

Thema:

Neuroscientific approaches to general intelligence and cognitive ageing

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Just as I dedicated my doctoral dissertation to my son Richard, who was born three months before I submitted that thesis, I would like to dedicate this habilitation thesis to my daughter Sophia, who was born exactly three months before the submission of this work.

List of the submitted articles (alphabetic)

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Introduction: A broader perspective

The nature of intelligence

The overarching aim of the research that led to this habilitation thesis was to inquire the neurological foundations of human interindividual differences in intelligence and its normative age-related change, while taking a broader biological perspective that included genetic, medical, and evolutionary considerations. For simplicity, I start off with a consensual expert definition of intelligence as a "...very general capability that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience. It is not merely book learning, a narrow academic skill, or test-taking smarts. Rather, it reflects a broader and deeper capability for comprehending our surroundings—'catching on', 'making sense' of things, or 'figuring out' what to do. Intelligence, so defined, can be measured, and intelligence tests measure it well" (Gottfredson, 1997a). Insights I gained about the nature of intelligence from my own work should become apparent later on. Historically, the psychological construct of intelligence has always been intimately intertwined with the psychometrical ability tests that measure it. Over a century of psychometric research has shown that performance on different cognitive ability tests, even if diverse in content, yield positive-manifold intercorrelations, allowing for the extraction of a general latent factor. This statistical construct, known as 'general intelligence' or 'general cognitive ability' and denoted as '*g*', captures about 50% of the common variance among different tests. It has later been found to be independent of specific test batteries (Johnson, te Nijenhuis, & Bouchard, 2008) and is the level of analysis that captures the most reliable and also genetic variance (see Deary, Penke, & Johnson, 2010). The *g* factor also shows considerable predictive validity for a broad array of important life outcomes, from school performance, occupational success and social mobility to coping with minor everyday challenges to morbidity and mortality (Deary, Whalley, & Starr, 2008; Gottfredson, 1997b). Therefore, I concentrated on *g* (or IQ as a psychometrically distinct but highly overlapping surrogate) in most of the analyses in this thesis.

These facts about the *g* factor of intelligence are firmly established knowledge in psychology, but they are less well appreciated in neighbouring disciplines, including neuroscience. An example of this neglect is a study by Charlton and colleagues (2008), which examined associations between age, brain white matter integrity (as assessed by diffusion tensor imaging mean diffusivity in a large cerebral region of interest), and a battery of ten cognitive ability tests. For their analyses, they grouped the ten tests into four cognitive domains (processing speed, mental flexibility, working memory, and fluid intelligence) and hypothesised a complex (and debatable) web of causal relationships between them, which they modelled using path analysis (Figure 1A).

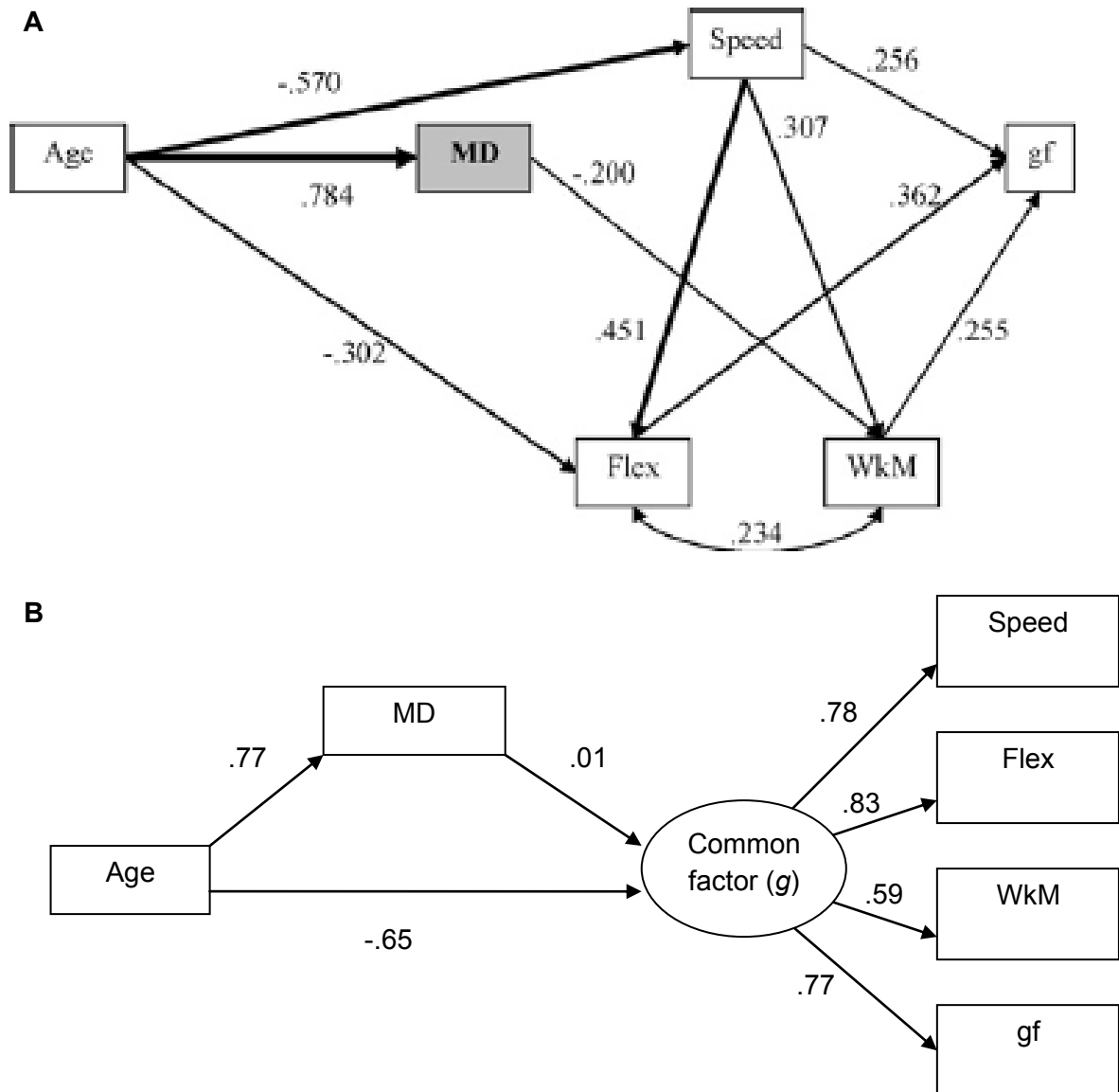


Figure 1. A: The “final model” from Charlton et al. (2008). Their initially hypothesised model included every possible path except from age to gf and from MD to gf. **B:** The alternative common factor (*g*) model from Penke & Deary (2010), based on the correlation matrix from Charlton et al. (2008). The four cognitive ability composites were formed by Charlton et al. by averaging z-scores of the following tests (for details, see their Table 1): ‘Speed’: AMIPB information processing speed, WAIS-R digit symbol, and grooved pegboard; ‘Flex’ = flexibility: D-KEFS trails, Wisconsin Card Sorting Test, and Stroop; ‘WkM’ = working memory: WMS-III digit span backwards and letter-number sequencing; ‘gf’ = fluid intelligence: WASI matrix reasoning and block design. MD = mean diffusivity.

Since this article was highly relevant to my own work in the Disconnected Mind Project (see below), I was curious how the results would look like when a latent *g* factor was modelled in their data, which I did based on the (clearly positive-manifold) correlation matrix from their article (Figure 1B). Interestingly, there was no significant path from white matter integrity to *g*, nor to any of the four cognitive domains when *g* was part of the model (not shown in Figure 1B). Apparently the conclusion drawn by Charlton and colleagues that their data showed a mediation effect of white matter integrity between age and cognitive ability is highly dependent on how they modelled their data. Due to pertinacious reviewer requests, the Penke and Deary (2010) article we published in response to Charlton et al. (2008) became more of a brief guide to latent variable structural equation modelling, but the main point we wanted to make was that cognitive neuroscience could benefit from considering the established *g* factor of intelligence. For the same reason, we included a detailed introduction to general intelligence, including the criticisms and controversies surrounding it, into our review of the structural and functional neuroscience studies of human intelligence differences, which was aimed at a broad audience (Deary et al., 2010).

At least since Galton (1869), intelligence is intensively studied from a biological perspective, and there is now an abundance of evidence from quantitative behavioural genetic studies that intelligence is highly heritable (Deary, Penke, & Johnson, 2010). Heritability is often over-used as an argument, since the precise estimates of heritability matter less than many researchers believe and a high heritability does by no means increase the probability of identifying specific genetic variants associated with that trait (Johnson, Penke, & Spinath, in press), which is illustrated by the (initially) surprisingly meagre yield of molecular genetic studies of intelligence so far (Deary et al., 2010). However, significant and replicable heritability estimates do indicate that biological factors somehow influence a trait directly or indirectly. In the case of intelligence, a wide range of brain parameters have been identified as correlates, including brain size, grey (i.e. nerve cell) and white (i.e. nerve fibre) volumes, the thickness, gyrification, and developmental plasticity of the cortex, white matter integrity, and neuronal efficiency (Deary et al., 2010). As always, these correlational findings do not imply causal relationships, even when methods such as large-sample lesion mapping (Gläscher et al., 2010) provide almost quasi-experimental support. However, taken together the available evidence strongly suggests that general intelligence relies on parieto-frontal brain networks (Jung & Haier, 2007), though different people might use their structurally different brains in different manners (e.g. with different activation patterns and neuronal efficiency, Neubauer & Fink, 2009) to reach similar levels of cognitive performance (Deary et al., 2010).

What brain size really tells us about intelligence

It was an evolutionary perspective that got me first interested in the relationships between intelligence and the brain: Not only do multiple quantitative reviews (e.g. Miller & Penke, 2007; Rushton & Ankney, 2009) and a meta-analysis (McDaniel, 2005) testify a substantial correlation (about $r = .30 - .40$) between brain size and intelligence *within* the human species, but brain size differences *across* species have also long been used as a proxy for species differences in intelligence (Roth & Dicke, 2005). Since the within-species correlation between brain size and intelligence is also substantially genetically mediated (Miller & Penke, 2007), it seems reasonable to study brain size as an endophenotype for intelligence when interested in its evolutionary genetics. To approach this topic, Geoffrey Miller and I (Miller & Penke, 2007) calculated the coefficient of additive genetic variation (CVA) for in vivo magnetic resonance imaging measures of brain size. Unlike the heritability coefficient, which standardises genetic variance in a trait by its phenotypic (genetic plus environmental) variance, the CVA standardises genetic variation by the trait's mean, reflecting the absolute amount of genetic variation in the trait. Calculating CVAs is only meaningful if the trait is measured on a ratio scale (i.e., with a non-arbitrary zero point), which is why it cannot be calculated for intelligence scores directly, but it can be done for brain size. In evolutionary biology, CVAs are used as estimates of a trait's evolvability, or potential to react to natural selection. Since virtually all theories on the evolution of human intelligence predict recent directional selection towards higher intelligence, we expected to find a high CVA for human brain size. To our surprise, however, we found that the CVA was comparatively low, indicating recent stabilising selection. Since it is unlikely that all theories on the evolution of intelligence are wrong, the most plausible interpretation of this finding is that at least in recent evolutionary history, brain size did not contribute much to increases of human intelligence, deeming it unsuitable as an endophenotype to study the evolution of human intelligence. This interpretation is actually in line with evidence that polymorphisms in genes like ASPM and MCPH1, which profoundly affected the evolution of human brain size and show signatures of recent evolutionary selection (Evans et al., 2005; Mekele Bobrov et al., 2005), are unrelated to current intelligence differences (Bates et al., 2008). It is also in line with the recent finding that modern human and Neanderthal brains differ much more in their developmental trajectories than in their overall size (Gunz, Neubauer, Maureille, & Hublin, 2010). Of note in this context, cortical developmental plasticity seems to be more important for high intelligence than absolute cortical thickness during childhood (Shaw et al., 2006).

Of course, the low current CVA of human brain size does not imply that encephalization played no role in the evolution of vertebrate or mammalian intelligence. But it is a reminder that there can be completely different causes for between- and within-species differences in

intelligence: While structural changes in brain architecture were likely causal in the evolution of higher cognitive capabilities such as theory of mind, language and imitation (Roth & Dicke, 2005), brain size differences might just be a correlate of human intelligence differences, without direct causal relevance. Indeed, so far there appears to be no good rationale why the mere volume of nerve cells (grey matter) and connections (white matter), clearly the sources of individual differences in brain size, should *cause* differences in intelligence (Deary et al., 2010).

The neurodevelopmental stability hypothesis of intelligence

An alternative and more plausible hypothesis is that individual differences in intelligence are caused to a substantial degree by individual differences in neurodevelopmental stability (Prokosch, Yeo, & Miller, 2005): Intelligence seems to rely on the efficient operation of complex and widespread parieto-frontal cortical networks (Jung & Haier, 2007; Neubauer & Fink, 2009; Deary et al., 2010), so many pre- and postnatal disturbances during neuronal development (including pathogens, toxins, and malnutrition) have the potential to disrupt its performance, leading to decreases in intelligence of various degrees. Furthermore, inherited or *de novo* genetic mutations in disparate genomic regions can be additional disturbing factors or interfere with the ability of the organism to buffer disturbances. People will differ in how many such mutation accumulated in their genomes to form their individual mutation loads. Indeed, a balance between accumulating disruptive mutations and counteracting purifying evolutionary selection (mutation-selection balance) is currently perhaps the most plausible explanation for the standing genetic variation in intelligence (Miller & Penke, 2007; Penke, Denissen, & Miller, 2007), and it also becomes increasingly popular among geneticist as an explanation for genetic variation in mental disorders and other complex diseases (e.g. McClellan & King, 2010; Mitchell & Porteous, 2010).

More widely studied than the developmental stability of the brain is the developmental stability of the body, and the symmetry of the face and bilateral body parts is assumed to be a direct measure of it. Since there is no reason to assume that facial or body symmetry could cause differences in intelligence or vice versa, the most reasonable explanation for an association between the two is that developmental stability is a causal factor common to both of them. In order to test the neurodevelopmental stability hypothesis of intelligence, we measured facial symmetry in a large sample of old adults and related it to their concurrently assessed general intelligence and information processing speed (Penke et al., 2009). When controlling for directional asymmetry, an important but often neglected methodological detail, we found the predicted relationships, though only in men and sometimes only marginally

significant. Still, a meta-analysis that appeared only a year later and included these results as well as unpublished null results from my dissertation project confirmed the significant correlation between symmetry and intelligence, with no moderating effect of sex (Banks et al., 2010). The effect size was small ($r = .12 - .20$), but weak effects are to be expected in this case due to the imperfect theoretical relationship between developmental stability and symmetry (Gangestad & Thornhill, 1999) and the difficulty to measure symmetry reliably. To amend the second point, I am currently establishing a symmetry lab with precise state-of-the-art 3D scanners for body and face at the University of Edinburgh, so I hope I can present more definite results on the neurodevelopmental stability hypothesis in a few years.

The common cause hypothesis of cognitive ageing

Even the impressive rank-order stability of intelligence over the lifespan ($r = .73$ over a period as long as 66 years, corrected for population stratification) leaves room for a substantial amount of change: About 50% of the old-age variance in intelligence is not explained by childhood intelligence (Deary et al., 2008). It follows that there is differential cognitive ageing, and since it is usually (though not exclusively) leading to lower intelligence in the second half of life, it is also known as age-related cognitive decline. In my work, I have concentrated exclusively on normal, non-pathological cognitive ageing. The determinants of differences in normal cognitive ageing are not fully understood, but there are contributions furthering their understanding from genetics, general health and medical disorders such as atherosclerotic disease, biological processes such as inflammation, neurobiological changes, diet and lifestyle. Many of these effect sizes are small, some are poorly replicated and in some cases there is the possibility of reverse causation, with prior intelligence causing the supposed 'cause' of intelligence in old age (Deary et al., 2009).

There is however a growing appreciation that factors affecting general bodily ageing also influence intelligence in old age. This so-called 'common cause hypothesis' (see Deary et al., 2009) implies a role of overall body condition or 'system integrity' in cognitive ageing. It bears marked resemblance to the neurodevelopmental stability hypothesis, only with a changed focus from early or even prenatal development to lifelong development and ageing. In Penke et al. (2009), we also test the hypothesis that neurodevelopmental stability plays a role in cognitive ageing as well, making use of the special characteristics of our sample. This sample was the Lothian Birth Cohort of 1921, Scottish participants born in 1921 who had been tested for IQ as part of the Scottish Mental Survey of 1932 when they were 11 years old and who had been followed up at 79 and 83 years of age (Deary et al., 2008). This data allowed us to relate their facial symmetry at age 83 years to their individual cognitive ageing

rates between age 11 and 79 and between age 79 and 83. Results indicated that facial asymmetry correlated substantially with cognitive decline over the 4-year period between age 79 and 83 in men ($r = .35$ for the best measure of asymmetry), but not with cognitive change over the almost seven decades between age 11 and 79. The latter null result emerged because intelligence at neither age 11 nor age 79 was significantly predictive of facial symmetry at age 83. Overall, this pattern of results suggests that facial symmetry is a marker of developmental stability (including neurodevelopmental stability) that is very sensitive to ageing effects in old age. This conclusion is further supported by cross-sectional evidence that asymmetry means and variances increase markedly over the lifespan. As predicted by the common cause hypothesis, overall body condition/system integrity might increasingly (and differentially) deteriorate with age due to accumulated stress, affecting both symmetry and intelligence, and potentially overriding any symmetry-intelligence associations that had been present earlier in life. Longitudinal studies of age-related changes in symmetry would clearly be desirable at this point, but they are unfortunately completely absent from the literature. Still, these findings make symmetry an interesting marker for ageing research, beyond the popularity it already received in the evolutionary literature as a marker of fitness. At least in men, that is, since none of these associations were found in women. While stronger associations in men than in women can be explained to some degree by sex differences in ageing, sexual selection, and lower male somatic investment over the lifespan (Penke et al., 2009), the complete absence of any findings in women is surprising and puzzling indeed. Replication with more sensitive symmetry measures, which we plan for the future, might reveal a similar, weaker pattern in women as well.

The cortical disconnection hypothesis of cognitive ageing

Another prominent idea in cognitive ageing research, complementary to the common cause hypothesis, is the cortical disconnection hypothesis. According to this hypothesis, age-related decline in cortical white matter (i.e. neuronal axon fibres) leads to impaired information transfer between different brain areas that need to operate synergistically to allow higher cognitive functions like intelligence to emerge. White matter ageing is thus assumed to be a cause of cognitive decline (see Deary et al., 2009, 2010). Significant loss of white matter integrity appears as focal hyperintense (bright) areas on fluid-attenuated inversion recovery (FLAIR) and T2-weighted magnetic resonance images (MRI). Such white matter lesions are usually measured through expert ratings, though some more automated procedures exist to quantify them objectively (Penke et al., submitted). A more sensitive method to assess white matter integrity is diffusion tensor imaging (DTI), an MRI procedure

based on water diffusion patterns in the brain. While water molecules show equal Brownian motion in every direction when in a boundary-free environment (isotropic diffusion), their motion is restricted in complex cell structures like the brain, leading to anisotropic diffusion. However, in environments that show a clear directional structure, as the tube-like axon fibres that form the brain's white matter do, water can diffuse rather unrestrictedly along one, but much less so along all axes. DTI can measure directional water diffusion in the brain and allows for calculating overall indices of directionality from the diffusion tensors, such as fractional anisotropy (FA) and mean diffusivity (MD or $\langle D \rangle$). More specific indices can separately quantify water diffusion along (axial diffusion: λ_{ax}) and perpendicular to (radial diffusion: λ_{rad}) axonal fibres, with the former being interpreted as an indicator of axonal damage and the latter as an indicator of myelin damage. To be meaningful measures of white matter integrity, these indices must be calculated for voxels that actually contain white matter, and an elegant method for this purpose is probabilistic neighbourhood tractography (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007). This procedure starts with a seed point in a major white matter fibre in the brain, which is identified automatically using comparisons to reference tracts, and then traces the remainder of the tract along DTI parameters using a probabilistic algorithm. Tractography allows for calculating single DTI indices for each specified white matter tract, thus considerably and meaningfully reducing the amount of data compared to voxel-based methods. The two studies in this thesis that assessed white matter integrity (Penke et al., 2010a, b) used DTI tractography.

Most studies of white matter integrity and cognitive ageing are like the Charlton et al. (2008) study discussed above in that they rely on cross-sectional analyses of age-heterogeneous samples. While convenient, this design has the inherent drawback that it cannot distinguish true (potentially causal) correlated change of two variables like white matter integrity and intelligence from parallel, yet non-causal age-related trajectories of the two variables. A preferable alternative are longitudinal studies of age-homogeneous samples (Hofer & Sliwinski, 2001; Penke & Deary, 2010). The three original imaging studies in this thesis (Penke et al., 2010a, b, in press) are pilot reports from the Disconnected Mind Project (www.disconnectedmind.ed.ac.uk) based on the Lothian Birth Cohort of 1936, a sample of Scots that participated in the second Scottish Mental Survey of 1947. Therefore there is again IQ data available from when these participants were 11 years old (Deary, Whalley, & Starr, 2008). The Disconnected Mind sample, which has a very narrow age range, was tested for cognitive ability at ages 70 and 72 years, and underwent neuroimaging (including DTI) at age 72 years.

In Penke et al. (2010a) we used DTI tractography to assess FA, MD, λ_{ax} , and λ_{rad} in three bilateral white matter tracts and two parts of the corpus callosum. There were not many noteworthy associations of the DTI indices for any individual tract with intelligence, information processing speed, or memory ability (but see Penke et al., 2010b). However, we discovered that for each of the four DTI indices of white matter integrity, intercorrelations between the eight tracts showed a positive manifold, allowing us to extract a strong general factor of white matter tract integrity for each of the indices (explained variances > 40%). These general factors, which have since been replicated in the full Disconnected Mind sample (N > 600) and a sample of children (both unpublished), indicate that whatever factors determine individual differences in white matter tract integrity appear to be global (i.e., affecting multiple tracts simultaneously) and not specific to individual tracts. Furthermore, the general tract integrity factors for FA (which is considered to be a more sensitive index than MD) and λ_{rad} (indicating myelin integrity) were significantly associated with processing speed. This finding could also be replicated in the full Disconnected Mind sample (unpublished data) and complements some earlier reports of associations between processing speed and white matter integrity assessed globally for the whole brain, in broad regions of interest, and for individual tracts (see Penke et al., 2010a). The incremental value of this study is the demonstration that it is specifically the integrity variance *common* to different white matter tracts that relates to information processing speed. Since processing speed is regarded as an important, ageing-sensitive elementary cognitive function this result can also be seen as support for the common cause hypothesis.

The only tract that showed rather weak loadings on the general tract integrity factors in Penke et al. (2010a) was the splenium of the corpus callosum. This tract stood out in that it was the only one that did not project to the frontal lobe, which has long been assumed to be the only part of the brain where correlates of intelligence should be found due to its crucial role in working memory and executive functions. From this stance it would be hardly surprising if splenium integrity was unrelated to intelligence. However, in recent years a whole bunch of neuroimaging studies have also found associations of intelligence with posterior brain regions (Jung & Haier, 2007; Deary et al., 2010), including the splenium (Luders et al., 2007), thus challenging the frontal perspective. Having a closer look at splenium integrity in our data, we indeed found associations with intelligence in old age as well. Furthermore, these associations remained significant when IQ at age 11 was statistically controlled, indicating that higher splenium integrity in old age predicts more favourable cognitive ageing over the lifespan (Penke et al., 2010b). In addition, we found that both splenium integrity (but none of the other seven tracts) and lifetime cognitive ageing were associated with a functional polymorphism in the β_2 -adrenergic receptor gene

(*ADRB2*), with splenium integrity partly mediating the relationship between *ADRB2* and cognitive ageing. We became interested in this particular gene because it is not only expressed in the brain, but it also shows a signature of recent evolutionary selection and had been found to show opposite associations with intelligence (and also hypertension) in young and old adults (Bochdanovits et al., 2009). Interestingly, it was the evolutionarily old genetic variant that related to higher splenium integrity and more benign cognitive ageing, but decreased intelligence in younger individuals. Such age-related antagonistic pleiotropy effects can potentially explain why genetic variance in cognitive ageing is maintained in the population and they are thus interesting from an evolutionary genetic perspective (Penke et al., 2007). Based on the existing literature, we speculated that both the *ADRB2* effect on the splenium might relate to memory-based compensatory strategies that come into play when cognitive functions decline, though our finding clearly needs replication first.

The final study in this thesis (Penke et al., in press) concerns a potential mechanism how age-related decline in white matter and subsequently intelligence can occur. White matter lesions are associated with markers that overlap considerably with risk factors for cardiovascular problems, including hypertension, diabetes, atherosclerosis, homocysteine levels, and markers of oxidative stress (Launer, 2004). This similarity suggests that cerebral microangiopathy (dysfunction of small blood vessels in the brain) might cause loss of white matter integrity and cognitive ageing. One form of microangiopathy are brain microbleeds, small focal hemorrhages that are not seldom detected in clinically otherwise unsuspecting subjects. When the blood from these bleedings is metabolised, residual iron is left in the brain. Iron deposits accumulate with age and appear as hypointense (dark) focal patches on computer tomography and T2*-weighted MRI scans, though they are often confused with calcium deposits. Their relationship with normal cognitive ability is hardly known. As part of the Disconnected Mind Project, my colleague Maria Valdés Hernández has developed a semi-automatic procedure to fuse differently weighted MRI scans, which can be submitted to a variance quantification algorithm to calculate brain parameters based on their differential visibility on differently weighted scans. When used with T2*-weighted and FLAIR scans, this procedure can quantify iron deposits in the brain, which can be distinguished from calcium when compared to T1-weighted scans. Using this novel procedure, we were able to detect iron deposits in about half of our 72-year-old sample. The amount of deposited iron correlated significantly with intelligence (but not processing speed or memory ability) in old age ($r_s = -.27$ to $-.31$). These relationships were only slightly attenuated when childhood IQ was statistically controlled, suggesting that the accumulation of brain microbleeds over the lifespan (as indicated by the iron deposits) affects lifetime cognitive ageing even in the normal, non-pathological range. However, most interestingly age 11 IQ also significantly

predicted the amount of iron deposits assessed 61 years later ($r = .19$), indicating 'reverse causation' (see Deary et al., 2009) or, more plausibly, that lifelong-stable individual differences in intelligence and cerebrovascular integrity share a common cause early in life or prenatally. These results can thus be interpreted as supportive of the neurodevelopmental stability hypothesis and the common cause hypothesis of cognitive ageing. A direct test whether the effect is indeed, as we suspect, mediated by a loss of white matter integrity (the cortical disconnection hypothesis) was not part of this pilot study, but will be conducted based on the full Disconnected Mind sample. However, initial results from mouse models of brain hypoperfusion that are also part of the Disconnected Mind Project are encouraging.

Conclusion

Much has been learned about the neuroscience of intelligence (Deary et al., 2010) and cognitive ageing (Deary et al., 2009) in recent years. While brain size might still be the most robust neuronal correlate of intelligence, its explanatory value appears to be limited, even from an evolutionary perspective (Miller & Penke, 2007). Instead, individuals seem to be able to use their structurally different brains in different manners (i.e., they activate their brains differently, applying different strategies) to solve cognitively challenging tasks, and these patterns appear to be able to adapt to age-related loss (Deary et al., 2010). The neurodevelopmental stability hypothesis of intelligence is especially well suited to accommodate this perspective since it emphasises causal heterogeneity and equifinality (different causes can lead to similar outcomes). In the context of cognitive ageing, the common cause hypothesis also implies that any factor that compromises general condition or system integrity can potentially decrease intelligence over time, putting a similar emphasis on causal heterogeneity and equifinality. The cortical disconnection hypothesis is more specific in that it proposes white matter integrity as a proximate cause of intelligence differences, but the more distal factors that influence white matter integrity appear to be as heterogeneous as the neurodevelopmental stability and common cause hypotheses suggest. The empirical studies in this thesis (Miller & Penke, 2007; Penke et al., 2009, 2010a, b, in press) are broadly supportive of all three hypotheses and suggest that more research should be dedicated to them in the future.

The remainder of this habilitation thesis consists of eight published articles, which are presented in the order I discussed them in this introduction.

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