between-individual *degeneracy* (Friston and Price, 2003). There is increasing evidence for such a many-to-one brain-behaviour mapping. For example, recent evidence suggests that differences in emotional states are better seen as a broad network of regions showing a different activation profile, rather than activity in individual regions in isolation mapping onto individual emotional states (Lindquist et al., 2012). Similarly, many concurrent and partially independent neural properties determine individual differences in broad cognitive skills such as general intelligence (Kievit et al., 2012; Ritchie et al., 2015b). In a SEM framework, this prediction means that variability in each endophenotype will make partially independent contributions to variability in the phenotype in line with a so-called *MIMIC* model (Multiple Indicators, Multiple Causes; see Jöreskog and Goldberger, 1975; Kievit et al., 2012).

1.3.4 *Hierarchical dependence*

A defining characteristic of the watershed model is *hierarchical dependence.* That is, the influence of upstream causes are presumed to 'flow through' lower levels (endophenotypes). Statistically, such a

relationship is known as *d-separation* (Pearl, 2000); a form of conditional independence popularized in graphical representations. This concept formalizes the notion that in a hypothesized causal chain, such as X->Y->Z, the intermediate variable (Y) "d-separates" the relationship between X and Z, such that taking it into account renders X and Z statistically independent. In the present context, we hypothesize that the endophenotype of PS ('Y') d-separates the influence of WM integrity ('X') on fluid intelligence ('Z'). In the SEM formalization of this hypothesis below, any direct paths between WM and FI will be a source of model misfit.

Taken together, it is possible to capture all these statistical predictions in a single structural equation model. This model is a multi-level version of the MIMIC model (shown graphically in Figure 6). This model assumes that a latent variable (here FI) represents the phenotypic endpoint. The unidimensionality of this phenotype is tested by fitting a confirmatory factor model to the various behavioural measures available (four sub-scores of the Cattell test in the present data). At the second level, we hypothesize that various measures of PS: a) cannot be captured by a single factor, b) provide partially independent predictions of the fluid intelligence, and c) the latent variable of FI 'shields off' all direct effects of speed measures on the observed Cattell scores. Likewise, the WM tracts should have partially independent influences on the PS variables, but should have no direct paths to FI when fitting a full model. The statistical predictions described above can either be tested as part of the full model such that violations will lead to model misfit, or by explicit testing of individual elements. We will fit a MIMIC model in stages, so as to build up to the full the watershed model, and examine whether the predictions at the various stages described above are corroborated by our data.

2. Methods and Experimental Procedures

2.1 Sample

A healthy, population-derived sample was collected as part of Phase 2 ("700") of the Cambridge Centre for Ageing and Neuroscience (Cam-CAN), described in more detail in (Shafto et al., 2014). Exclusion criteria included low Mini Mental State Exam (MMSE, 24 or lower), poor hearing, poor vision, poor English (non-native or non-bilingual English speakers), self-reported substance abuse and

current serious health conditions. Prior to analysis, we defined outliers as values for any variable that were more than 4 standard deviations from the mean (0.27% of all values) and included all participants with scores on all variables. The final sample contained 562 people, 277 female, age range 18-87, M=53.98, SD=18.27. A subset of these data have been reported in (Kievit et al., 2014). The R code used to run all analyses data are available for download through this private link http://figshare.com/s/97eb627e36ce11e5b10206ec4bbcf141. The covariance matrix is in the Appendix A. The raw data is available upon signing a data sharing request form to comply by our ethics approval.

2.2 Processing speed

We operationalized PS by measuring reaction times in three different cued-response tasks: simple response time (SRT), choice response time (CRT) and audio-visual cued response time (AVRT). These tasks differed in their demand characteristics, such as the nature of the cue and the predictability of the stimulus, and so may tap different aspects of PS. Unlike the other two tasks, participants were not explicitly instructed to respond as quickly as possible, so this variable captures the natural response time in the absence of specific instructions to respond speedily. For procedural details, please see (Shafto et al., 2014) p. 6 (for SRT and CRT) and p. 16 (for AV). We include the mean and standard deviation for all three tasks, leading to a total of 6 measures of PS (SRTspeed, CRTspeed, AVspeed, SRTcons, CRTcons and AVcons). All six variables were inverted (so that higher scores reflect speedier and more consistent responses respectively). Figure 2 A, B and C illustrate the three processing speed tasks respectively.

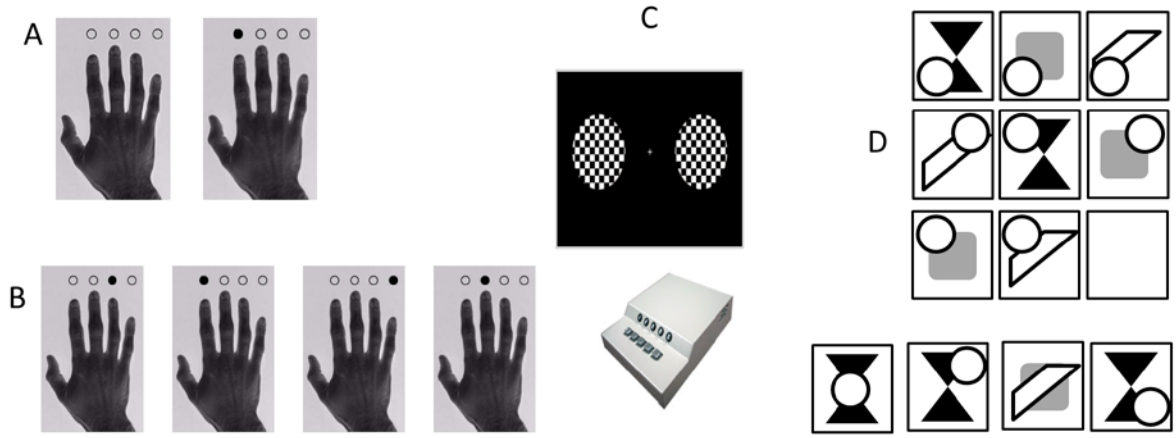

***Figure 2**: Behavioural measurements. Simple RT (a), choice RT (b), AV RT (C) and Cattell (d) (fictional example item shown)*

2.3 Fluid intelligence

FI was measured using the Cattell's Culture Fair, Scale 2, Form A (Cattell, 1971), administered according to the standard protocol. This is a pen-and-paper test, consisting of four subtests with different types of abstract reasoning tasks, including series completion, classification, matrices and conditions. These four subtests yield a sum-score representing the total number of correct responses. Figure 2d shows an example test item.

2.4 White matter Integrity

In order to assess how different white matter tracts contribute to different cognitive functions, we computed mean fractional anisotropy (FA) values in various regions of the brain. Fractional anisotropy is a measure of the diffusivity of water molecules, thought to reflect axonal diameter, the degree of myelination and fiber density. For more detail on the white matter pipeline, see Appendix D. We computed mean FA for ten tracts as defined by the Johns Hopkins University white-matter tractography atlas (Hua et al., 2008): The uncinate fasciculus (UNC), superior longitudinal fasciculus (SLF), inferior fronto-occipital fasciculus (IFOF), anterior thalamic radiations (ATR), forceps minor

(FMin), forceps major (FMaj), cerebrospinal tract (CST), the inferior longitudinal fasciculus (ILF), ventral cingulate gyrus (CINGHipp) and the dorsal cingulate gyrus (CING) – see Figure 5A).

2.5 SEM

All models were fit using the package Lavaan (Rosseel, 2012) in R (Team, 2014). Prior to model fitting, variables were scaled to a standard normal distribution and log transformed where necessary to increase normality. All models were fit using Maximum Likelihood Estimation (ML) using robust standard errors and report overall model fit using the Satorra-Bentler scaled test statistic. Model fit was assessed with the chi-square test, RMSEA and its confidence interval, the Comparative Fit index and the standardized root mean squared residuals (Schermelleh-engel et al., 2003). We define good fit as follows: RMSEA<0.05 (acceptable: 0.05-0.08), CFI>0.97 (acceptable: 0.95-0.97) and SRMR <0.05 (acceptable: 0.05-0.10) and report the Satorra-Bentler scaling factor for each model. Models are compared using a chi-square test when nested and using the AIC in other cases. The model fit minimizes the discrepancy between the observed covariance matrix and the estimated covariance matrix $\sum(\Theta)$. The estimated covariance matrix is modelled as follows:

$$\sum(\Theta) = \Lambda\left(I - B\right)^{-1}\Psi(I - B)^{'-1}\Lambda'+\Theta$$

where Λ is a matrix of the factor loadings, B is a matrix of latent regression terms, I is the identity matrix of regressions, Ψ is the variance/covariance matrix of the latent variables and the neural predictors and Θ is a matrix of error terms.

3. Results

To examine the predictions of the watershed model, we will build up the full model, starting at the 'top'. First, we fit our measurement model, namely relating the latent variable FI to the four scores on the Cattell subtests. This model fit the data well: χ2 = 4.452 (N=562), df =2, p=0.108, RMSEA = 0.047 [0.000 0.106], CFI = .996, SRMR = 0.01, Satorra-Bentler scaling factor=1.019, suggesting that performance could be captured by a single dimension, as predicted by the watershed model. As expected, scores on the latent variable showed steep age-related decline. A linear regression explained 43.98% of the variance (*N*=562, *F*(1,560)=441.3, p < 0.0001, adjusted R^2=.4398) and a second-order polynomial explained 46.82% of the variance (*N*=562, *F*(2,559)=247.9, p < 0.0001, adjusted R^2=.4682), with the AIC slightly favouring the polynomial (steeper decline in later life, AIC_{linear}= 1177.59, AIC_{poly}= 1149.32). Furthermore, a Breusch-Pagan test showed that residuals increased slightly suggesting greater inter-individual variability in later life (BP= 18.878, df=2, p= 0.000079). Model fit and age-related differences are shown in Figure 3.

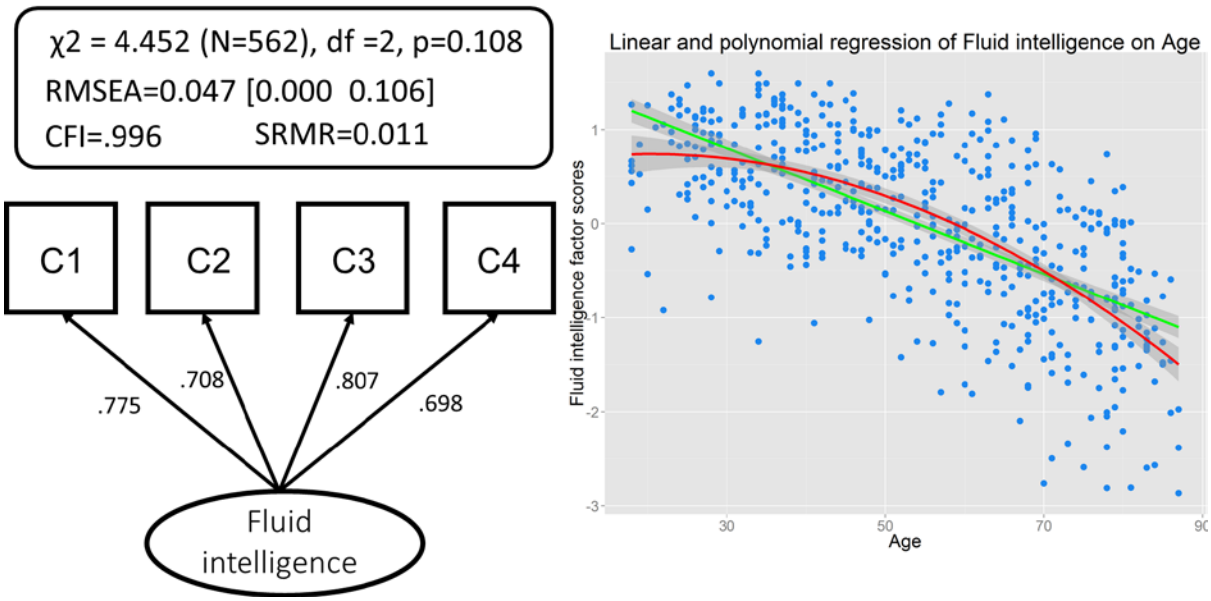

Figure 3. A single-factor confirmatory factor analysis for Cattell fits data well (left). Linear and polynomial fit of age-related differences in fluid intelligence (right).

In order to establish the relationship between PS and FI, we first examined the dimensionality of the PS measures. The watershed model suggests that variables more 'upstream' may be partially independent, as they have a multitude of potentially independent genetic and neural antecedents. To assess whether this holds for our measures of PS, we fit a single factor model to the six PS measures. This model fit the data very poorly: $\chi2 = 705.268$, df =9, $p < 0.0001$, RMSEA = 0.371 [0.349 0.394], CFI = 0.551, SRMR =0.162, Satorra-Bentler scaling factor=1.08. We then examined whether a model with two latent variables, one for speed (measured by SRT_{speed}, CRT_{speed}, AV_{speed}) and one for consistency (SRT_{cons}, CRT_{cons} and AV_{cons}) would fit better. This model also fit poorly: $\chi2 = 671.750$, df =8, $p < 0.0001$, RMSEA = 0.384 [0.361 0.408], CFI = 0.572, SRMR = 0.157, Satorra-Bentler scaling factor=1.131 as did a final competing model with a latent factor for each task (SRT, CRT and AV) $\chi2 = 123.628$, df =6, $p < 0.0001$, RMSEA = 0.187 [0.160 0.215], CFI = 0.924, SRMR = 0.047, Satorra-Bentler scaling factor=1.085).

The watershed model predicts that the six variables (if truly relevant) will make partially independent contributions to fluid intelligence. To test this hypothesis, we fit the simple MIMIC model shown in Figure 4. This showed excellent fit to the data: $\chi2 = 17.912$, df =20, P=.59, RMSEA =0.000 [0.000 0.032], CFI = 1.00, SRMR =0.010, Satorra-Bentler scaling factor=1.034. Most strikingly, five out of the six PS variables (all but SRT_{speed}) predicted unique variance in fluid intelligence. Together these PS measures explained 58.7% of the variance in fluid intelligence. Perhaps surprisingly, AV_{speed} had a modest *negative* path, suggesting that those with higher FI scores are those who had fast response speed when instructed to respond quickly, but slower response speed when not so instructed. This is line with recent evidence suggesting that mental speed is multifaceted and that different elements play complementary roles in supporting higher cognitive abilities (Schubert et al., 2015).

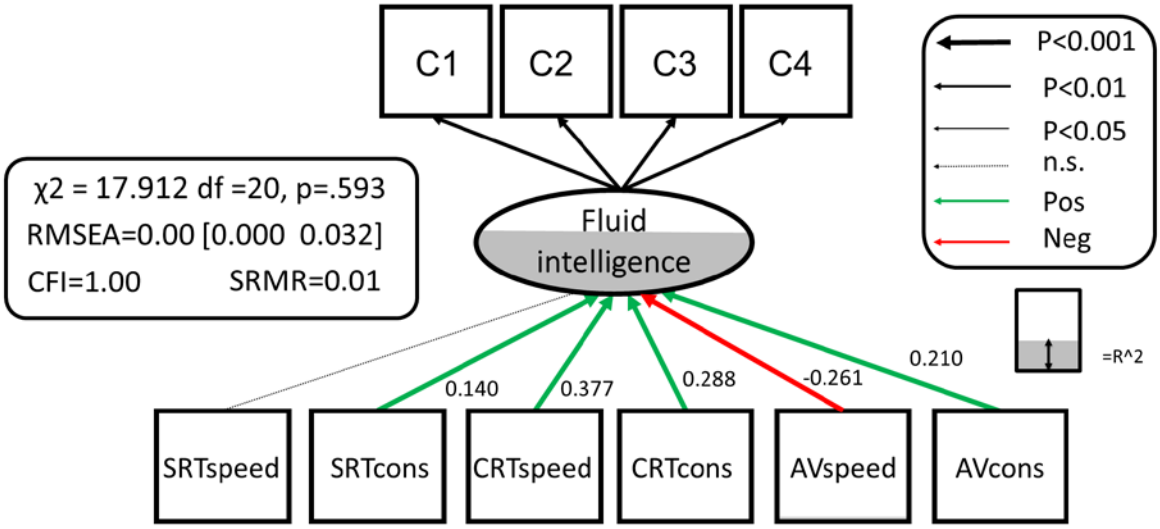

Figure 4. MIMIC model for Processing Speed and Fluid intelligence. Below age-related trajectories for each processing speed measure ranging from strong CRTspeed, r=-0.64) to absent (AVspeed, r=0.03, n.s.)

Figure 4 shows the partially independent contributions of the PS measures to FI and their different age-related differences, ranging from very steep (CRT_{speed}, r=-0.64) to absent (AV_{speed}, r=0.03, n.s.). This is in line with previous work showing that measures of PS (Babcock et al., 1997; Schubert et al., 2015) do not fit a single factor model. The lack of unidimensionality and the partially independent statistical predictions of the PS measures supports the suggestion by Salthouse (2000) that they may reflect 'somewhat distinct processes' (p. 41). An exploratory factor analysis with promax rotation suggests that 3 factors are required to ensure the model is not rejected (see Appendix B). Together, these findings suggest that PS measures from tasks that vary only slightly in task demands can tap into distinct underlying processes, and that individual differences in these PS processes combine to explain a considerable portion of individual differences in fluid intelligence.

The 'lowest' layer of our model pertains to WM integrity. The covariance of WM structure across individuals is informative as its dimensionality can reveal possible mechanisms driving individual differences. We fit a single factor model to the mean FA of the ten, bilaterally averaged, WM regions of interest (Figure 5a) based on the Johns Hopkins white matter tractography atlas (Hua et al., 2008, see Experimental Procedures); distinct age-related trajectories of each ROI-based tract

(Figure 5B). This single factor model showed poor fit ($\chi2$ = 428.344, df =35, p < 0.0001, RMSEA =0.141 [0.130 0.153], CFI =0.822, SRMR =0.069, Satorra-Bentler scaling factor=1.138). The poor fit of the single-factor model was not driven by differential ageing of the tracts: We refitted the model to the age-corrected residuals of the 10 tracts, but this also fit the data very poorly ($\chi2$ = 439.026, df =35, P~0.00, RMSEA =0.143 [0.132 0.154], CFI = .227, SRMR =0.073, Satorra-Bentler scaling factor=1.214). Inspection of the modification indices showed no plausible alternative model that would show better fit. Of course, the misfit of a single factor does not imply that the tracts are uncorrelated: As has been found in many studies before, white matter covariance across tracts is virtually uniformly positive, as can be seen in Appendix A. To estimate the dimensionality of white matter in an exploratory fashion, we ran an exploratory factor analysis with promax rotation on the ten tracts, as shown in Appendix C . Here a saturated model with six white matter factors was required to explain the covariance between the tracts (i.e. an exploratory factor analysis was not rejected). This suggests that, although overall white matter tracts are positively correlated, the dimensionality of this covariance is quite complex. Note that these findings do not necessarily conflict with those in (Penke et al., 2010) who used a Principal Component Analysis to extract a dominant principal component – Although this approach can be a valuable tool, and illustrates the positive correlations among white matter tracts, it is not, strictly speaking, a test of model fit of a single underlying white matter factor (Fabrigar et al., 1999). Together these findings show that the covariance pattern for FA shows considerable dimensionality, replicating recent findings supporting multidimensional WM structure (Laukka et al., 2013; Lövdén et al., 2013a), although see Ritchie et al. (2015a).

Finally, we can test the prediction that, if the influence of WM integrity is indirect, we expect a lower total R^2 when relating WM to FI directly (since a higher R^2 of WM on FI would imply residual direct relations between WM and fluid intelligence). This prediction too was supported, with WM tracts together explaining 41.2% of the variance in fluid intelligence, compared to the previous 58.7% explained by PS measures. We now move to fitting the full model.

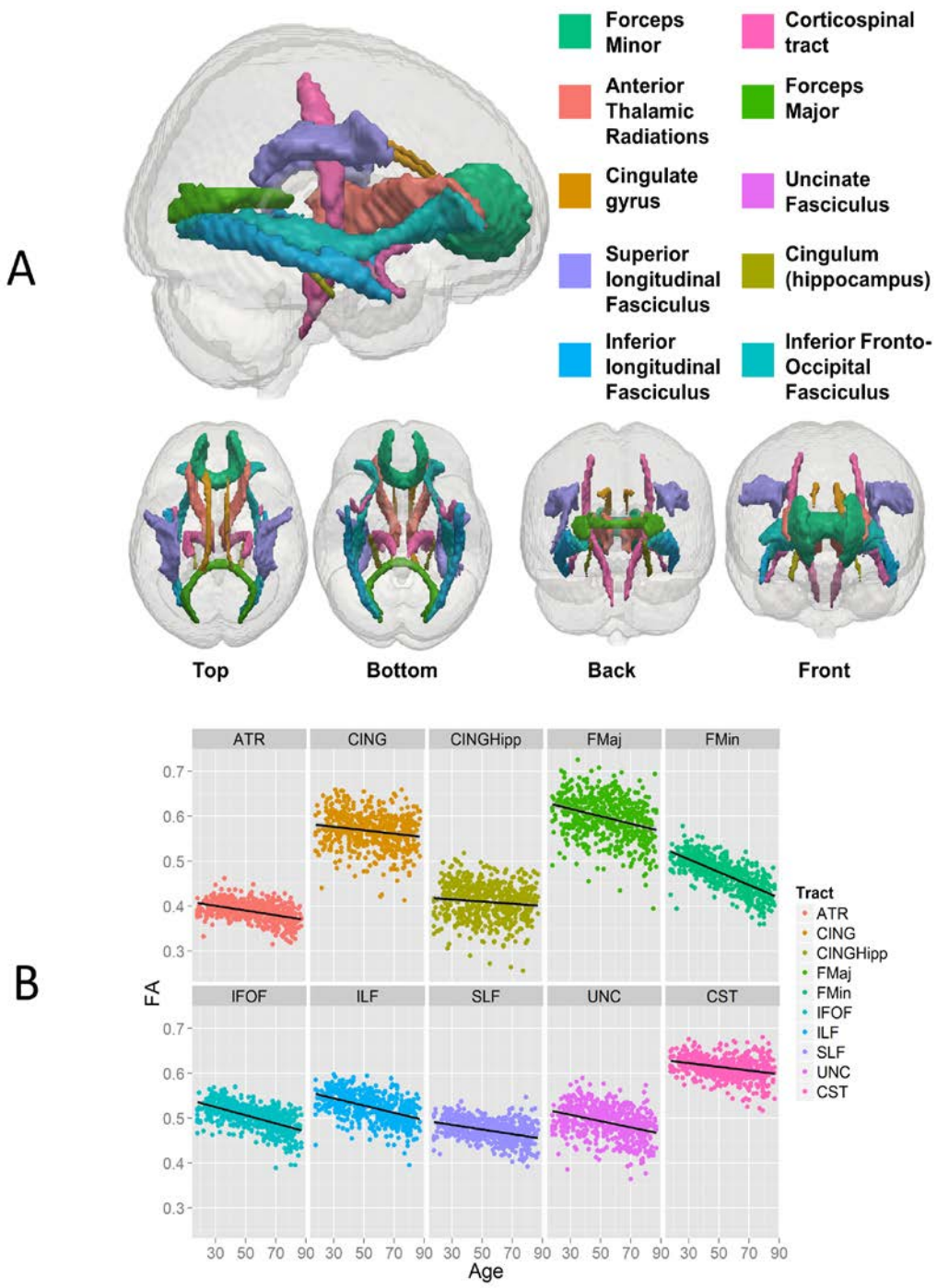

Figure 5. A) All ten JHU tracts used in our analysis, based on the JHU atlas . B) Differential ageing of the ten tracts, correlations ranging from -0.72 (Forceps Minor) to -.11 (Ventral Cingulum, or CINGHipp

3.1 Full model

So far, the findings are in line with the predictions of the watershed model, so we can now fit the full watershed model (Figure 6), integrating fluid intelligence, PS and WM integrity. Doing so we can simultaneously test the hierarchical structure and many-to-one mapping predicted by the watershed model. In this model, we allow for residual covariance *within,* but not *between* layers. This model captures the assumption that all influence that WM tracts have on FI should go through the layer of PS (i.e., any residual covariance between WMI and the latent variable of fluid intelligence, or any of the subtests, would be a source of misfit). Finally, any influence of PS on the Cattell subtests should go via the latent variable of fluid intelligence. The overall watershed representation in Figure 6 showed that the relationships between the four levels fits the data very well: $\chi 2$ = 103.579, df =60, P=0.000, RMSEA =0.036 [0.024 0.047], CFI = .986, SRMR =0.034, Satorra-Bentler scaling factor=1.034). This suggests that the observed covariance pattern in our data is compatible with the statistical constraints imposed by the watershed model; in other words, that the data are compatible with the hypotheses that the three explanatory levels stand in a hierarchical relationship, such that FA determines PS, which in turn determines fluid intelligence. To establish that the fit of the full model was not merely a consequence of some more general property of the covariance matrix, we performed control analyses to test the nature of the hierarchical relationship. Firstly, we *inverted* two lower layers, such that PS affected WM integrity which in turn directly affected FI (again allowing for residual covariances between all WM tracts, but precluding direct influence between PS and fluid intelligence). The original watershed model fit the data considerably better (AIC_{diff}=225.383). As there are more WM variables than PS (which might affect model comparison), we next exhaustively compared all 210 combinations of 6 tracts (the same number as the PS variables) to an inverted model with the same subset of tracts. In every model comparison, the watershed model outperformed the inverted model (AIC_{diff} ranged from 142.9 to 266.9 in favour of the watershed model).

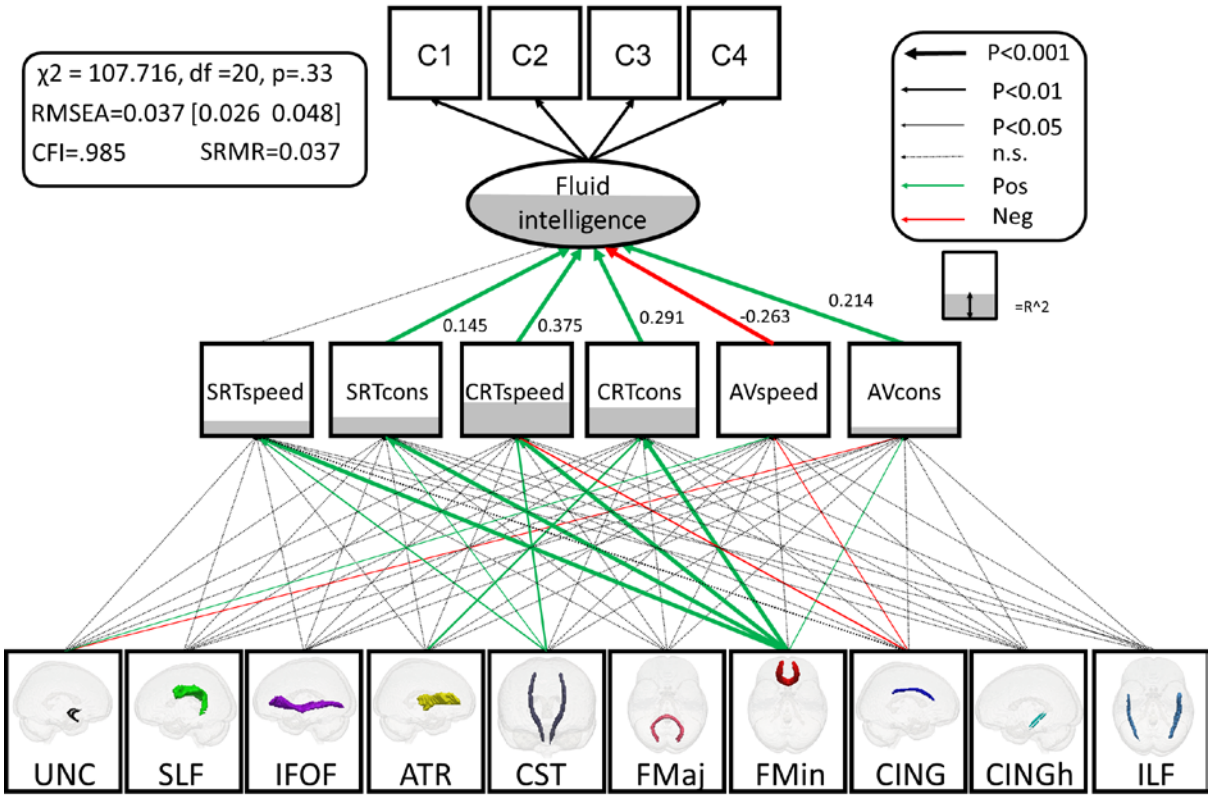

Figure 6: Full watershed model. Significant parameters are shown in green and red, R-squared is represented as the degree of shading of the variables. See Appendix A for the full covariance matrix.

Notable is that the strongest prediction of various measures of PS was WM integrity in the Forceps Minor (also known as the anterior forceps), passing through the genu of the corpus callosum. It explained significant amounts of variance in five of the six response time measures, both for speed and consistency. Moreover, this relationship was strongest for the most 'executive' of PS variables, the mean and variability of the Choice RT task, in line with previous findings that suggest an important role for prefrontal WM in such tasks (Davis et al., 2009). The second strongest effect was of the cortico-spinal tract, affecting three speed measures above and beyond the variance already captured by Forceps Minor (see also Duering et al., (2013) and Lövdén et al., 2014). Note that the absence of

pathways does not imply the absence of zero-order correlations, merely that they do not add explanatory power above and beyond other pathways already present; see the covariance matrix in Appendix A for zero-order relations. Together these findings provide significant support for the watershed model: white matter, processing speed and fluid intelligence stand in a hierarchical, many-to-one relationship that requires measuring a broad spectrum of variables at each explanatory level (WM and PS).

4. Discussion

In our population-derived, age-heterogeneous sample, we found strong evidence for a hierarchical relationship between fluid intelligence, processing speed and white matter. Specifically, individual differences in WM anatomy predicted individual differences in processing speed, which in turn predicted over 58% of the variance in fluid intelligence scores. This model performed significantly better than control models that inverted the direction of effects. This watershed model is based on theoretical considerations, is in line with a wealth of empirical evidence, and provides an overarching framework for modelling causal relationships. All five statistical predictions derived from the watershed model were supported by our data. First, our outcome measure (fluid reasoning) fit a single factor model, whereas no low-dimensional models fit for either PS or WM, and an increasing number of significant pathways was necessary to explain observed patterns. Second, fluid reasoning was unidimensional and close to normally distributed, despite having multidimensional antecedents. Third, there was evidence for a many-to-one mapping, such that multiple individual variables at the processing speed and WM levels explained unique variance in higher explanatory levels. Fourth, the overall model fit significantly better than various alternatives, providing evidence for hierarchical dependency. Finally, the amount of variance explained was greater for the more direct mapping from PS to FI than from WM to FI. These findings have important implications for both the understanding of age-related declines in intelligence, and for the proscriptive ability of cognitive neuroscience to potentially inform successful interventions within aged communities. We expand on the findings and implications below.

Five out of the six processing speed measures predicted unique variance in fluid intelligence, supporting the hypothesis that processing speed is a multidimensional construct, and that these subtle aspects are important for understanding higher, abstract cognitive abilities. Similarly for WM, in line with recent work (Lövdén et al., 2013a), we found that individual differences in WM are multidimensional, and that these different dimensions have partially independent predictions for processing speed. The strongest influence was that of the Forceps Minor, which predicted five distinct processing speed measures, with the corticospinal Tract and the Inferior Fronto-Occipital Fasciculus also explaining considerable variance. In contrast to views that aging represents a monolithic decline, the current findings support the idea that distinct brain regions and distinct cognitive abilities decline in different ways, and that only models which strive to incorporate this multiplicity in their explanations of age-related decline (Andrews-Hanna et al., 2007; Kievit et al., 2014; Lövdén et al., 2014) can capture the entirety of age-related processes.

These findings may have implications for the design and implementation of cognitive training intervention. The watershed model suggests that transfer to other cognitive domains (see also (Taatgen, 2013) may only be achieved if the intervention is of sufficient length and intensity to affect the entire hierarchy of relationships, including the mapping of lower processing speed to higher cognitive processes. Such a suggestion is supported by work showing that WM acts as a cognitive scaffold supporting many distinct cognitive functions (Burzynska et al., 2013).For example, to truly improve fluid reasoning and not just observed scores (Hayes et al., 2015), training would have to be of such duration that lower levels (such as processing speed and WM) are also measurably affected (Keller and Just, 2009; Scholz et al., 2009), which can then generalize to other domains (Lövdén et al., 2010; Schmiedek et al., 2014). Behavioural evidence for such a pattern was found by Edwards et al. (2002), who showed transfer of speed of processing training to multiple cognitive domains in older adults.

In addition to the empirical findings reported here, there are methodological advantages to implementing this model. By visualizing the full model, including statistical quantification of the

strengths of association such as R^2, it immediately emphasizes not just which ties are strong and well-established, but also shows where our knowledge is lacking. For example, not all variance can be explained in either fluid reasoning or processing speed (see also Rabbitt et al., 2007b), suggesting we need to explore other metrics of processing speed (e.g. inspection time, or digit-symbol substitution), additional cognitive determinants (e.g. working memory; Engle, Tuholski, Laughlin, & Conway, 1999), and additional neural markers such as prefrontal activity (e.g. Christoff et al., 2001), integrity (Waltz et al., 1999; Woolgar et al., 2010), grey matter (Kievit et al., 2014; Stuss et al., 2003) or additional WM metrics such as MD and AD (Tamnes et al., 2012) to get a more complete picture.

One limitation of the model as implemented here is that our sample is cross-sectional, not longitudinal. This means that although we can model the extent to which *individual differences* are in line with the watershed model, but we cannot make claims concerning intra-individual changes over the lifespan (Raz and Lindenberger, 2011; Salthouse, 2011). To truly get at the developmental dynamics, it would be necessary to follow people over time, most crucially during the critical periods of adolescence and later-life aging. The watershed model would predict that, at sufficient temporal resolution, developmental changes in WM integrity would precede changes in processing speed, which in turn precede changes in fluid reasoning. A second limitation is the selection of tasks. Although those we included cover four domains of fluid reasoning (series completions, odd-one-out, matrices and topology), they are all subtests of a single test. Ideally, a model should include additional fluid reasoning tasks (such as Raven's Matrices) to capture a broader spectrum of reasoning abilities. Similarly, all our processing speed measures focus on response time, where a broader spectrum of tasks tapping processing speed (e.g. inspection time or digit-symbol substation, cf. Deary & Ritchie, 2016) would allow for even more detailed investigation of the key hypotheses tested here, as well as expanding the range of white matter metrics to include measures of diffusivity and magnetisation transfer ratio (e.g. Penke et al., 2012; Yang et al., 2014).

In summary, the watershed model provides a powerful conceptual framework that organizes our knowledge and generates testable models of the expected covariance patterns within and across

individuals. A strength of the model is that it naturally accommodates extensions in both 'directions'. For example, findings in this model could be integrated with the study of other, even broader phenotypes. One notable and important extension of the model would be the inclusion of long- and short-memory measures, or measures of attention, which assess both an important aspect of higher functioning and also are notable in their age-related loss. By integrating multiple hierarchical models the interrelationships between cognitive phenotypes may become clearer. For instance, it may be possible to integrate a model like the above with a larger study of psychopathology that has known impairments to cognitive abilities similar to fluid reasoning (e.g. schizophrenia, Snitz et al., 2006). Although we here do not include the 'lowest' level of the watershed model, namely genetic effects, recent evidence from two large neuroimaging and genetic samples shows striking convergence with the predictions that follow from the watershed model with respect to white matter and processing speed. Kochunov et al., 2016 use quantitative genetic models to show that, in two independent samples (N=145 and N=481), 'Quantitative genetic analysis demonstrated a significant degree to which common genes influenced joint variation in FA and brain processing speed.' (p.190), and conclude that 'specific genes influencing variance in FA values may also exert influence over the speed of cognitive information processing' (p. 19). The advent of larger, multimodal neuroimaging cohorts will allow us to integrate previously isolated empirical findings into larger explanatory models, thereby mapping the mechanistic pathways in increasing detail. Ultimately, mapping the full hierarchy from genotypes to phenotypes may provide novel insights into the cascade of developmental effects on complex cognitive abilities in both health and disease.

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RAK conceived the model, analysed the data, and designed the SEM figures. MC developed the white matter analysis pipeline. SWD and RAK made the white matter figures. RAK, SWD, JG and RNH wrote the paper. All authors contributed to the final written product. This article was written in the absence of any conflicting financial interests.

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The Cam-CAN corporate author consists of the project principal personnel: Lorraine K Tyler, Carol Brayne, Edward T Bullmore, Andrew C Calder, Rhodri Cusack, Tim Dalgleish, John Duncan, Fiona E Matthews, William D Marslen-Wilson, James B Rowe, Meredith A Shafto; Research Associates: Karen Campbell, Teresa Cheung, Linda Geerligs, Anna McCarrey, Abdur Mustafa, Darren Price, David Samu, Jason R Taylor, Matthias Treder, Kamen Tsvetanov, Janna van Belle, Nitin Williams; Research Assistants: Lauren Bates, Tina Emery, Sharon Erzinçlioglu, Andrew Gadie, Sofia Gerbase, Stanimira Georgieva, Claire Hanley, Beth Parkin, David Troy; Research Interviewers: Jodie Allen, Gillian Amery, Liana Amunts, Anne Barcroft, Amanda Castle, Cheryl Dias, Jonathan Dowrick, Melissa Fair, Hayley Fisher, Anna Goulding, Adarsh Grewal, Geoff Hale, Andrew Hilton, Frances Johnson, Patricia Johnston, Thea Kavanagh-Williamson, Magdalena Kwasniewska, Alison McMinn, Kim Norman, Jessica Penrose, Fiona Roby, Diane Rowland, John Sargeant, Maggie Squire, Beth Stevens, Aldabra Stoddart, Cheryl Stone, Tracy Thompson, Ozlem Yazlik; and administrative staff: Dan Barnes, Marie Dixon, Jaya Hillman, Joanne Mitchell, Laura Villis.

Appendix A

	age	cattell1	cattell2	cattell3	cattell4	SRTspeed	SRTcons	CRTspeed	CRTcons	AVspeed	AVcons	ATR	CST	CING	CINGHipp	FMaj	FMin	IFOF	ILF	SLF	UNC
age	334.0604	-10.2894	-9.36761	-10.8386	-8.74285	-6.32705	-7.70746	-11.2395	-10.396	0.545779	-3.40095	-7.77698	-5.02834	-3.06277	-1.92008	-5.18757	-12.2041	-9.30063	-7.93372	-6.00511	-6.48613
cattell1	-10.2894	1.014777	0.523818	0.633796	0.555469	0.276907	0.345905	0.530027	0.522459	-0.07842	0.128422	0.318784	0.173973	0.135446	0.099069	0.20642	0.424283	0.363543	0.298019	0.232802	0.263608
cattell2	-9.36761	0.523818	0.976111	0.566801	0.509942	0.249226	0.316156	0.49534	0.470085	-0.05104	0.149577	0.298921	0.244484	0.137761	0.165932	0.122674	0.375803	0.314522	0.235568	0.240807	0.210953
cattell3	-10.8386	0.633796	0.566801	0.983333	0.539663	0.27925	0.375032	0.498372	0.507615	-0.04553	0.164859	0.340778	0.215941	0.147429	0.100369	0.202479	0.46972	0.382966	0.311923	0.259092	0.313627
cattell4	-8.74285	0.555469	0.509942	0.539663	1.005774	0.242755	0.318599	0.469375	0.480094	-0.05992	0.162905	0.308886	0.20128	0.162953	0.08435	0.150403	0.399114	0.31773	0.246025	0.226457	0.246612
SRTspeed	-6.32705	0.276907	0.249226	0.27925	0.242755	0.903974	0.633709	0.517152	0.332406	0.28101	0.264552	0.222354	0.194485	0.143963	0.056476	0.13149	0.329313	0.262494	0.222269	0.206207	0.195226
SRTcons	-7.70746	0.345905	0.316156	0.375032	0.318599	0.633709	0.912755	0.489941	0.423823	0.120978	0.235653	0.282328	0.190459	0.175107	0.065424	0.127181	0.373467	0.291908	0.245656	0.237653	0.217762
CRTspeed	-11.2395	0.530027	0.49534	0.498372	0.469375	0.517152	0.489941	0.895308	0.727204	0.061433	0.2263	0.369855	0.22404	0.168871	0.080323	0.212728	0.489944	0.405392	0.319382	0.277966	0.283328
CRTcons	-10.396	0.522459	0.470085	0.507615	0.480094	0.332406	0.423823	0.727204	0.902361	-0.00463	0.208465	0.365528	0.147044	0.199488	0.061037	0.182848	0.460601	0.378646	0.317461	0.248897	0.295451
AVspeed	0.545779	-0.07842	-0.05104	-0.04553	-0.05992	0.28101	0.120978	0.061433	-0.00463	0.950509	0.651469	-0.01209	0.056961	0.062572	0.014209	0.012895	0.019189	0.037079	0.02802	0.026815	-0.02233
AVcons	-3.40095	0.128422	0.149577	0.164859	0.162905	0.264552	0.235653	0.2263	0.208465	0.651469	0.879145	0.172276	0.127752	0.150787	0.052955	0.106019	0.213965	0.199922	0.128824	0.158586	0.112807
ATR	-7.77698	0.318784	0.298921	0.340778	0.308886	0.222354	0.282328	0.369855	0.365528	-0.01209	0.172276	0.902629	0.232745	0.404952	0.073937	0.210452	0.572014	0.583724	0.374655	0.429401	0.470889
CST	-5.02834	0.173973	0.244484	0.215941	0.20128	0.194485	0.190459	0.22404	0.147044	0.056961	0.127752	0.232745	0.805298	0.243926	0.310549	0.123016	0.275676	0.310545	0.299492	0.368095	0.192864
CING	-3.06277	0.135446	0.137761	0.147429	0.162953	0.143963	0.175107	0.168871	0.199488	0.062572	0.150787	0.404952	0.243926	0.865935	0.128464	0.095865	0.440823	0.382023	0.256202	0.417387	0.422976
CINGHipp	-1.92008	0.099069	0.165932	0.100369	0.08435	0.056476	0.065424	0.080323	0.061037	0.014209	0.052955	0.073937	0.310549	0.128464	0.92416	0.173338	0.158967	0.128958	0.255491	0.235255	-0.00623
FMaj	-5.18757	0.20642	0.122674	0.202479	0.150403	0.13149	0.127181	0.212728	0.182848	0.012895	0.106019	0.210452	0.123016	0.095865	0.173338	0.779948	0.313137	0.350057	0.329671	0.204754	0.285276
FMin	-12.2041	0.424283	0.375803	0.46972	0.399114	0.329313	0.373467	0.489944	0.460601	0.019189	0.213965	0.572014	0.275676	0.440823	0.158967	0.313137	0.868012	0.626538	0.519734	0.481993	0.49485
IFOF	-9.30063	0.363543	0.314522	0.382966	0.31773	0.262494	0.291908	0.405392	0.378646	0.037079	0.199922	0.583724	0.310545	0.382023	0.128958	0.350057	0.626538	0.779568	0.605175	0.529707	0.599205
ILF	-7.93372	0.298019	0.235568	0.311923	0.246025	0.222269	0.245656	0.319382	0.317461	0.02802	0.128824	0.374655	0.299492	0.256202	0.255491	0.329671	0.519734	0.605175	0.796148	0.510462	0.385808
SLF	-6.00511	0.232802	0.240807	0.259092	0.226457	0.206207	0.237653	0.277966	0.248897	0.026815	0.158586	0.429401	0.368095	0.417387	0.235255	0.204754	0.481993	0.529707	0.510462	0.70851	0.396426
UNC	-6.48613	0.263608	0.210953	0.313627	0.246612	0.195226	0.217762	0.283328	0.295451	-0.02233	0.112807	0.470889	0.192864	0.422976	-0.00623	0.285276	0.49485	0.599205	0.385808	0.396426	0.949558

Appendix B

Processing Speed Exploratory Factor Analysis (promax rotation)
Loadings:

	Factor1	Factor2	Factor3
SRTspeed	-0.156	1.073	
SRTcons	0.182	0.622	
CRTspeed	0.749	0.196	
CRTcons	1.081	-0.184	
AVspeed	-0.126		1.001
AVcons	0.196		0.711

Variance:

	Factor1	Factor2	Factor3
SS loadings	1.842	1.613	1.515
Proportion Var	0.307	0.269	0.252
Cumulative Var	0.307	0.576	0.828

Factor Correlations

	Factor1	Factor2	Factor3
Factor1	1	-0.281	0.175
Factor2	-0.281	1	-0.624
Factor3	0.175	-0.624	1

Appendix C

White Matter Exploratory Factor Analysis (promax rotation)
Loadings:

	Factor1	Factor2	Factor3	Factor4	Factor5	Factor6
ATR	1.003					
CST			0.747		0.271	
CING				0.977		
CINGHipp			0.653			
FMaj						0.584
FMin	0.632					
IFOF	0.401				0.381	
ILF		0.993				
SLF		0.308	0.297			
UNC					0.617	0.332

Variance:

	Factor1	Factor2	Factor3	Factor4	Factor5	Factor6
SS loadings	1.644	1.187	1.104	1.011	0.704	0.575
Proportion Var	0.164	0.119	0.11	0.101	0.07	0.057
Cumulative Var	0.164	0.283	0.394	0.495	0.565	0.622

Appendix D

WM tracts

Diffusion-weighted images (DWI) were acquired at the MRC Cognition and Brain Sciences Unit, using a 3T Siemens TIM Trio MRI scanner, and a 32-channel head coil. A twice-refocused spin-echo sequence was used to minimise eddy-currents, with 30 uniformly spaced gradient directions for each of two b-values (1000 and 2000 s/mm^2), and three non-diffusion weighted images (b-value = 0). Other imaging parameters were: TR=9100ms, TE=104ms, 2x2x2mm^3 resolution, FoV 192x192mm^2, 66 axial slices and GRAPPA acceleration factor of 2. A structural MPRAGE was also acquired for each participant (see Shafto et al. (2014) for sequence details). Traditionally, DWI data is motion corrected at the post-acquisition level by using image registration techniques to co-register each diffusion-weighted image to the first acquired b=0 image. However, as discussed in Ben-Amitay et al. (2012) , when high b-values are used this technique will fail to correct for distortions and motion, and may also introduce additional artefacts. For this reason, we did not apply registration-based motion correction to the DWI data in this study. Instead, we used an automated method to identify datasets affected by

striping and signal voids (a common artefact resulting from severe motion in interleaved acquisitions), and those datasets were excluded from further analysis. Further detection and exclusion of outliers was performed at the analysis level to avoid including datasets affected by artefacts and distortions. All pre-processing and modelling of MRI data was performed using a combination of functions from FSL version 5.0.8 (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012), SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), and custom scripts written in C and Matlab, integrated in the Automatic Analysis (aa) package (Cusack et al., 2014). After removal of non-brain tissue, a non-linear diffusion tensor model was applied to the DWI data. Non-linear fitting of the diffusion tensor provides better noise modelling when compared to standard linear model fitting, resulting in more accurate and un-biased estimates of the diffusion tensor and its different metrics (Jones & Basser, 2004). The diffusion tensor's eigensystem was used to compute the fractional anisotropy (FA) at each voxel. The FA maps were then spatially normalised into a standard stereotactic space as follows: firstly, the average of the three b=0 images for each subject was coregistered to the MPRAGE; secondly, the MPRAGE data was processed using DARTEL (Ashburner, 2007), and the normalisation parameters derived from this analysis were used to define the spatial transformation of each subject into standard MNI space; finally, the transformation parameters derived from these two steps were applied to the FA maps. The resulting FA images in MNI space were also smoothed with a 1mm FWHM Gaussian kernel to reduce residual interpolation errors.

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