NEUROBIOLOGY OF INTELLIGENCE: SCIENCE AND ETHICS

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Human mental abilities, such as intelligence, are complex and profoundly important, both in a practical sense and for what they imply about the human condition. Understanding these abilities in mechanistic terms has the potential to facilitate their enhancement. There is strong evidence that the lateral prefrontal cortex, and possibly other areas, support intelligent behaviour. Variations in intelligence and brain structure are heritable, but are also influenced by factors such as education, family environment and environmental hazards. Cognitive, psychometric, genetic and neuroimaging studies are converging, and the emergence of mechanistic models of intelligence is inevitable. These exciting scientific advances encourage renewed responsiveness to the social and ethical implications of conducting such research.

FLUID INTELLIGENCE (Gf). 'On the spot' reasoning and novel problem-solving ability.

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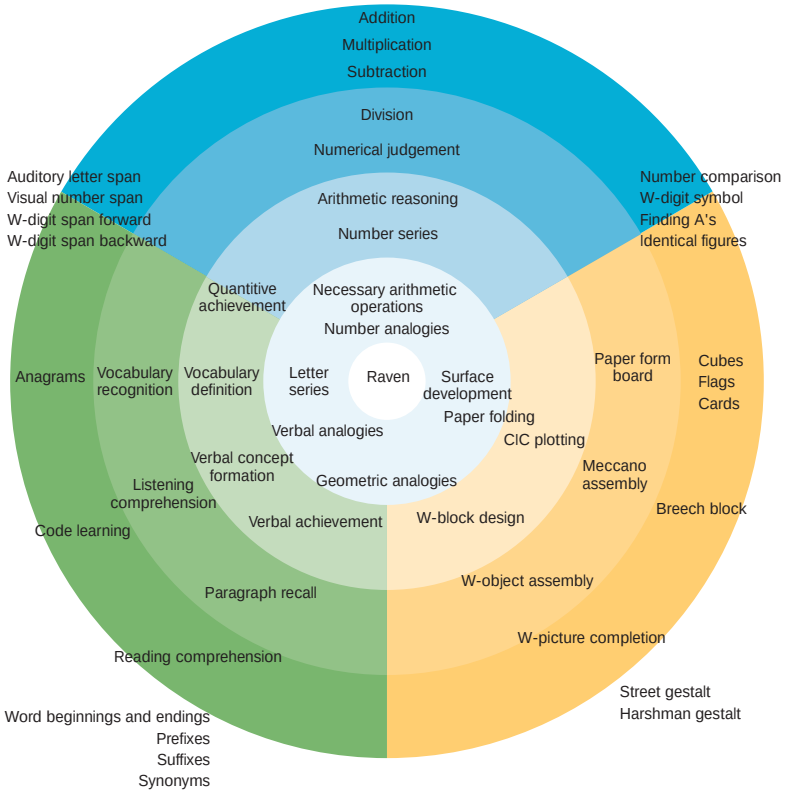
In the United States, it is mildly impolite to dwell on an obvious fact — individual differences are the rule, not the exception. Parents and educators are aware that their young charges have different sensitivities and strengths in varying domains. Employers would be foolish not to take differences in performance into account when making decisions about hiring, retention and compensation. And yet it is indecorous to accord such differences more than passing attention in casual conversation, because they seemingly (but wrongly[1,2]) imply a trait-like quality — that differences in behaviour not only exist but reflect inherent differences that are independent of context and impervious to change. Conceptions of mental ability have far-reaching implications for theories of human nature[3–5]. In turn, the implications for society are nothing short of "incendiary"[6] (see also REFS 5,7). Attending to such differences seemingly undermines the higher ethical principle of human social equality (see REF. 3 for discussion). Strictly speaking, such fear is unwarranted because it presupposes that the way things are implies something about how they ought to be (in the sense of ethical or moral implications) and this does not follow[8]. In other words, a mechanistic understanding of human abilities hardly constrains social policy, if at all[9]. Nonetheless, the fear is not entirely irrational — if a group is stereotyped as being of lower intelligence, for example, this can seem to justify actions that adversely affect the group's achieved intelligence, or justify the neglect of actions that could help to enhance it.

It is distinctly impolite to suggest that individual differences in ability have a biological basis[3,10]. The root fear is that evidence about the brain might be misconstrued as evidence about an individual's or group's inherent quality or fitness, in the sense of an immutable social and moral value[4,7]. Gould concluded[10] that there is no reliable evidence for "intelligence as a unitary, rankable, genetically based, and minimally alterable thing in the head", and even less evidence that intelligence is associated with demographic variables, such as race or social class. For better or worse, however, recent progress in the psychometric, social psychological, cognitive neuroscientific and genetic study of human abilities has been dramatic.

In this review, we emphasize intelligence in the sense of reasoning and novel problem-solving ability (BOX 1). Also called FLUID INTELLIGENCE (Gf)[11], it is related to analytical intelligence[12]. Intelligence in this sense is not at all controversial, and is best understood at multiple levels of analysis (FIG. 1). Empirically, Gf is the best predictor of performance on diverse tasks, so much so that Gf and general intelligence (*g*, or general cognitive ability) might not be psychometrically distinct[13,14]. Conceptions of intelligence(s) and methods to measure them continue to evolve, but there is agreement on many key

Box 1 | Defining and measuring intelligence



It is difficult to improve on the consensus description of the term 'intelligence' agreed on by a task force convened by the American Psychological Association[15]: "Individuals differ from one another in their ability to understand complex ideas, to adapt effectively to the environment, to learn from experience, to engage in various forms of reasoning, to overcome obstacles by taking thought. Although these individual differences can be substantial, they are never entirely consistent: a given person's intellectual performance will vary on different occasions, in different domains, as judged by different criteria. Concepts of 'intelligence' are attempts to clarify and organize this complex set of phenomena."

Intelligence is almost always inferred from behaviour. A person responds quickly to a simple stimulus or selects an answer to a question from several possibilities. The person's performance is then rated for speed, accuracy or more subtle aspects such as learning. People differ considerably in their performance, and people who do well on one test tend to do well on many other tests. Scores on various tests can be factor-analysed to give *g*, a single summary measure of cognitive ability (also called Spearman's *g*). *g* is made up of a small number of (non-independent) subfactors that represent more specific abilities[14,17]. These facts are not controversial, but their interpretation is.

One view is that the general factor (*g*) is largely responsible for better performance on various measures[40,85]. A contrary view accepts the empirical, factor-analytic result, but interprets it as reflecting multiple abilities each with corresponding mechanisms[141]. In principle, factor analysis cannot distinguish between these two theories, whereas biological methods potentially could[10,22,36]. Other perspectives recognize the voluminous evidence for positive correlations between tasks and subfactors, but hold that practical, creative[142] and social or emotion-related[73] abilities are also essential ingredients in successful adaptation that are not assessed in typical intelligence tests. Further, estimates of individual competence, as inferred from test performance, can be influenced by remarkably subtle situational factors, the power and pervasiveness of which are typically underestimated[2,136,137,143].

Fluid intelligence (Gf, for general intelligence — fluid) refers to reasoning and novel problem-solving ability[11]. It is distinct from crystallized intelligence (Gc), which refers to overlearned skills and static knowledge such as vocabulary. Empirically, Gf is strongly associated with working memory[18,45,52] and with *g*, as illustrated in the figure (reproduced, with permission, from REF. 144 © (1984) Erlbaum). This multidimensional scaling solution illustrates how specific tasks correlate with *g* — strongly in the centre, weakly at the periphery.

points; for example, that intelligence is not fixed, and that test bias does not explain group differences in test scores[15]. Intelligence research is more advanced and less controversial than is widely realized[15–17], and permits some definitive conclusions about the biological bases of intelligence to be drawn.

We first review the neural bases of intelligence and related work on reasoning, and then the genetic bases. Finally, we consider an ethical issue — research into population-group (race) differences in intelligence — that if left to fester could compromise further empirical advances.

Neural bases of intelligence

Imaging and patient-based studies have related brain structure and function to intelligence. In light of previous reviews[18–20], we emphasize recent work which indicates that the field is moving beyond relatively non-specific questions (for example, about head size and intelligence; for a meta-analysis see REF. 19) to addressing more specific cognitive and neural mechanisms.

Patients with brain damage provided early data that are still important — causal evidence that intelligent behaviour depends on the integrity of specific neural structures. More than 125 years ago, the frontal lobes were implicated in abstract reasoning[21]. Modern studies have reinforced and refined these conclusions (for reviews see REFS 22–24). One notable finding of many studies is that patients with damaged frontal lobes often have normal INTELLIGENCE QUOTIENTS (IQs) as assessed by tests that typically measure skills and knowledge (CRYSTALLIZED INTELLIGENCE (Gc); for example, the Wechsler Adult Intelligence Scale (WAIS)). By contrast, posterior lesions often cause substantial decreases in IQ[23]. Duncan and colleagues suggested that the frontal lobes are involved more in Gf and goal-directed behaviour than in Gc[25] (FIG. 2). In addition, Gf is compromised more by damage to the frontal lobes than to posterior lobes[24,25] (FIG. 2). Other studies indicate that the frontal lobes are crucial for integrating abstract relationships[26], a key aspect of resolving many reasoning problems (but not of previously learned skills or knowledge).

Modern neuroimaging methods reveal aspects of brain function with greater spatial precision than patient studies, and can do so in healthy individuals. Imaging studies provide correlational rather than causal evidence (for discussion see REF. 27), but they have contributed considerably to our understanding of the neurobiology of intelligence.

Imaging studies of intelligence and brain structure. Correlations between intelligence and total brain volume or grey matter volume have been replicated in magnetic resonance imaging (MRI) studies, to the extent that intelligence is now commonly used as a confounding variable in morphometric studies of disease. MRI-based studies estimate a moderate correlation between brain size and intelligence of 0.40 to 0.51 (REF. 28; see REF. 29 on interpreting this correlation, and REF. 30 for a meta-analysis). One MRI study determined the volume of 13 brain regions, and found that the brain regions

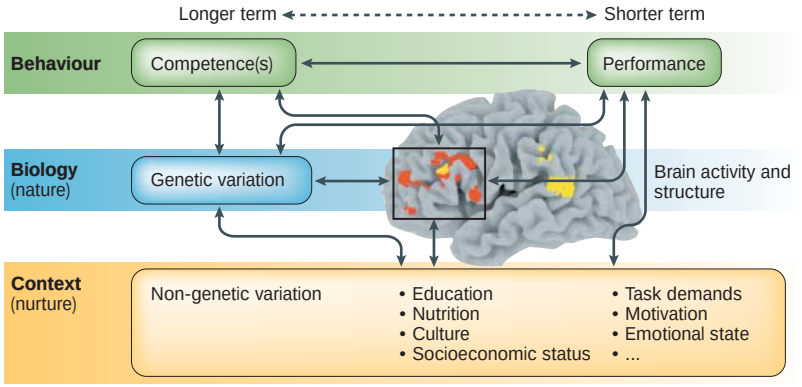


Figure 1 | **Studies of the biological bases of intelligence have identified relationships between variables at three broad levels of analysis: behaviour, biology and the wider context.** A neurobiological model of intelligence requires an understanding of these complex relationships in terms of specific causes and effects. Causal relationships can be bidirectional and operate at different timescales, from evolutionary time (natural selection) to milliseconds (changes in brain electrical activity and behavioural performance). Image reproduced, with permission, from *Nature Neuroscience* REF. 27 © (2003) Macmillan Magazines Ltd.

intercorrelated substantially — a general factor (the first unrotated principal component in a factor analysis) accounted for 48% of the variance[31]. We found that *g* was significantly linked to differences in the volume of frontal grey matter, which were determined primarily by genetic factors[32] (FIG. 3). As noted in REF. 33, this analysis underestimated the extent to which grey matter volume in each brain region correlates with *g*. We reported partial correlations that indicated the association between the volume of each brain region and *g*, independent of other brain regions. In other words, the volume of frontal grey matter had additional predictive validity for *g* even after the predictive effect of total brain volume was factored out (as is common in morphometric studies).

Posthuma *et al.*[34] extended these findings using a cross-twin cross-trait (bivariate genetic) analysis to compute genetic correlations. They showed that the linkage between volume of grey matter and *g* is mediated by a common set of genes. Intelligence therefore depends, to some extent, on structural differences in the brain that are under genetic control, indicating a partly neuroanatomical (structural) explanation for the high heritability of intelligence. However, brain structure is not completely determined by genes — learning a difficult perceptual–motor skill (juggling) induced a 3% increase in the volume of grey matter in visual attention areas[35]. Although such plasticity has not been shown in all regions of the brain, it is possible that the volume of grey matter is correlated with intelligence partly because more intelligent individuals seek mentally challenging activities that increase the volume of their grey matter.

Imaging studies of intelligence and brain function. Measuring brain activity while participants are performing an intelligence test, and contrasting it with activity under control conditions, reveals common regions of activation that probably support intelligent behaviour. Duncan *et al.*[36] predicted and found that only one region is consistently activated during three different intelligence tasks when compared to control tasks (FIG. 4b). The surface features of the tasks differed (spatial, verbal, circles) but all were moderately strong predictors of *g* (*g* LOADING; range of *r*, 0.55–0.67), whereas control tasks were weaker predictors of *g* (range of *r*, 0.37–0.41). Neural activity in several areas, measured by a positron emission tomography (PET) scan, was greater during high-*g* than low-*g* tasks. Crucially, only the lateral prefrontal cortex was activated during all three tasks. This result has intriguing implications for debates about the structure of intelligence[36] (compare with REF. 22). Unitary or general intelligence (*g*) theories predict the activation of a single brain region (but see caveats below), whereas theories of multiple intelligences predict widespread activity. The data of Duncan *et al.*[36] are consistent with a unitary view. However, three other studies using a similar design[37–39] revealed widespread activity during the performance of intelligence tests, including activation of posterior regions, as did a study using an individual-differences approach[27]. The apparent discrepancy might stem from the use of functional MRI (fMRI) rather than PET, or from the use of tasks that varied in their capacity to predict *g*. Imaging data are intrinsically correlational, so activation of areas other than the prefrontal cortex might reflect recruitment by the prefrontal cortex (although this of itself does not explain why one study should identify a single area and others should identify multiple areas).

Perhaps surprisingly, the discrepancy is not central to the broader question about the structure of intelligence. One of the main insights of cognitive neuroscience is that the 'functional units' of higher cognition are networks of brain areas, not single areas. So identifying an activated network could be just as supportive of the unitary theory as identifying a single activated area, if the putative network could be shown to constitute a functional unit (using, for example, effective connectivity analyses and diffusion tensor imaging). Identifying such a network (or single area) when contrasting results from a high-*g* task with those from a low-*g* task is consistent with a unitary view of intelligence, and is an important result. Better evidence could be derived from measurements of brain activity in a large number of people while they performed many tasks, the *g* loading of which varied. Identification of a brain region (or network) for which the correlation between psychometric *g* and brain activity in a given task depended on the *g* loading of the task would be better evidence for a unitary view of intelligence. This would be an application of Jensen's method of correlated vectors[40] — if higher-*g* tasks revealed a stronger relationship between psychometric *g* and brain activity, it would implicate the region(s) in intelligence with high specificity (because individual variation and task variation cross-validate each other). If the tasks were numerous, varied greatly in content and *g* loading, and included aspects of intelligence not typically assessed during standardized tests, then such a result would be good evidence for a unitary theory.

Frontal and parietal regions that are activated during intelligence tests are also activated during WORKING MEMORY tasks[41–43]. Moreover, a theoretical analysis of a reasoning-based intelligence test (Raven's Advanced

INTELLIGENCE QUOTIENT (IQ). Intelligence scaled by age, standardized to have a population mean of 100 and SD of 15 (mental age divided by chronological age). It produces an intelligence ranking relative to other individuals of the same age, which tends to be stable across the lifespan of the individual.

CRYSTALLIZED INTELLIGENCE (Gc). Performance guided by overlearned skills or knowledge, such as vocabulary.

g LOADING (OF A TASK) A measure of how strongly individual differences in performance on a particular task predict differences in general intelligence (*g*). A task with a high *g* loading will better reveal differences between people of higher and lower intelligence.

WORKING MEMORY A cognitive/neural system for maintaining information actively in mind (storage) and manipulating it (executive processing), or holding it in mind despite potential distraction or interference (control of attention).

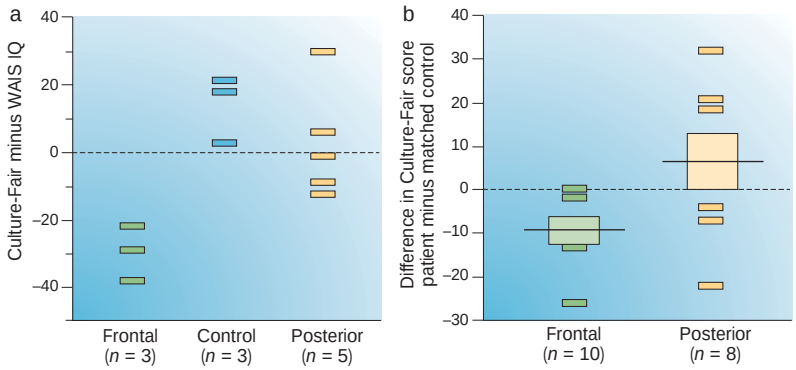


Figure 2 | **Frontal brain damage compromises fluid intelligence more than crystallized intelligence. a** | Difference between reasoning ability (fluid intelligence: Cattell's Culture-Fair IQ) and knowledge (crystallized intelligence: Wechsler Adult Intelligence Scale (WAIS) IQ) for patients with frontal brain damage, matched controls and controls with posterior lesions[25]. **b** | Fluid intelligence scores are impaired more by damage to frontal than posterior brain structures[24] (the boxes represent mean difference with approximate standard error of the mean). Each point represents a difference between a patient and a closely matched control. Based on data from REFS 24,25.

Progressive Matrices (RAPM)) implicates working memory processes[44]. The importance of working memory is further bolstered by extensive behavioural work on individual differences in Gf and aspects of working memory, particularly the executive control of attention to overcome distraction or interference[18,45,46].

Other group-based imaging studies examined brain activity during reasoning tasks. Several abstract reasoning tasks recruit parts of working memory circuits[43,47,48]. In theoretical and behavioural work, important component processes of reasoning have been identified, including relational integration and subgoal processing, which recruit the anterior regions of the lateral prefrontal cortex[49–51].

Individual differences. A complementary empirical approach is to examine how people, rather than tasks, differ[52,53]. Both are needed for a full understanding[27]. Here, the focus is on individual differences in brain activity, and how they correlate with differences in PSYCHOMETRIC INTELLIGENCE. Studies using electroencephalograms and event-related potentials indicate that the speed and reliability of neural transmission are related to higher intelligence (reviewed in REFS 15,20). Early neuroimaging studies using PET found that intelligence correlated negatively with cerebral glucose metabolism during mental activity[54] (for a review, see REF. 55), leading to the formulation of a 'neural efficiency' hypothesis. According to this hypothesis, more intelligent individuals expend fewer neural resources to perform at a given level. Ongoing work bolsters this hypothesis[55] although the effect might be found only in male participants[56] and positive correlations have also been reported[27,36,57].

In the largest imaging study of individual differences in intelligence (n = 48; REF. 27), we tested whether Gf is mediated by neural mechanisms that support the executive control of attention during working memory. This hypothesis was based on a large body of cognitive literature emphasizing resistance to distraction or interference under these conditions[18,58,59]. Participants performed verbal and non-verbal working memory tasks in which they had to indicate whether a current item exactly matched the item they saw three previously ('3-back') while their brain activity was measured using event-related fMRI. Importantly, the demand for attentional control varied greatly across trials within the 3-back task owing to differences in trial-to-trial interference (as inferred from mean accuracy and response time). The performance of participants with higher Gf (as measured by RAPM; assessed outside the scanner) was more accurate. These participants also showed greater event-related neural activity in many regions, including the frontal, parietal and temporal lobes, dorsal anterior cingulate and lateral cerebellum (FIG. 4c). Crucially, these patterns were most distinct during high-interference trials, even after controlling for behavioural performance and for activity on low-interference trials within the same regions during the same scanning run. (This analysis is related conceptually to the correlated vectors approach[40], but has only two task conditions: high-interference trials (more difficult) and low-interference trials (less difficult)). Path analyses indicated that only the lateral prefrontal and parietal regions mediated the correlation between Gf (RAPM score) and task performance (accuracy).

The correlated vectors logic[40] indicates that a brain region that is involved in intelligence should not have activity correlated with intelligence under conditions that place little demand on intelligence. In one study, brain activity was measured while 22 participants watched videos[57]. RAPM scores obtained outside the scanner predicted brain activity in a single left parietal/temporal region, and not in the frontal lobes. For the lateral prefrontal cortex, this result provides a low-g control condition — the lack of relationship contrasts with studies using individual differences in higher-g tasks (such as working memory, which find a relationship in lateral prefrontal cortex[27]).

Another study with very low working memory load involved INSPECTION TIME, which is correlated with intelligence (although the reason for this is not fully resolved[20]). An exploratory fMRI study[60] (n = 7) indicated that parietal areas are involved in inspection time tasks, specifically Brodmann area (BA) 40 and the ventrolateral prefrontal cortex (BA47) but not the dorsolateral prefrontal cortex (BA9, 44–46). The inspection time data are also intriguing because cholinergic drugs enhance both inspection time (for a review see REF. 61) and the efficiency of working memory networks[62]. A novel hypothesis is that faster inspection time is associated with higher intelligence because it represents more efficient perceptual representations which lead to lower working memory load.

Gc might have a different relationship to brain activity than Gf[25]. However, three imaging studies that involved verbal Gc (for example, as assessed by years of education and two vocabulary-based tests[63,64] or by the WAIS-R vocabulary[65]) have provided mixed results, for which no firm generalization can presently be formulated.

PSYCHOMETRIC INTELLIGENCE
Intelligence as measured by an IQ-type test, typically assessing the accuracy of a response (and not the speed).

INSPECTION TIME
The minimum duration of exposure to a visual stimulus that a study participant requires to respond accurately about that stimulus.

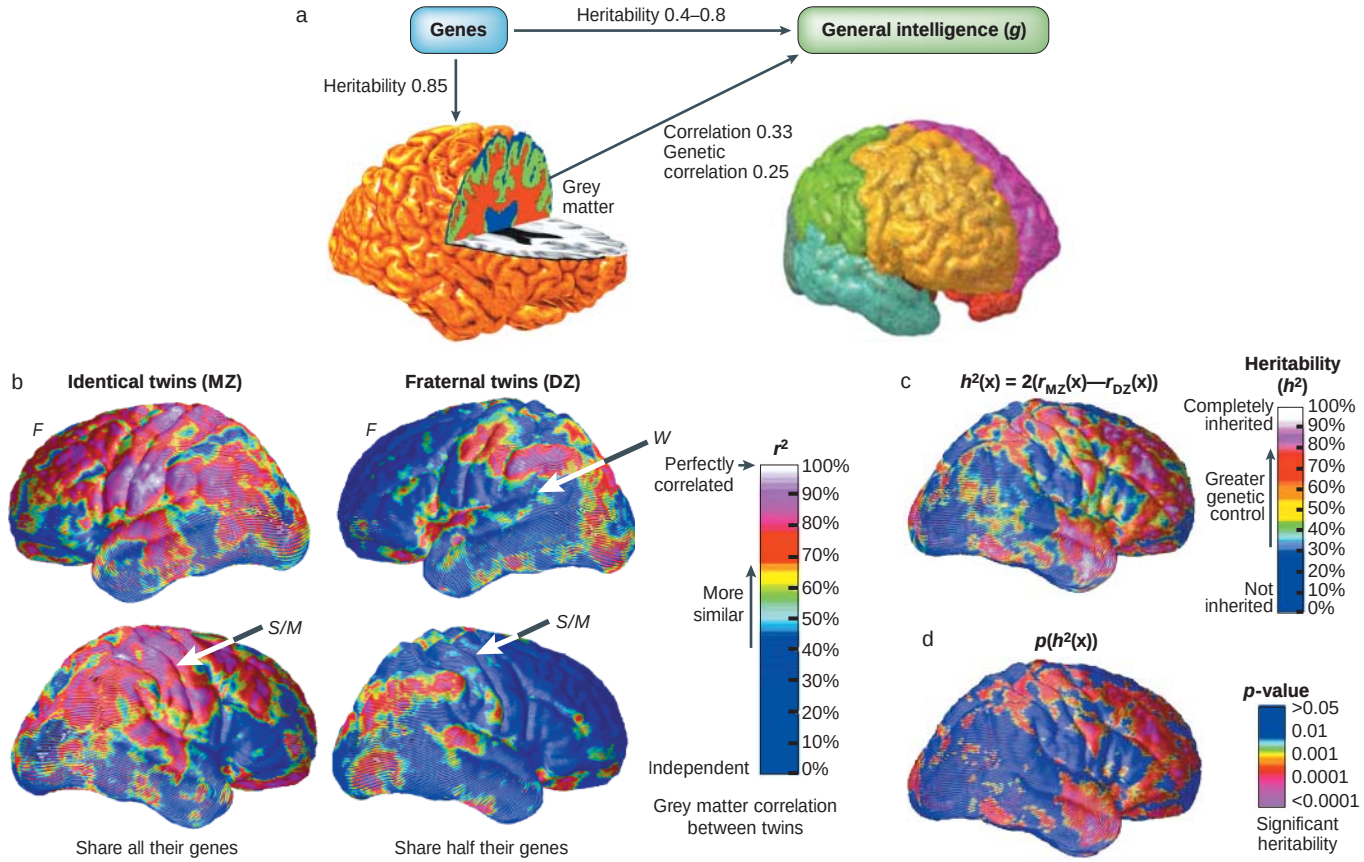


Figure 3 | **Linking genes, brain structure and intelligence. a** | Genetic influences on intelligence have been assessed directly (top arrow). The consensus of many studies is that at least 40% of the variability in general cognitive ability (*g*) can be attributed to genetic factors[89]. Gene effects on brain structure can be assessed by collecting MRI brain scans (left) from twins or extended families, and comparing volumes of grey matter (green), white matter (red) or cerebrospinal fluid (blue). Overall brain volume is 85% heritable[34] and correlates with psychometric intelligence (0.33) (REF. 30). Genetic modelling has shown that *g* and grey matter volumes depend on the same set of genes[34] (the genetic correlation is about 0.25). The volume of grey matter in each lobe is genetically influenced to different degrees (the volume of grey matter in the frontal lobe, shown at right in yellow and pink, is highly heritable). **b** | Genetic influences on brain structure can be assessed using statistical maps. In the classical twin design, a feature is heritable if within-pair correlations (typically called intraclass correlations) are higher for pairs of identical twins (who share all their genes, except for rare somatic mutations) and lower for same-sex fraternal twin pairs (who, on average, share half their genes). To better understand genetic influences on brain structure, correlations are shown for regional grey matter volumes in sets of identical (monozygotic (MZ)) and fraternal (dizygotic (DZ)) twins. These correlations vary across the brain surface (red, highly correlated; blue, less well correlated). The structure of the brains of identical twins is more similar than that of fraternal twins. F, frontal cortex; S/M, primary sensorimotor cortex; W, Wernicke's area. Adapted, with permission, from *Nature Neuroscience* REF. 32 © (2001) Macmillan Magazines Ltd. **c** | Twice the difference between the MZ and DZ correlations (h^2) is a simple estimator of the heritability of grey matter volumes at each location in the cortex. **d** | Statistical significance of the heritabilities. These can also be estimated from path analyses. Variations in grey matter volumes are strongly influenced by genetic factors, especially in frontal brain regions (for example, the dorsolateral prefrontal cortex). A subsequent study in a larger, independent sample[34] found that variations in total grey matter volume were almost entirely attributable to genetic factors (but three-dimensional maps of these effects were not created). These genetically mediated differences in brain structure explain a proportion of the variation in general cognitive ability. This ability is also influenced by non-genetic factors such as education and nutrition[97,151], prenatal and family environments, training[35] and environmental hazards such as lead poisoning. Adapted, with permission, from *Nature Neuroscience* REF. 32 © (2001) Macmillan Magazines Ltd.

Overall, intelligence in the sense of reasoning and novel problem-solving ability is consistently linked to the integrity, structure and function of the lateral prefrontal cortex, and possibly to that of other areas. Regions within both the lateral prefrontal cortex and posterior areas are under genetic control (FIGS 3,4). The lateral prefrontal cortex supports the executive control of action and attention[66], but how this brain area (and other regions) contributes specifically to intelligent behaviour is less well understood (as discussed in REF. 27). Several imaging studies indicate that the parietal cortex and other areas (such as the anterior cingulate cortex) might also contribute. Patient-based studies support this view, but only for Gc[23] and not for Gf (for example, FIG. 2).

Outstanding questions about the neural bases of intelligence include the relationships between psychometric intelligence and: (i) the specific computational or functional contribution of different brain regions to reasoning[27] and other abilities; (ii) functional neurochemistry[67,68]; (iii) functional connectivity between components of working memory networks, as indicated by electroencephalogram-based studies[69,70]; (iv) relationships between brain structure and activity; (v) gender differences in neurobiological mechanisms[56]; (vi) neural efficiency and reliability[56,71]; (vii) neural plasticity[72]; and (viii) relationships between speed of processing, inspection time and neural mechanisms[20,60]. Conceptual and psychometric advances will also be

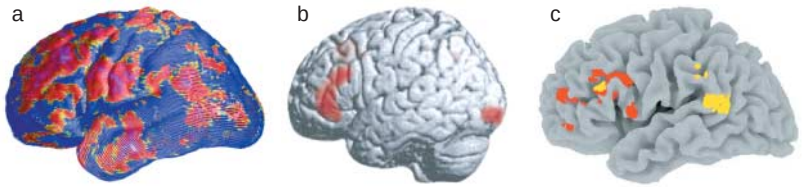


Figure 4 | **Different methods of assessing the relationship between intelligence and the brain implicate similar brain regions.** All panels show left hemisphere. **a** | Regions in which the volume of grey matter is primarily under genetic control are shown in red. Reproduced, with permission, from *Nature Neuroscience* REF. 32 © (2001) Macmillan Magazines Ltd. **b** | High-*g* tasks recruit the lateral prefrontal cortex to a greater degree than low-*g* tasks, for both verbal and non-verbal tests. Activity in the spatial high-*g* task is shown here when it is significantly greater than activity during the spatial lower-*g* control task. Reproduced, with permission, from REF. 36 © (2000) American Association for the Advancement of Science. **c** | Individual differences in fluid intelligence are correlated with activity during the interference conditions of verbal and non-verbal working memory tasks[27]. Red indicates areas showing this correlation within *a priori* regions; yellow indicates areas identified across the whole brain at a more conservative threshold (requiring a stronger correlation). All correlations were positive. Reproduced, with permission, from *Nature Neuroscience* REF. 27 © (2003) Macmillan Magazines Ltd.

crucial. Beyond reasoning and cognitive abilities, the neural bases of other aspects of intelligence must be clarified[12,73,74] before neurobiological methods can be brought to bear on the debate about the structure of intelligence.

Genetic bases of intelligence

It is now widely accepted that genes and environment both have crucial roles in the transmission and expression of disorders. Genetic relationships also influence cognitive skills in normal, healthy individuals[75–77]. Here, we briefly review genetic influences on intelligence, noting interpretive caveats and unexpected findings. The fact that intelligence is heritable does not necessarily have implications for the basis of population-group differences. Group differences can potentially be explained in purely environmental terms, even if intelligence is strongly heritable.

Heritability. Genetic influences on intelligence can be detected by correlating GENETIC POLYMORPHISMS with cognitive differences, or by comparing test scores of related individuals using quantitative genetic techniques. In the simplest approach, a heritability statistic (h^2; FIG. 3) reflects the percentage of the variation in test scores that is attributable to genetic differences. This contrasts with the percentage due to all other factors ('environment', including nutrition, education and experience, or experimental errors such as lack of reproducibility in the test). Test scores of relatives with different degrees of affinity — for example, twins or adopted siblings — are then compared. More complex statistical designs use path analysis to reveal co-variation between other types of relatives[78–80]. Proportions of the observed variance are then attributed to individual genetic differences, and differences in shared and individual-specific environments. Sharing the same family environment makes family members more alike, so fraternal twins are also typically studied for comparison — if only environment were important, it would not matter whether twins were identical or fraternal.

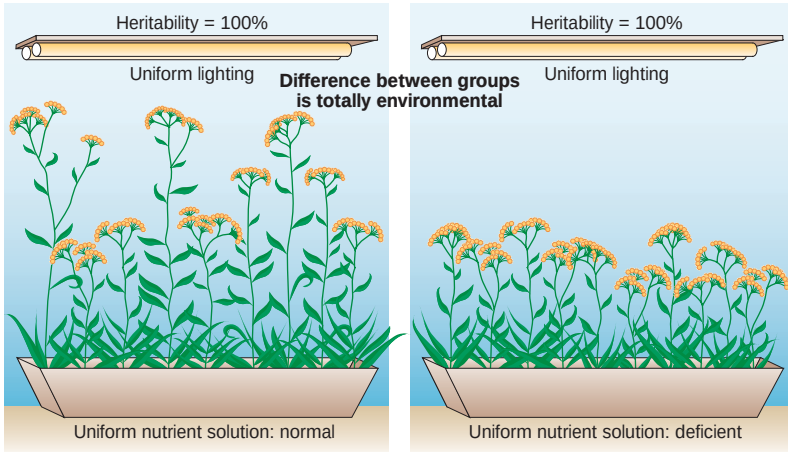
GENETIC POLYMORPHISMS
Different variants of the same gene.

Correlations between related individuals show that both nature and nurture influence intelligence[75]. Monozygotic twins raised separately following adoption show a correlation of 0.72 for intelligence; that is, one twin's intelligence strongly predicts the other's, despite their different rearing environments. Twin data indicate that there is a strong genetic component to intelligence, but several non-genetic factors that make monozygotic twins more similar could confound this association. For example, identical twins might be selectively placed into similar (but separate) adoptive homes. Sharing the same fetal environment might make identical twins more or less alike cognitively through twin–twin competition for nutrition, transfusion effects and so on. Also, fraternal twins might inadequately control for the effects of shared family environments; for example, identical twins might receive more similar treatment from their parents than fraternal twins (assimilation effects), leading to more highly correlated scores, and this would spuriously inflate estimates of heritability[81,82].

Nonetheless, studies with a more rigorous adoption or extended family design, which adjust for these biases, have largely confirmed the genetic relationships found in twin studies. For 48 identical twin pairs separated in early infancy and reared apart, Bouchard *et al.*[83] found remarkably high between-twin correlations for verbal scores on the WAIS (0.64) and for the first principal component of special mental abilities (0.78). Correlations for three other intelligence measures fell in-between these scores. The intraclass correlation between intelligence scores of identical twin pairs, adopted and reared apart, directly measures heritability, as long as the twins have minimal contact and are not adopted into similar homes[84]. Heritability estimates differ for different tests — not all mental tests recruit the same biological systems, nor are they equally reliable. Jensen[40] proposed (appealing to his correlated vectors logic) that the more a mental test score correlates with *g*, the higher its heritability. If true, this favours a biological over a purely statistical explanation of *g*. The construct validity of *g* is debated by its advocates[40,85] and detractors[4,10,86]. Nonetheless, psychometric *g* has been shown to be highly heritable in many studies, even more so than specific cognitive abilities ($h^2 = 0.62$, REF. 87 compare with REF. 88; $h^2 = 0.48$, REF. 89; $h^2 = 0.6$–0.8, REFS 90,91).

The heritability of intelligence also increases with age — as we grow older, our phenotype reflects our genotype more closely. A strictly environmental theory would predict the opposite. Some genes are not activated until adolescence or adulthood, but a more plausible explanation of age-related changes in heritability might be gene–environment correlations[92,93] (BOX 2). As individuals select or create environments that foster their genetic propensities throughout life, genetic differences in cognition are greatly amplified[94]. Similar gene–environment effects might help explain the paradox of high heritability but strong effects of environment on the intelligence of children[72,95].

Box 2 | Gene–environment interactions



Because genetic and environmental effects on intelligence are not always independent of each other, understanding the specific causal pathways of gene action is vital when evaluating any genetic account of mental ability. Gene effects might be direct; they might depend on the environment (gene–environment (GE) interaction); and they might act indirectly through correlated environments (GE correlation). About half of the population variance in intelligence is attributed to genetic differences, yet the environment also influences intelligence. Dutch 18-year-old men tested in 1982 scored 20 IQ points (SD=15) higher than 18-year-old men tested in 1952 (REF. 145), a widely replicated population-level increase in intelligence known as the 'Flynn effect'.

Large environmental influences on IQ can be reconciled with high heritability estimates if individuals' environments become increasingly matched to their genotypic preferences[95] (GE correlation). Gifted individuals might create or evoke situations that further enhance their intellectual ability (active and reactive GE correlation, respectively[146]). If environments are not randomly assigned to each individual but are, in part, individually selected on the basis of genetically influenced preferences (GE autocorrelation), it becomes impossible to discern which genetic effects act directly on intellectual function and which result from the action of environmental variation that is causally linked to genetic differences (compare REFS 147,148). One form of GE correlation can be estimated explicitly in adoption designs — the environment that parents provide to their offspring. Active and reactive correlations are more difficult to estimate, leading to suggestions that the notion of heritability conflicts with common sense[149].

Heritability does not imply inevitability, because environment can determine the relative impact of genetic variation (GE interaction). For example, phenylketonuria — a genetic cause of mental retardation — is 100% heritable, yet affected individuals can avoid its consequences by eliminating phenylalanine from their diet.

Finally, heritability within a group does not imply that group differences are due to genetic factors. Environmental factors could completely explain group differences, even in a case where genetic factors completely explain within-group differences. Lewontin's metaphor[150] illustrates this point. As shown in the figure (reproduced, with permission, from REF. 147 © (1995) Elsevier), plants grown under uniformly normal conditions exhibit genetically determined variation in height from plant to plant. The same species grown under uniformly deficient conditions also shows completely genetic control of height. Yet the second group is shorter than the first — a group difference entirely caused by the deficient environment, despite complete heritability. This example emphasizes that any account of group differences in intelligence cannot use within-group heritability to explain between-group differences.

A common misinterpretation of the heritability findings is that, if genetic factors contribute to individual differences in intelligence, then there is no point trying to educate or be educated[96]. It is important to remember that many environmental factors affect intelligence either favourably or adversely[97,98]. Prenatal environment affects intelligence, and premature birth can impair it. In a meta-analysis of 212 studies of intelligence, Devlin *et al.*[89] showed that although heritability was high (around 48%), fetal environment accounted for 20% of the correlation of intelligence between identical twins and for 5% of the correlation between non-twin siblings that shared the same womb consecutively. Maternal drug or alcohol use, or exposure to environmental toxins such as lead, can also adversely affect the achieved intelligence of offspring (see studies cited in REF. 89). The duration of breastfeeding during infancy has been associated with higher IQ in a group of more than 2,000 children assessed at age six[99]. However, this association has been disputed, as it is confounded by maternal age, intelligence and education, as well as by smoking during pregnancy. After adjusting for these confounding factors, breastfeeding during infancy is still associated with enhanced childhood cognitive development (by 2–5 IQ points for full-term infants and 8 points for those of low birth weight)[100].

After birth, the environment in which a child is raised also affects their intellectual function. Bouchard *et al.*[83] found that growing up in the same family increased IQ similarities for all types of relatives. Individual's IQs were more highly correlated with those of their monozygotic twins, non-twin siblings and parents (0.86, 0.47 and 0.42, respectively) if they grew up with them. The strength of the correlations decreased if individuals were raised separately from these relatives (0.72, 0.24 and 0.22). Adopted children's IQs are also correlated with those of their adoptive siblings (0.34) and adoptive parents (0.19). So 20–35% of the observed population differences in IQ are thought to be due to differences between family environments. Intriguingly, the influence of shared family environments on IQ dissipates once children leave home — between adult adoptive relatives, there is a correlation of IQ of –0.01 (REF. 101). Environmental influences on IQ that persist are thought to be those experiences that an individual does not share with others. Interpreted broadly, these include the biochemical environment in the womb, and the multitude of random events in human life that are difficult to quantify or control.

In a recent study of 320 pairs of twins born in the 1960s and given IQ tests at age seven, Turkheimer *et al.*[102] found that environmental factors have a much greater influence on childhood IQ in impoverished families relative to those in families of higher socioeconomic status. The heritability of IQ at the low end of the wealth spectrum was just 0.10. By contrast, it was 0.72 for more wealthy families, indicating that nature is more significant than nurture when socioeconomic status is high, while the reverse is true when socioeconomic status is low. That the genetic contribution to intelligence differs in different environments is a caveat against general inferences based on heritability data.

Genes that affect intelligence. Assuming that intelligence is heritable, specific sources of genetic variation must contribute to it. Identifying these genes might clarify the neurophysiology of intelligence — key genes that have a role in neural development and metabolism might also influence intelligence. All heritable behavioural traits arise from variations in DNA known as genetic polymorphisms. Passed from parents to offspring, these

polymorphisms can alter molecular function and ultimately behaviour. If the genomes of two randomly selected individuals were aligned, 0.1–0.2% of the nucleotides would differ. About 85% of these sequence variations are single nucleotide polymorphisms (SNPs) — at least 1% of the entire human population has a different base at these positions[103]. SNPs occur once in about every 350–1,000 base pairs in the genome. About half of these SNPs (~200,000) occur in protein-coding or regulatory regions, and probably account for almost all human heritable variation. By altering a protein's amino-acid sequence or expression pattern, these functional SNPs modify behavioural traits, disease susceptibility and response to treatment.

There is a concerted effort to associate intellectual function in healthy individuals with polymorphisms of specific genes expressed in the brain. For example, Chorney *et al.*[104] discovered an allelic variation in a gene on chromosome 6, which codes for an insulin-like growth factor-2 receptor (IGF2R), that was linked with high intelligence, although subsequent efforts to replicate the finding were not positive. Two initial case/control studies compared groups of children with IQs over 160, around 135 and around 100 (average IQ). One form of the gene was twice as common in the high-IQ group (32% versus 16% in the average-IQ group). In a follow-up study[105], the 'high-IQ' variant of IGF2R was found in only 19% of high-IQ children and in 24% of those with an average IQ. Later studies identified a second IQ-related polymorphism in the *IGF2R* gene, and others in the cathepsin D (*CTSD*) gene, in the gene for an acetylcholine receptor (*CHRM2*)[106], and in a HOMEOBOX GENE (*MSX1*) that is important in brain development[107,108]. The influence of each polymorphism was minimal — variants of CHRM2 accounted for a range of only 3–4 IQ points, whereas different forms of CTSD accounted for about 3% of the variation between people. None of these associations has yet been replicated by other research groups.

This type of study can screen the entire genome for QUANTITATIVE TRAIT LOCI by linkage disequilibrium, followed by individual genotyping at promising markers[109]. Another approach is individual genotyping of thousands of SNPs using microarrays[110]. The identification of relevant genes is difficult because all known behavioural traits are POLYGENIC. Molecular and computational models are required to disentangle these interactions. Data mining algorithms, based on machine learning and self-organizing maps[111], are breaking new ground in this field and could potentially detect associations between genotype and intellectual function.

Genes, brains and behaviour. The quest to validate molecular- and systems-level models of intellectual function will be made easier if intermediate phenotypes (ENDOPHENOTYPES) — physical or physiological differences that correlate with intelligence — are found. Functional and structural brain mapping provide several such correlates. Genetic, demographic and interventional effects on these endophenotypes can be investigated in large populations (for example, $n = 7{,}000$, REF. 112). Genes influence several identifiable aspects of brain morphometry[32,34,113–118] (reviewed in REF. 119), so many genetic loci that modulate brain structure will probably be identified. Bond *et al.*[120] found that the size of the abnormal spindle (*asp*) gene product parallels brain size across several species. In both cortical development and evolution, this gene determines whether the daughters of a mitotic cell stop dividing and become neurons or continue dividing to form a larger brain. Some patients with microcephaly also possess the *ASPM* mutation, indicating that a shortened version of the gene might lead to the development of fewer cerebral neurons and a smaller head. The notion that mitotic spindle activity regulates brain size is an intriguing one, and *asp* is one of many interesting genes bearing on the evolutionary and developmental increase in brain size and mental ability.

Gene polymorphisms also influence aspects of brain function that are potentially relevant to intelligence. Polymorphism in the human brain-derived neurotrophic factor (*BDNF*) gene is associated with impaired performance on memory tests[121], and the catechol-O-methyltransferase (*COMT*) gene influences the activation of working memory circuits[122]. COMT polymorphisms seem to be highly specific to some prefrontal cortex-dependent tasks in children[123]. Dopamine receptor (DRD4) and monoamine oxidase A (MAOA) polymorphisms are associated with differences in performance and brain activity during tasks that involve executive attention[124]. Computational modelling studies[72] indicate that individual differences in neural plasticity could explain many psychometric findings, so gene polymorphisms related to plasticity are worth seeking.

Beyond the data: the good, the bad and the ugly

In our view — which is shared by most investigators — the data unambiguously indicate a neurobiological basis for intelligence, particularly for reasoning and novel problem-solving ability (which strongly predicts psychometric *g*). Neuroimaging and neuroanatomical data are consistent with sophisticated behavioural studies of intelligence and specific aspects of working memory. From this vantage point, the formulation of detailed neurobiological models of intelligence is inevitable.

The field is at an exciting juncture because nuanced conceptual and empirical approaches are now available, and intelligence is important for both practical[15,125,126] and theoretical[20,36,127] reasons. Biological models of intelligence will help elucidate the structure of intelligence (unitary/multiple) and the processes and mechanisms that underlie intelligent behaviour. These mechanisms might indicate avenues for enhancing intelligence, where society deems this to be useful[96]. As genetic variations that contribute to differences in intelligence become better understood, there might be greater potential to identify, eliminate or enhance many gene–environment interactions to positively manipulate intelligence. We have highlighted the successes and the neurobiology, but a great deal remains to be discovered both within and between levels of analysis. Neurobiological and genetic measures have much to contribute to the study of human abilities, but psychometric and social psychological research is equally indispensable.

HOMEOBOX GENE
A key regulator of embryonic development, highly conserved across species, which controls cell and organ differentiation. Homeobox genes can activate many other genes, producing entire body segments.

QUANTITATIVE TRAIT LOCUS (QTL). A genetic polymorphism that affects the expression of a continuously distributed phenotype. Typically, QTLs are statistically associated with trait variations that depend on multiple interacting loci.

POLYGENIC
A complex trait is polygenic if it is determined by multiple genes that each have small effects and that can interact with each other to produce effects.

ENDOPHENOTYPES
Gene products (phenotypes) that are not visible.

The empirical successes also raise ethical issues[128–130] that the science does not — and in principle cannot[8,9,128] — resolve. The ethics of how knowledge is applied are very important, and have been discussed in detail elsewhere[128–131]. For example, there are evolving standards concerning privacy and concerns about equitable access to methods for enhancing intelligence. Public scientific literacy is vital for informed discussion of policy options. Intelligence research is relevant to social policy (and so scientific literacy is crucial), but the data in no way force any particular policy. Even so, scientific literacy alone is unlikely to resolve all of the ethical concerns regarding intelligence research.

We consider in detail a practical concern about a highly polarized research topic. Is it ever ethical to assess population-group (racial or ethnic) differences in intelligence (for example, recent projects described in REF. 5)? It is easier to set aside such difficult and distasteful questions. In reviewing the neurobiological bases of intelligence it is not necessary, on scientific grounds, to consider race. Most of the variance in intelligence is within racial groups not between them[9], and the causes of individual differences are relatively tractable with available methods, whereas the causes of racial differences are not. Although the topic of race differences is only a minor area within the field of intelligence research, it has had a disproportionately large (and strongly negative) impact on the public perception of intelligence research[5,132,133]. Science is generally perceived as a noble and honourable pursuit, yet "The field of intelligence itself is widely suspect"[132]. Given the history of misuse of intelligence research[7,10], a statement about biology and intelligence that ignores the question of race can be mistaken as being complicit with a racist agenda. To a non-specialist, the field of intelligence research has become stereotyped as elitist and socially divisive. We disavow — and hope to weaken — these unfortunate and unnecessary associations.

Further, we offer the opinion that research on race and intelligence is unethical if it lacks the consent of the target group. Intelligence and race are rarely addressed in neuroethics, which has emphasized individual-level issues (but see REFS 5,96,128; for a discussion of the term 'race', see REF. 134). The issue of race is not unique to biological investigations of intelligence, but it is more visceral in a biological context (in part because heritability can be misunderstood to imply both that group differences must be genetic and that intelligence is a fixed rather than a context-sensitive ability — both of these interpretations are incorrect). Many scientists find the question of group differences in intelligence to be distasteful to contemplate, let alone investigate — we are among them. But it is probably more harmful to simply censor all such work because this would set a terrible precedent of allowing an extrascientific agenda to constrain objective inquiry[3,5,128]. The existence of knowledge is not an ethical problem in itself. Freedom of inquiry is rightly defended on the basis that scientific knowledge is inherently neither good nor bad[5,8,128]. At the same time, it is also firmly established that ethical safeguards must constrain the conduct of science.

Informed consent is a bedrock principle of research with human participants. In the arena of potential race differences, however, the imperative to investigate seems to have been placed above the imperative to obtain consent. For example, some have argued that it is unethical not to investigate the world as we find it, including the possibility of group differences in intelligence, with no apparent consideration of consent[5,133,135]. Yet one person's feeling of an obligation to explore leads to the identity and psychic space of a great many people being rudely probed without consent or recourse.

In light of such unresolved ethical issues, many neuroscientists have been reluctant to investigate individual or group differences in intelligence. Few scientists investigate race differences in intelligence; those who do are overwhelmingly white. Under the *status quo*, target groups will continue to feel alienated and attacked, unimpressed by the need for freedom of inquiry when other important freedoms are lacking. The credibility of intelligence research is suffering. The quality of the science will be affected in turn if there is a (mistaken) perception that most scientists who study intelligence are tacitly racist or tolerate racism among their colleagues[5].

The key dilemma is how to preserve freedom of scientific inquiry while upholding the highest standards of ethical conduct; neither can be compromised. We are not seeking to stimulate research on potential race differences in intelligence. Nor can we advocate censorship. In healthcare, patients are given the final say over testing and treatment to be performed for their own benefit[128]. Can such principles of informed consent and self-determination be generalized to a group level? Probably not perfectly, yet there are doubtless advantages to be gained from making the effort. In our view, a study of race differences in intelligence that does not meet the following criteria is ethically dubious. We consider the following to be points for discussion, not prohibitions: (i) all participants contributing to any group comparisons should be fully debriefed about the study's aims and predictions, and given a chance to withdraw from the study and have their data destroyed (or excluded from racial comparisons in datasets in the public domain or other databases); (ii) target groups should actively support the study, including financially. If the experimental aims are dubious, such support would be difficult to secure. Appropriate representatives should endorse the design, conduct, interpretation and dissemination of the study and its results. An advisory group could include experts in the science and ethics, as well as advocates for the interests of the target group; (iii) the procedures must eliminate all known confounds, including asking participants to indicate their race before they take a test. This simple act induces stereotype threat[2,136], which impairs test performance by diverting working memory resources[137] — threat-related emotion (anxiety) can modulate the activity of the lateral prefrontal cortex[138,139]; (iv) groups should be matched using pair-wise matched controls (including matching for age, parental education, health and nutritional history, and familiarity and fluency with testing procedures).

Appropriate sampling of the true populations must be ensured. Samples must be large enough to allow inferences to the population — samples of convenience should not be used; (v) descriptions of the results should use non-inflammatory language; for example, in terms of percentage of the variance explained[135]. There is much more variation within groups than between them, which should be emphasized[9]. It should be noted that the findings are necessarily correlational and potentially confounded by environmental effects (see the figure in BOX 2).

Such standards are difficult to achieve, but are worthwhile to pursue. If there is an inclusive consensus that each specific study has a legitimate motivation (scientific inquiry), then the process remains both inherently open and protected from being hijacked by extrascientific agendas.

Another way to preserve freedom of inquiry and reduce the potential for mischief (or worse) might be to require any studies of race and intelligence to be conducted by adversarial collaboration[140]. This framework offers important advantages over exchanges in the peer-reviewed literature, because investigators on both sides agree beforehand on the precise research question and the methods for testing it. They then commit themselves before data is gathered to specific interpretations of the possible outcomes, and a neutral third party conducts the work. However, adversarial collaboration speaks less directly to the issues of consent and self-determination.

Conclusions

Research on human intelligence has recently advanced at multiple levels of analysis — social, cognitive, psychometric, neural and genetic. By bridging these levels[52,53] and including measures from *in vivo* brain imaging and genetics, the field is now taking early steps towards a credible mechanistic understanding of individual variation. Intelligence research has implications for conceptions of human nature, so all ethical issues must be addressed proactively. Concerted efforts to encourage the highest standards for conducting research can only help to bolster public confidence in the legitimacy and value of research on human mental abilities.

Note added in proof

Three germane articles came to our attention too late to be discussed in the text (REFS 152–154).

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3. Pinker, S. *The Blank Slate* (Viking, New York, 2002).
A strong critique of the standard social science position that individual differences result only from differing environment (the 'blank slate' view of human nature). It emphasizes that such a view is not merely incorrect but also dangerous.
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Competing interests statement

The authors declare that they have no competing financial interests.

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