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Ian J. Deary*, Lars Penke* and Wendy Johnson*

*Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, Edinburgh EH4 2EE, Scotland, UK.

All authors contributed equally to the work.

Correspondence to I.J.D.

e-mail: i.deary@ed.ac.uk

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Abstract | Neuroscience is contributing to an understanding of the biological bases of human intelligence differences. This is principally along two empirical fronts: genetics — quantitative and molecular — and brain imaging. Quantitative genetic studies have established that there are additive genetic contributions to different aspects of cognitive ability — especially general intelligence (*g*) — and how they change through the lifespan. Molecular genetic studies have yet to identify well-replicated contributions from individual genes. Structural and functional brain imaging studies have identified differences in brain pathways, especially parieto-frontal, that contribute to intelligence differences. There is also evidence for brains being more efficient in individuals with higher intelligence.

People differ along mental continua. Such individual differences are the domain of differential psychology. Most research in this area of psychology focuses on cognitive and personality differences, which can be investigated as quantitative traits. Differential psychology has three main aims with respect to its traits of interest: to describe them accurately, to discover the real-life impact of trait differences, and to discover the aetiologies of trait differences, including their biological bases. The field that investigates the biological bases of individual differences in these traits is differential neuroscience. Here we review the differential neuroscience of human intelligence.

Individual differences in intelligence are usually measured using psychometric tests. These tests cover cognitive domains such as reasoning, processing speed, executive function, memory, and spatial ability. Although cognitive domains are sometimes thought of as independent, differential psychology has firmly established that they are not; people who perform better in one domain also tend to perform better in the others. This is recognised in the term 'general intelligence', which is usually summarised as '*g*' (Box 1 and below). Some individual tests—such as Raven's Progressive Matrices, a test of non-verbal reasoning—are good indicators of *g*. In this Review we discuss how neuroscience can inform us about the origins of differences in this general cognitive ability.

We recognise that much of cognitive neuroscience tends to focus on the cognitive domains themselves. However, the neuroscientific aspect of general intelligence is important because general intelligence is responsible for much of the predictive validity of cognitive tests, and neuroscientific studies of general intelligence have yielded some clear results. Definitions of general intelligence are shown in Box 1. The terms (general) cognitive ability, mental ability, intelligence and IQ — in its lay and technical usages — are used interchangeably to describe the strong common core that cognitive tests share. To illustrate

the importance of scores on psychometric tests, we first describe their characteristics and their impact on life.

The distribution of intelligence differences in the population is approximately normal, with the exception of a slight excess at the lower end of the distribution caused by severe disorders that involve disrupted cognitive abilities. Males have a slight but consistently wider distribution than females at both ends[1]. Individual differences in human intelligence are among the most robust observations in psychology. They are relatively stable in rank order throughout development[2], and even over very long time spans. A single 45-minute test of general intelligence test had a correlation of 0.63 (0.73 when disattenuated for restriction of range) in people tested twice, at ages 11 and then 79 years[3]. General intelligence differences are associated with important life outcomes including school achievement[4]. In a study involving tens of thousands of children, general intelligence at age 11 years had a correlation of over 0.8 with scores on national tests of educational achievement five years later[5]. General intelligence is strongly predictive of occupational attainment, social mobility[6], and job performance[7]. People with higher general intelligence in childhood or early adulthood have better health in middle and later life, and are less likely to die young[8]. For example, among one million men followed for about 20 years after taking intelligence tests at about age 20, a standard deviation advantage in general intelligence was associated with a 32% reduction in mortality[9]. Intelligence is also important in everyday decision-making[7].

The psychometric properties of intelligence

Well-established results from differential psychology studies have shown that it is inappropriate to assume that performing any cognitive task involves only one relevant mental module (or faculty). Consider the individual differences that show up on a test of arithmetic involving fractions. Do some people perform better than others because they differ on general

intelligence, which we know contributes to all cognitive tasks, irrespective of their content? Or is there some cognitive faculty that contributes to tasks involving mathematical tasks in general, but not to other activities such as verbal and spatial tasks? Or do people differ on the specific ability involved in doing fractional arithmetic in ways that have nothing to do with ability on any other cognitive task, even other mathematical tasks? Or is it simply that people differ in their exposure to and practice with fractional arithmetic tasks?

Each of these possibilities is correct to some degree, for the following reasons. First, scores on cognitive ability tasks of all kinds are positively correlated. This is known as the positive manifold. In typical test batteries consisting of 10-15 different cognitive tasks involving a wide variety of materials and content, a general intelligence (*g*) factor almost always accounts for 40% or more of the total variance. Second, each individual cognitive test also shows substantial amounts of more specific variance, generally ranging from 20-50% of the total variance. Some of this is error variance or variance due to fatigue, mood, motivation, etc., but some of it is systematic variance specific to each test, thus reflecting the particular abilities involved in it. Third, tests that are more similar in content are more highly correlated with each other than with tests that have different content. That is, people tend to have areas of relative strength and weakness in certain broad domains of cognitive ability. For example, some are very good at all kinds of problems involving spatial manipulation but not quite as good at verbal problems, whereas others have the opposite pattern. These individual differences in broad cognitive domains—though given much attention in cognitive neuroscience—contribute small amounts of variance by comparison with *g* and the specific tests. Fourth, some of the variance also reflects individual differences in exposure to testing in general and exposure to the specific tests involved in particular.

An example of how the hierarchical structure of intelligence variance emerges from test scores is shown in Figure 1. This general, hierarchical pattern of cognitive ability variance

components has been known for about a century[10]. It has been replicated in hundreds of datasets[11]. Spearman proposed that the general intelligence (mental ability) factor reflects a general cognitive ability that is applicable to any kind of cognitive problem[10]. He termed it *g*, intending to avoid value judgements and arguments by using a character that was free from prior connotations and misunderstandings. Despite this, *g* has been the subject of controversy ever since (Box 2). It is important to emphasise *g*: it accounts for a relatively large amount of variance, it is the source of most of the predictive power of cognitive tests and, as we shall see, it is the locus of most of the genetic variance.

Seguing into neuroscience

The neuroscience of intelligence is constrained by—and must explain—the following established facts about cognitive test performance: about half the variance across varied cognitive tests is contained within general cognitive ability; there is a relatively small proportion of variance within broad-ish domains of capability; there is some variance in specific abilities; and there are distinct ageing patterns for what are called fluid and crystallised aspects of cognitive ability.

The existence of *g* creates a complicated situation for neuroscience. The fact that *g* contributes substantial variance to all specific cognitive ability tests is generally interpreted as indicating that it contributes directly in some way to performance on those tests. That is, when domains of thinking skill such as executive function and memory, or specific tasks such as mental arithmetic and non-verbal reasoning on the Raven's Matrices test, are studied, neuroscientists are observing brain activity related to *g* as well as the specific task activities. This undermines the ability to determine localized brain activities specific to the task at hand. That is, cognitive task and cognitive ability are not isomorphic: cognitive tasks draw upon multiple abilities at different levels of generality. Moreover, studies that investigate

biological associations with intelligence are rarely conducted using a statistically-derived *g* factor or psychometrically validated factors representing the major cognitive domains that are more specific than *g*. Instead, they generally rely on total IQ scores from a battery of tests, or single tests believed to load highly on the general cognitive ability factor. Fortunately, this actually matters surprisingly little: results are similar whatever measure is used, which accentuates the complications of studying the neural correlates of intelligence.

In differential psychology there has been a tradition of seeking fundamental parameters of cognitive processing or single biological variables that might account for intelligence differences. The harvest has been sparse[12], but two biological findings have persisted and accumulated: general intelligence differences are substantially heritable[13]; and general intelligence and brain size show modest, positive correlations[14]. Of course, finding correlations does not explain how one thing affects another, and explaining such correlations is a scientific task of a different order of difficulty from finding them. Nevertheless, these two persistent findings were the basis for the two principal approaches to the present-day neuroscience of general intelligence: genetics and brain imaging.

Basic genetic influences on intelligence

Investigation of the presence of genetic influences on general intelligence dates back to the 19th century, when Francis Galton published two papers concluding that mental abilities were transmitted via heredity from one generation to another[15]. Despite an intermittently hostile political reception, many studies since then—based principally on twin and adoption samples—have replicated this observation, and none has contradicted it[16]. Estimates of how much of the total variance in general intelligence can be attributed to genetic influences range from 30-80%. General intelligence factors, in the form of latent traits from which measurement error has been removed, fall at the high end of this range. Broad domains of

cognitive ability—such as verbal and perceptual-organisational abilities—generally show similar amounts of genetic influence[17-20], although the genetic influence on memory tends to be somewhat smaller[17-21]. However, much of the heritability of these domains is due to genetic effects on general intelligence, with which they are very highly correlated. Consistent with the presence of measurement error in variance unique to specific tests, genetic influences on specific abilities are generally substantially lower.

The heritability of general intelligence increases with age[22-24]. It is about 30% in very young childhood[25], and grows to as much as 70% to 80% in adulthood[17,26,27]. Because this is now well established, recent studies have shifted to investigating how genetic influences on various mental abilities are related and how they change with development. For example, in a Dutch twin study, the same individuals were given mental test batteries repeatedly to assess general intelligence from age 5 to age 12[28]. The heritability of general intelligence was 26% at age 5, 39% at age 7, 54% at age 10, and 64% at age 12. Rank order of general intelligence showed very high stability over time, largely due to the genetic influences on *g* (See Box 3).

Shared genetic influences between brain structure/function and intelligence?

In adults, there are strong genetic influences on many brain structures and regions — including on the density and the volume of gray and white matter in corpus callosum, superior frontal and temporal cortex, medial frontal cortex, amygdala, hippocampus, Broca's area, anterior cingulate, Heschl's gyrus, and postcentral gyrus — and on overall brain volume; this explains 70% to 90% of the variance in these measures[29-33]. This is true of aspects of brain functioning too, such as the dynamic complexity of brain oscillations thought to be involved in executive function[34], and information processing capacity and efficiency such as executive function[35] and inspection time[26]. Variations in these structures and functions may be endophenotypes for intelligence; that is, they might be intermediate

physiological markers that contribute directly to intelligence. Therefore, they might be linked more closely to the genes involved in intelligence than is intelligence itself. In fact, in all studies to date the genetic influences on these structures and functions were highly correlated with those on general intelligence[29,31,32,36]. This important result — that at least some neural correlates of intelligence owe their associations to shared genetic influences — is drawn from multivariate genetic studies (see Box 4).

Brain development in childhood clearly involves morphological change, which is under some form of genetic control[37,38]. A longitudinal brain imaging study of children and adolescents examined twins and singletons ranging in age from 5 to 18[39]. They were recruited in 2001, and have been assessed at approximately 2-year intervals. In this sample, developmental trajectories of cortical thickness predicted IQ at age 20 better than did differences in cortical thickness at age 20[39]. There were strong genetic influences (77% to 88% of the variance) on the thickness of the midsagittal area of the corpus callosum, the volume of the caudate nucleus, and gray and white matter volumes of the total cerebrum, parietal lobes, and temporal lobes. Genetic influences on the volumes of the cerebellum and lateral ventricles were smaller (both 49%). Again, these point to a distributed pattern of brain correlates of general intelligence, which is addressed below. Complicating the situation for brain imaging studies, genetic influences on general intelligence that were shared across brain regions were stronger than those specific to any one region.[39] Genetic influences on brain regions tended to be strongest when brain regions were under greatest development: the primary sensory motor cortex, which develops early in childhood, showed stronger genetic influences during that period, and the dorsal prefrontal cortex and temporal lobes, which develop rapidly in adolescence showed stronger genetic influences during that period[40]. Total variance in overall brain morphology generally increased with age, but in white matter it was genetic variance that increased and in gray matter it was environmental variance.

Molecular genetic studies

Despite its high heritability, it is, as yet, difficult to name even one genetic locus that is reliably associated with normal-range intelligence in young, healthy adults, though some 300 genes are known to be associated with mental retardation[41]. After a thorough survey of over 200 published studies on the 50 or so genes that have been implicated in differences in cognitive abilities, it was stated that,

> if the question were to be asked "after 14 years of cognitive genetic research what genes can we conclusively say are responsible for the variation in cognition or its decline with age in healthy individuals?" the answer would have to be "none".[42]

Most of the genes that have been investigated in studies to date are associated with neurotransmitters (two thirds of the studies), disease, development or metabolism. Many studies have reported associations between particular polymorphisms and cognitive performance, but the associations were often small and most could not be replicated in other samples[13,42]. There are, however, reliable associations, largely limited to older people, between *APOE* polymorphisms and general cognitive ability, episodic memory, processing speed and executive function, with the first two of these showing an increasing effect size with age[43]. The increased effect with age is possibly due to the fact that APOE has a role in neuronal repair[44].

There may be faint signals in the noise among molecular genetic studies of intelligence to date. For example, a meta-analysis of 16 studies (total N > 9,000) found that a common polymorphism in the gene that codes for catechol-O-methyltransferase (*COMT*) was significantly and robustly associated with IQ scores (taken to represent general intelligence)[45]. However, the polymorphism accounted for only 0.1% of variance. Further evidence for a contribution of the *COMT* polymorphism to intelligence has been provided by

brain imaging studies in humans, pharmacological studies in animals, and transgenic and gene knockout studies in animals[46]. The valine-to-methionine amino acid substitution involved in this polymorphism reduces the activity of this dopamine-degrading enzyme, and the polymorphism is thought to affect dopamine function in the prefrontal cortex.

The Val66Met polymorphism in the gene coding for Brain-Derived Neurotrophic Factor (*BDNF*) is another commonly-studied genetic variant in association with cognitive abilities. Most studies report significant effects of this polymorphism on intelligence[42,47]; however, the studies differ with respect to which allele is associated with better cognitive performance. Overall, candidate-gene studies of intelligence and specific cognitive abilities have been criticised for "Inadequate sample size, population stratification, environmental exposure, publication bias, variation in classification and measurements are all examples that may make one group's findings different from those of another"[42].

At this point, it seems unlikely that single genetic loci have major effects on normal-range intelligence. For example, a modestly-sized genome-wide study of the general factor derived from ten separate test scores in the CANTAB cognitive test battery found no genome-wide significant single nucleotide polymorphisms or copy number variants, and did not replicate genetic variants that had previously been associated with cognitive ability[48]. It is possible that genetic variance in intelligence results from a mutation-selection balance, which is the cross-generational accumulation of many mildly harmful mutations that natural selection has not yet wiped from the population[49,50]. Because such variants would be rare and our primary methods of identifying genetic association require that variants be common, this possibility would be consistent with the fact that we can isolate genetic variants involved in mental retardation but not variants involved in normal-range intelligence.

It would be easy to fill this Review with studies published to date that apparently show gene-intelligence associations[13,42,48]. However, we think that it would be describing straws in

the wind, as most of these studies' findings have not been replicable. Even the associations between genetic variations such as *COMT* and *BDNF* and intelligence in the normal range — for which the studies are quite numerous — are still equivocal.

The emerging view of genetic influences on intelligence (and indeed many other complex, particularly quantitative, phenotypes that have been studied so far, such as height[51]) is that a very large number of genetic variants have very small effects. There might also be roles for copy number variations and for rare variants in individual differences in intelligence. Consortia formed to produce genome-wide scans will, in the near future, report genetic associations with cognitive functions based on subject samples of 10,000 and more. To what degree results from these studies prove reliable remains to be seen.

Brain imaging and intelligence differences

Bigger is better

Historically, the central working hypothesis in the neuroscience of human intelligence differences has been that size matters[52,53]. Empirical research in this tradition began in the 19th century, when scholars such as Paul Broca and Francis Galton studied intellectual ability and achievement in relation to brain size. The latter was mostly approximated by measures of head size, sometimes validated by post-mortem information. Current data indicate that intelligence is correlated with head size ($r \sim .20$)[54] and intracranial volume ($r \sim .40$)[55]. The clearest single body of evidence is that, in healthy people, total brain volume (measured using structural MRI) is moderately correlated with intelligence ($r \sim .30$ to $.40$)[14,54]. However, this does not mean that the correlation is understood.

With the advent of MRI technology, it became possible to extend the study of intelligence–size relations to individual brain regions *in vivo*. These studies found associations between intelligence and volumes of frontal, parietal and temporal cortices as

well as the hippocampus, all seldom larger than r = .25[14,55-58]. Using MRI, it is also possible to separate volumes of gray matter (i.e. mostly nerve cell bodies, but also dendrites and supportive glia cells) from those of white matter (i.e. nerve cell axons, their interconnections). This approach usually yields slightly higher correlations between intelligence and overall gray matter (r ~ .31) than between intelligence and overall white matter (r ~ .27), although differences are usually small[59].

Several studies have used voxel-based morphometry on MRI scans to measure the volumes of gray matter (and less frequently white matter) in specific brain regions and relate them to measures of intelligence. Most of this work has been summarized by Jung and Haier[60], who assigned the existing results to Brodmann areas (BA) and concluded that a network of brain regions, including areas in the dorsolateral prefronatal cortex, the parietal lobe, the anterior cingulate, and specific regions in the temporal and occipital lobe relate to individual differences in intelligence (Figure 2).

According to this Parieto-Frontal Integration Theory of intelligence (P-FIT), the extrastriate cortex (BAs 18, 19) and fusiform gyrus (BA 37) are involved in intelligence test performance because they contribute to the recognition, imagery and elaboration of visual input. just as Wernicke's area (BA 22) does for syntactic auditory input. Information captured via these pathways is then processed in the supramarginal (BA 40), superior parietal (BA 7), and angular (BA 39) gyri of the parietal lobe, in which structural symbolism, abstraction, and elaboration are thought to emerge. These parietal regions may then interact with parts of the frontal lobe (especially BAs 6, 9, 10, 45, 46 and 47) to form a working memory network that compares different possible task responses. Once a task response is selectee, the anterior cingulate (BA 32) supports response engagement and inhibition of alternative responses. These interactions among brain regions are dependent on the white matter fibers that connect them, such as the arcuate fasciculus. For most of these brain regions, the left hemisphere

seems to be somewhat more important to cognitive task performance than the right. As subsequent studies[61,62], and also studies using different methodologies (see below), have generally confirmed this theory (but see Ref. 63), P-FIT can be considered the best available answer to the question of where in the brain intelligence resides.

Cortical thickness, which reflects the cytoarchitectural characteristics of the neuropil much better than measures of gray matter volume[59], has been related to intelligence in four studies so far[29,59,64,65]. They all found generally (though not exclusively[29,59]) positive correlations between intelligence and cortical thickness, especially in the prefrontal cortex[29,59,64] and temporal lobes[29,59,65], as well as clustered around areas of multimodal association[64].

All these studies on (sometimes extremely fine-grained) measures of brain size and intelligence are correlational; the exact relation between the quantity of brain tissue and the quality of cognitive functions is largely unknown[66,67]. Although larger brains, greater gray matter volumes, and thicker cortices usually are associated with more neurons, it is unclear how and why this should lead to better intellectual performance, especially as brain development — and presumably intelligence development — involve substantial neuronal pruning[68]. This issue is also relevant in macroencephaly, where pathologically enlarged brains are associated with decreased rather than increased cognitive functionality. Related questions were raised in a longitudinal study by Shaw and colleagues[37]. They showed that the trajectories of development of cortical thickness in children differed for groups of different intelligence. Children with the highest intelligence scores had comparatively thin cortices in early childhood, but showed more rapid increases in thickness in the prefrontal and temporal lobes until puberty, when all cortices slowly thinned. Thus, it is possible that differences in brain development have currently underappreciated roles in intelligence differences.

A different, more direct way to test whether a brain area is crucially involved in intelligence differences is provided by studies of people with brain lesions. Although lesion studies have a long history in the neuroscience of intelligence, it was only recently that the limited generalization and specificity of case or small-sample studies of focal brain damage were overcome by Gläscher and colleagues, who collected cognitive data from a large sample of 241 patients with brain lesions[69]. Using voxel-based lesion mapping, they found highly specific lesion-deficit relations in left frontal and parietal cortex for working memory efficiency, in the left inferior frontal cortex for verbal comprehension, and in right parietal cortex for perceptual organization — all subfactors of general intelligence.

The (dis)connected mind

The emerging consensus from studies of regional brain sizes is that intelligence does not reside in a single, narrowly circumscribed brain region such as the frontal lobe. Rather, intelligence seems to be best described as a 'small world' network[70-73]. A necessary implication is that high intelligence probably requires undisrupted information transfer among the involved brain regions along white matter fibres.

One way to study white matter in relation to intelligence is to quantify white matter lesions on MRI or CT scans. Because white matter is especially prone to age-related decline, these lesions have been studied mainly in elderly subjects. These studies found weak but consistent relations indicating that people with more white matter lesions have lower cognitive ability[74,75]. The small effect sizes reported in this literature are probably partly due to the fact that most studies rely on lesion rating scales that allow for a considerable degree of subjectivity. Improving these by using multiple raters somewhat increased the association[76].

So far, 11 studies across a range of age groups have applied ^{1}H-magnetic resonance spectroscopy to examine white matter integrity in relation to intelligence[77]. Although

methods and results were quite heterogeneous, the studies generally found positive correlations between intelligence and concentrations of N-acetyl aspartate, a metabolite of the oligodendrocytes that form the myelin sheath around nerve fibers, and various white and gray matter areas in the brain, supporting the proposed role of white matter in intelligence.

Studies using diffusion tensor (DT)-MRI showed significant correlations between water diffusion parameters that quantify white matter integrity and intelligence in children[78,79], young adults[80] and old adults[78,81], especially in the centrum semiovale. Consistent with these findings, two studies that applied tractography on DT-MRI data to calculate integrity indices for specific white matter tracts found positive correlations between cognitive ability and white matter integrity, especially for long association fibers, such as the arcuate and uncinate fasciculi[75,82]. One study using cognitive data spanning several decades, found a significant association between childhood IQ and white matter integrity in old age[78]. This suggests that, in addition to the likely direct contribution of white matter integrity to intelligence, higher intelligence might result in behaviours across the life-course that promote white matter integrity. Alternatively, it is possible that intelligence and white matter integrity have, from an early age, overlapping sets of genetic and/or environmental causes.

In a resourceful utilization of the 79 healthy adults from Ref. 82, Li and colleagues combined DT-MRI tractography and MRI with graph analysis to construct a global brain network[83]. They found significant correlations between intelligence and parameters that reflect white matter network efficiency, indicating that not only the integrity, but also the organizational efficiency of white matter is important for higher intelligence.

Efficient processing

Early functional studies of intelligence used behavioural measures of reaction and inspection time[12] and correlated them with various measures of cognitive ability. The well-established

finding is that more intelligent people react to and inspect visual and auditory stimuli faster. However, although such chronometric tasks are generally thought to be endophenotypes of intelligence, their better biological tractability has yet to be established.

Nowadays, electroencepahalography (EEG), positron emisson tomography (PET), regional cerebral blood flow (rCBF), and functional MRI (fMRI) have been used extensively on individuals performing intelligence-related tasks such as matrix reasoning, mental rotation, or playing the video game Tetris. The indices of brain functional activity provided by these methods were interpreted as measures of neuronal efficiency and related to performance on the concurrent task and/or on intelligence tests taken before or afterwards. This literature has been reviewed in detail recently[60,84], with two basic conclusions: first, similar to structural studies, functional studies support a distributed network perspective of intelligence, largely overlapping with the one shown in Figure 2 and discussed above[60]. Second, functional neuroimaging findings are generally consistent with the hypothesis that intelligent brains process information more efficiently (i.e., use fewer brain resources when performing cognitive tasks) than less intelligent brains[85], with the proviso that the cognitive task be difficult enough to discriminate among brighter and less bright individuals, but not so difficult that even the brightest individuals have to recruit all their brain resources to solve it. When the latter is the case, less bright individuals usually give up, resulting in a positive correlation between brain resource usage and intelligence[84].

The notion that brain efficiency has a role in intelligence is also supported by a study by van den Heuvel and colleagues[86]. As did Li et al. for white matter networks,[83] they used graph analysis to assess the efficiency of a global brain network constructed using a voxel-wise approach based on fMRI data obtained at rest. They found significant links between functional efficiency and IQ, especially in frontal and parietal regions. This is consistent with another fMRI study which reported significant correlations between IQ and resting-state

functional connectivity of an 'exploratory' network involving the frontal and the parietal, occipital and limbic lobes[87]. The brain areas that were activated as an efficient network during resting periods (less activity in brighter individuals) in these two studies matched the frontal and parietal regions that were found to be activated in intelligent subjects under high cognitive demand[60,84], indicating that brain activity distinguishes more and less intelligent people even when they are not cognitively challenged.

Many neuronal roads to intelligence

Where they have been tested, many studies on the neuroscience of intelligence show sex differences, some to a striking degree. For example, in males intelligence is more strongly correlated with fronto-parietal gray matter volume, whereas in females intelligence shows stronger correlations with white matter volume and gray matter in Broca's area[88]. Cortical thickness in frontal regions correlates more strongly with intelligence in females, whereas temporal-occipital cortical thickness shows stronger correlations in males[59]. White matter integrity seems to be more important for intelligence in females than in males: males even sometimes show negative relations between intelligence and DT-MRI integrity measures of fronto-parietal fibers after puberty. This suggests that fewer but thicker and more tightly packed fibers possibly underlie cognitive functions in males than females[89]. Males also seem to be more neuronally efficient (i.e., they show less brain activation) than females during spatial cognitive tasks with intermediate difficulty levels, whereas females seem to be more neuronally efficient than males during verbal tasks of medium difficulty[90]. This is consistent with established sex differences showing better spatial abilities in males and better verbal abilities in females[84,91]. These patterns are interesting because males and females show marked differences in brain size[54] and structure[92-94], but negligible differences in general

intelligence[95]. Apparently, males and females can achieve similar levels of overall intellectual performance by using differently structured brains in different ways[85].

Sex differences are a peculiar form of individual differences, because the two sexes are the only qualitatively different 'morphs' of the human species[96]. This makes it easy to group subjects by this variable. However, it is likely that there is within-sex variation in how individuals use their brain. Two individuals with identical intelligence test scores might have achieved them via different neuronal routes because their brain structures might differ, because they might have different expertise and training effects or because they might have used different cognitive strategies[63,84,97,98]. Similarly, people seem to be able to compensate for cognitive deficits (or respond to cognitive challenges) by recruiting brain areas with hitherto only indirect relations to intelligence, especially frontal and corresponding contralateral areas.[99] Such compensation results in a more distributed processing of information in the brain and thus more widespread activation patterns. This is of particular interest in (but probably not exclusive to) cognitive ageing[99,100]. Although certain brain structures and functional pathways seem more likely to be involved in intelligence than others, there is also considerable heterogeneity[63,65,98], which might be related to individual differences in strategies when solving cognitive tasks[101]. Differences in strategy are also detectable in fMRI activation patterns[102,103] that show genetic variation[104]. Thus, there seems to be substantial room for differences in how individuals use their brains for intelligent performance. This should be explored in future studies.

Conclusion

Results from genetic and brain imaging studies performed to date can inform the design of the next phase of neuroscience-based studies of intelligence. Such studies should have large samples and a developmental perspective, include brain imaging and genetic testing, and be

driven by theories about the brain underpinnings of intelligence differences. They should be psychometrically-minded, which means that they should have subjects who are tested on adequate batteries of psychometric tests, and that the brain measurements should have due regard to reliability and validity of their measures.

The first adequately-powered genome-wide studies of intelligence will appear soon. We anticipate that, like some other highly polygenic phenotypes such as height, there will be much missing heritability[105]. That is, we anticipate some small effects from a relatively large number of common genetic variants, but they will account for little of intelligence's high heritability. This means that other sources of genetic variation will need scrutinising. Studies using genetic sequencing — which will detect rare genetic variants — and the study of copy number variations will be important. Results from these are predicted by the 'rare variant – common disease' and mutation load hypotheses. Rare genetic variants might be population-specific and thus might not replicate across samples. More studies that simultaneously carry out genetics and brain imaging will be useful. There is a welcome trend towards larger samples in neuroimaging and genetics, allowing for much more definite results than those that make up most of the literature so far. However, it is still important to avoid statistical pitfalls; both genetic and imaging studies have been very prone to type I and type II statistical errors.

In addition to studies of the association between intelligence and genetic structure differences, there will also be a need to examine individual differences in epigenetic changes (e.g. DNA methylation), gene expression, proteomics, metabolomics, and gene-gene and gene-environment interactions that might account for individual differences in intelligence.

Studies of the biological functioning of intelligence must recognise that people do not differ only in their general cognitive ability, but most likely also in how they use their brain to reach particular levels of performance. To understand the neuroscience of intelligence, we

need to learn more about how brains can be used differently for the same tasks, both within and across age and sex groups.

We have little understanding of how what we recognize as intelligence develops. Intelligence is clearly some combination of ability to 'figure things out on the spot' and the ability to retain and repeat things that have been figured out in the past. Neuroimaging could help by comparing brain structure and activity in people with and without experience in performing cognitive test problems such as Raven's non-verbal reasoning. Studies of the biology of intelligence will be most useful if they have a developmental perspective, running from infancy to old age; not least because there is both continuity and change in the individual differences across most of the lifecourse.

Performance on all of the cognitive tasks and abilities studied in neuroscience and genetics are confounded by general intelligence. Therefore, if researchers are primarily interested in the brain areas or genes for a specific cognitive ability, it might be helpful to statistically control for *g*, which should isolate as well as possible what is unique to a single task (see Ref. 98).

Some people's brains are more efficient than others. The biological foundations of these differences are of great interest to basic and applied neuroscience. There are already some well-replicated general findings. The differential neuroscience of human intelligence thus has a strong mandate and a firm foundation from which to proceed.

Box 1 Definitions of intelligence

An early and seemingly circular definition of intelligence came from the American psychologist E. G. Boring in 1923, when he stated that, "Intelligence is what the tests test"[106]. Although this definition is often criticised by detractors of IQ-type tests, it was taken out of context. The apparently dismissive comment came after a summary of strong empirical findings — for example, that the tests showed marked individual differences, that the differences were stable over time, that children developed greater intelligence over time but tended to maintain the same rank order. The sentence immediately following the famous quote was that the famously glib definition, "is only the point of departure for a rigorous discussion of the tests." Boring was simply stating that the psychometric data had to be good and then linked to other evidence about the origins and outcomes of intelligence.

A broader definition, agreed by 52 prominent researchers on intelligence, ran as follows. "Intelligence is 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"[107].

Intelligence tests generally consist either of complex tasks that involve different aspects of reasoning, such as the Ravens Progressive Matrices, or batteries of tasks that require different kinds of cognitive performance such as providing definitions of words and visualizing from two-dimensional diagrams how three-dimensional objects would look when folded. Two properties of these kinds of tests are important. First, all intelligence tests, whether of single, relatively unitary tasks or complex, multi-faceted tasks, are correlated and tend to generate a strong general factor when applied to a large sample of people. Second,

whatever our definition, intelligence should be assessed by its construct validity, meaning the accumulated evidence that the tests measure something of relevance: evidence on practical outcomes of intelligence differences, consistency of psychometric structure, and relations with biological structures and processes. By that criterion, intelligence is a core and valid facet of individual differences among humans. As this article shows, irrespective of definition and test used, data from brain imaging studies and genetic studies show strong correlates with results from intelligence tests, providing validity for psychometric intelligence measures, contrary to criticisms that such test scores (as often expressed as IQ) are meaningless numbers.

Box 2. Controversies in intelligence, and criticisms of *g*

Controversies involving intelligence. Two types of controversy surround the measurement of intelligence: in some cases, empirical intelligence-related data exist but have been missed, unappreciated, ignored or even rejected; in other cases, no definitive intelligence-related data are yet available. Examples of the first type include arguments about whether there are 'multiple intelligences'; whether genetic factors contribute to intelligence differences; and whether brain size is related to intelligence. The data on these issues are substantial and there are few to no contradictory data. Examples of the second type include debates about whether and to what extent intelligence tests may be biased for or against specific groups; the existence and causes of sex and ethnic differences in intelligence; the causes of the well-known correlations among intelligence, education and social class; and the cause of the population-level increases in IQ test scores throughout the 20th century in Western societies (known as the Flynn effect). The tools (such as tests of measurement invariance) that are currently available to address these issues are inadequate to resolve them. This is because we can at present measure only intelligent performance, which develops over time. Its development in an individual is thus embedded in the individual's environment of origin.

Criticisms of g. *g* has been criticised on two major grounds. First, several theories have proposed that domains of cognitive ability might be independent. The best known of these are Thurstone's 'Primary Mental Abilities' (PMA), and Gardner's 'Multiple Intelligences' (MI). However, these theories have not held up well. Even Thurstone's own PMA data contained a strong *g* factor[108]. Gardner has intentionally avoided empirical tests of his theory, but those that have been made show most of his MI to be correlated too[109]; and some of the MI, such as kinaesthetic ability, are not what psychologists would think of as 'cognitive' abilities at all.

Second, Cattell and Horn suggested that, however robust it may be statistically, *g* might have no real significance in the brain because the *g*'s from different ability test batteries could be very different, resulting in very different rank orders among individuals[110]. This is incorrect. As long as test batteries are reasonably diverse, *g* factors from different test batteries are almost perfectly correlated[111]. That is, as long as one administers enough tests, the general intelligence from one group of tests will agree closely in ranking with the general intelligence factor from any other group of tests.

For more than a century it has been popular to wish *g* away, but the near-universal positive covariation among cognitive tests is a fact. The theories that do not accommodate this finding — such as those of Thurstone, Guilford, Sternberg, and Gardner — fail the most basic empirical tests. Prominent accounts arguing that *g* is a necessary artefact of the statistical analyses — such as principal components analysis — are incorrect[112]. But there are more subtle and effective ways in which *g* has been questioned than the mere denial of the positive manifold, two of which deserve attention.

First, Spearman had a continuous and often heated debate with Godfrey Thomson. Thomson suggested that the positive associations among cognitive tests might be explained not by individual differences in a single property — whatever *g* represented, such as the 'mental energy' proposed by Spearman himself — but by individual differences in the number or efficiency of 'bonds' in people's brains. Thomson's idea, borrowed from his friend R. L. Thorndike, was that brains were composed of a very large number of biological units (bonds) and that when a person attempted to solve mental test items, each item sampled a number of these bonds. The degree to which tests overlapped in the bonds they sampled accounted for their correlation. Thomson could not specify what the brain's units were — though guesses such as "neural arcs" imply effective connections — but the theory implied that intelligence differences could lie in the number and/or efficiency of the bonds. Recent re-

evaluation of Thomson's ideas has found that his and Spearman's models of intelligence can both account for the psychometric patterning of tests' intercorrelations, and that current neuroimaging, genetic, and psychophysiological evidence cannot distinguish between them[113]. A computationally and conceptually modern version of this argument based on the supposition of mutual interactions between cognitive processes has also been proposed recently[114].

Second, one must recognise the success of at least one aspect of the Cattell-Horn theory of fluid and crystallised intelligence[110]. Fluid intelligence (g_f) is intelligence-as-process, and typically is assessed using tests which require on-the-spot processing. Crystallised intelligence (g_c) is intelligence-as-product, and is typically measured using tests which assess stored knowledge, such as vocabulary and general facts. Though the two are highly correlated, there is a marked difference in the extent to which they change with age fluid intelligence changing like other physical abilities whereas crystallised ability shows little age-related decline. A neuroscientific account of intelligence differences must explain these differential trajectories.

Box 3. Measuring genetic influences on intelligence

Many studies investigating genetic and environmental contributions to intelligence have been performed using monozygotic and dizygotic twins, but studies have also made use of samples of adoptive and biological siblings, and parents and their adoptive and biological offspring, with very consistent results across different types of relationship groups[115]. There have also been systematic reviews of the genetic contribution to general intelligence[116]. The basic idea of such studies is that genetic influences are indicated when more closely biologically related pairs of individuals are more similar for the trait of interest than less closely biologically related pairs. Shared environmental influences are indicated when there is more similarity between pairs of family members than would be indicated by their biological relationship.

Kinship studies to determine the proportions of variance that can be attributed to genetic and environmental influences rely on the accuracy of some crucial assumptions. From a quantitative genetic perspective, arguably the most fundamental of these is the assumption that genetic and environmental influences are independent, but this assumption is often false. An example relevant to the development of intelligence is the association of socioeconomic status (SES) with intelligence. There is some evidence that, in childhood, genetic influences on IQ (but not on socioeconomic status) are relatively stronger in higher SES environments[117] (but see Ref [118)], possibly indicating that some genes involved in IQ tend to be expressed only in higher SES environments (gene-environment interaction). But IQ and SES are generally correlated[119], suggesting that one's intelligence can influence one's SES or vice versa. Moreover, parents pass both their genes for intelligence and the associated SES environment on to their offspring (gene-environment correlation). Understanding how genes are involved in this correlation would help to interpret the biological meaning of intelligence's high heritability. Of note, the issue of gene-environment correlation has not been addressed in the

interaction studies conducted to date. Statistical designs exist to capture gene-environment interactions and correlations simultaneously in behaviour genetic analyses[120], but the techniques currently available are not applicable to situations such as childhood SES, which is identical for twin offspring.

Box 4. Multivariate genetic studies

The methods used to estimate the proportions of variance that are attributable to genetic and environmental influences on one trait can be extended to estimate the genetic and environmental influences on the covariances among multiple traits. For example, is the correlation between intelligence and brain size due to genes that influence both traits, or is it due to environmental conditions that affect both? To what degree do the genetic and/or environmental influences on brain size also contribute to intelligence? Developing answers to these questions relies on comparing the cross-relative covariance between the two traits. That is, we might measure the degree to which intelligence in one member of each twin pair in a sample covaries with the brain size in the other member of each twin pair, and compare the results in mono- and dizygotic twins. Genetic influences common to intelligence and brain size would be indicated when there is greater cross-pair similarity in more closely biologically related pairs, and shared environmental influences would be indicated when there is greater similarity between pairs of family members than would be indicated by their biological relationship.

Such comparisons result in two kinds of statistics. Genetic and environmental correlations, like ordinary correlations, range from -1 to +1 and document the extent to which genetic and/or environmental influences on one trait, such as brain size, also influence the other trait, such as intelligence. Second, we can also estimate the extent to which the observed correlation between, for example, brain size and intelligence can be attributed to genetic and/or environmental influences. Results from one study indicated that various measures of brain size were correlated .24 to .29 with various measures of intelligence, and genetic influences on the measures of brain size were correlated .24 to .38 with genetic influences on intelligence. All of the observed correlation, however, could be attributed to genetic influences[32]. This emphasizes that genetic and environmental correlations are

independent of the extent of genetic and/or environmental influences on the traits. One trait can be under strong genetic influence but those genetic influences may not be related to those on another trait, even if that trait is also under strong genetic influences, and vice versa.

Genetic and environmental correlations, like estimates of genetic and environmental influences, are statistical measures that quantify covariance and variance. They thus cannot identify the specific genes involved, and provide little information about whether we should expect to be able to find any specific genes of measurable effect. Moreover, genetic and environmental correlations do not specify causes. It is certainly possible that a common set of genes may contribute directly to both traits, but genetic correlations may arise for other reasons as well. In particular, when one genetically influenced trait affects the development of another trait by influencing the (gene's, brain's or individual's) environment, those genetic influences will also contribute to the genetic influences on the second trait. And specific genes that are of major importance to one trait may be of only minor importance to the other.

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Figure 1. The hierarchy of intelligence differences

Figure 1a is constructed from analyses conducted by Salthouse[121]. They were based on 33 of his own studies, with almost 7000 subjects, who were aged from 18 to 95. The small squares represent 16 different cognitive ability tests. The 16 tests coalesce into five factors representing broad domains of mental ability. Note that each test has a high loading on one group factor; the numbers may be thought of as the correlation between the individual test and the higher-order latent trait/ability domain. It is important to note that all five domains have high associations with the general factor. Correlations among the broad domains are high (not shown), refuting the idea that there might be independent 'primary mental abilities' at this broad domain level. The fact that the factors representing broad domains are strongly associated with *g* means that much of the variance apparently arriving at the 16 individual tests from the broad domains actually comes from *g*. Take the example of Test Number 1. Its correlation with the 'Reasoning' domain is 0.89. But the 'perceptual organisation' domain has a loading of .97 on *g*, which is shared with all four other cognitive domains. By simply squaring the correlations (or loadings), which is not always appropriate, one finds that about 74% of the variance in Test Number 1 is due to *g* and only about 5% due to the domain of 'Reasoning'.

Figure 1b shows that the hierarchy also applies importantly to cognitive ageing. The main effect of age is on *g*, with additional, cognitive domain-specific influences on memory and processing speed[121]. Note the positive direct effect on vocabulary. Age effects with effect sizes below 0.1 are not shown, nor are effects of gender, education and health. There is a direct positive effect of age on vocabulary. This is tempered by the negative effect of age on *g*, with which vocabulary is highly associated, and results in an overall modest positive effect of age on vocabulary.

Such a hierarchy of intelligence differences is found in almost all of the hundreds of large datasets that have applied multiple cognitive tests to large samples[11]. The hierarchy is important in genetic studies, because the major additive genetic influence is on *g*, and the major source of genetic variance on the individual tests is typically via *g*[20]. This finding holds into old age where, even at age 80, the additive genetic contribution to *g* is still high, and where broad cognitive domains still have very high correlations with *g*[122]. The domain with the strongest non-*g* genetic influence is memory, though even with memory the largest source of genetic variance comes from the genetic influence on *g*. Figures based on data from REF. 120.

Figure 2. **The loci of intelligence differences**

Based on a review of all the structural and functional neuroimaging literature that was available to them at that time, Jung & Haier proposed the Parieto-Frontal Integration Theory of intelligence (P-FIT), which is arguably the best available description of how intelligence is distributed in the brain. The figure shows Brodmann Areas (BA) involved in intelligence as well as the arcuate fasciculus (arrow) as a promising candidate for a white matter tract that connects the involved brain regions. BA's in darker circles indicate predominantly left-hemispheric correlations and lighter circles predominantly right-hemispheric correlations with intelligence. Figure modified, with permission, from REF 60

Glossary terms

Raven's Progressive Matrices test
An established non-verbal test of inductive reasoning that is often regarded as a good marker of the general factor of intelligence.

Non-verbal ability
A broad subfactor of intelligence defined by tests that do not rely on verbal stimuli or responses. The term perceptual-organizational ability is often used synonymously.

Mutation-selection balance
An evolutionary genetic explanation for the maintenance of genetic variance in a trait, based on an equilibrium between novel detrimental mutations and purifying selection.

Small world network
A network characterised by a high levels of local clustering among nodes and short paths that globally link all nodes, resulting in all nodes being linked through relatively few intermediate steps despite few connections per node.

Long association fibers
A set of axonal tracks connecting distant brain areas within the same hemisphere.

Network efficiency
Short mean path lengths for parallel information transfer, as for example provided by a small world network structure.

Endophenotypes
Quantifiable phenotypes with assumed intermediate roles in the pathway from genes to complex phenotypes, which are supposed to be easier to understand biologically and genetically.

Functional connectivity
Correlations between the activation patterns of different brain areas.