Genes, brain and cognition

Robert Plomin and Stephen M. Kosslyn

By making maps of the differences in cortical gray matter volume between twins, Thompson *et al.* describe which brain regions are strongly determined by genetic factors; they further investigate how these brain differences correlate with measures of cognitive performance.

The 1990s were declared the "Decade of the Brain" for good reason, but the present decade might yield even more fundamental discoveries as neuroscience begins to capitalize on developments in genetics. The report by Thompson *et al.*[1] in this issue represents an important step forward because it bridges these two fields. The authors used magnetic resonance imaging (MRI) to create three-dimensional maps of gray matter and then computed correlations between these measures and general cognitive ability ('*g*'), derived from diverse cognitive tests for 40 individuals. What makes this study special is that the subjects were twins—10 pairs of monozygotic (MZ or identical) twins and 10 pairs of dizygotic (DZ or fraternal) twins—allowing the authors to estimate the genetic contribution to individual differences in gray matter volume in various brain regions.

The new study[1] focuses on the influence of naturally occurring genetic variation on normal interindividual variation, that is, the standard deviation found for nearly any characteristic assessed sensitively enough. Heredity is not only about passing species-general characteristics from parent to offspring, but also about transmitting variation in such characteristics (**Fig. 1**). Indeed, inheritance of variation is the mainspring of evolution, and thus a central focus of genetics. In contrast, most neuroscience research focuses on universal characteristics. Although perspectives are not right or wrong, just more or less useful for particular purposes, the species-universals perspective and the individual-differences perspective can arrive at different answers because they ask different questions.

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This distinction is in essence the difference between means and variance, which have no necessary connection, either descriptively or etiologically. Despite its name, the analysis of variance (the most widely used statistical test in science) is actually an analysis of mean effects, with individual differences included in the 'error term'. Most species-universal research is experimental in the sense that it manipulates an independent variable—such as genes, lesions, drugs or tasks—and asks whether the manipulation can have an effect. Individual differences research, in contrast, is correlational in the sense that it investigates factors that do have an effect in the world outside the laboratory.

Not all genetic research informs us about the basis for naturally occurring differences within a species. For example, although knocking out a gene can have major effects, such experiments do not imply that the gene has anything to do with the variation responsible for hereditary transmission of individual differences within a species. In contrast, quantitative genetic methods such as the twin method used by Thompson *et al.*[1] are rooted in the study of naturally occurring variation. Although 99.9% of the human DNA sequence is identical for all people, the 0.1% that differs—3 million base pairs—is ultimately responsible for the ubiquitous hereditary differences found for nearly all complex dimensions and disorders, including cognitive abilities and disabilities[2].

As the new study[1] demonstrates, valuable information can be gained by examining individual differences instead of averaging across groups and treating the differences as error. Indeed, such studies can provide a crucial bridge between neuroscience and genetics, leading to new insights not only about how genes affect cognition but also about how the brain works[3]. A full understanding of the relationships among genes, brain and cognition needs to encompass events at both levels of analysis (**Fig. 1**) and discover the links between them.

One exciting finding from the Thompson *et al.* study[1] is the high heritability for gray matter volume in several cortical regions. The remarkably high correlations (about 0.95) for MZ twins mean that MZ co-twins are virtually identical in their volume of gray matter. The same measures for DZ twins, who like any brother and sister are only 50% similar genetically, are much less correlated. Although previous twin studies reported high heritability for brain region volumes assessed by MRI (reviewed in ref. 4), the present study[1] goes beyond mere size to the more specific measure of gray matter volume, thus ruling out differences in white matter volume. Gray matter consists of neural cell bodies, whereas white matter consists of axons. Connections among neurons reflect, at least in part, the results of learning—which might be expected to differ among individuals as a result of experience. In contrast, the new findings[1] suggest that density of neurons may not be easily modified by experience.

Studies of individual differences have much greater demands for statistical power than studies of mean differences. Statistical power refers to the likelihood of detecting a true difference (more accurately, of rejecting the null hypothesis). A rule of thumb is to consider the power required to detect a true result of a specified effect size 80% of the time (in other words, in four of five studies). Ten pairs of MZ twins, as used by Thompson *et al.*, confers 80% power to detect a correlation only if the correlation is greater than 0.70 (one-tailed test, $p < 0.05$). If correlations for gray matter density are as high as 0.95 for MZ twins, as suggested by this study (and in studies of brain volume as well[5]), they can be detected reliably with just 10 twin pairs. However, MZ twins could be similar not simply because they have identical genes, but also because they were raised (and continue to live) in similar environments. To remove the coarsest contributions of common environment, heritability estimates are based on the difference in correlations for MZ and DZ twins. The essence of any esti-

mate of heritability is to subtract the correlation for DZ twins from that for MZ twins and double the difference.

Trying to detect such a difference in correlations more than doubles the demands for statistical power. For example, even if heritability is 0.90 based on an MZ correlation of 0.90 and a DZ correlation of 0.45, power is less than 40% to detect the heritability with 10 pairs of each type of twin. This means that a true heritability of 90% would not be detected as significant more than half the time. For more typical heritabilities of 0.50 (such as MZ and DZ correlations of 0.75 and 0.50, respectively), 80 pairs of each type of twin are needed to achieve 80% power. Comparing heritabilities—for example, asking whether heritability differs for brain regions—again raises the ante substantially. The Thompson *et al.* sample of 40 twin individuals is large for a neuroimaging study; studying many hundreds of individuals is daunting and may require multi-site collaborative efforts.

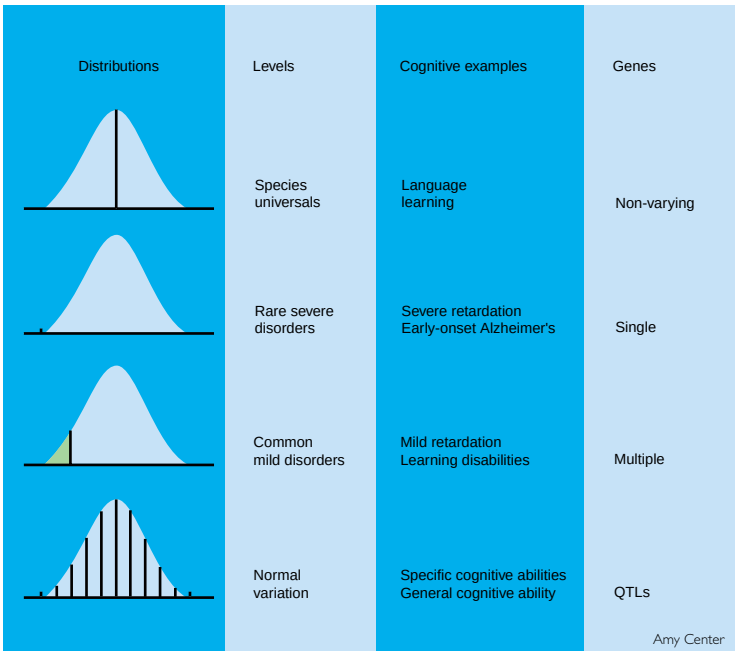

Fig. 1. Levels of analysis from species to individual differences. Interposed between these extremes are rare severe disorders, often caused by a single gene necessary and sufficient for the disorder, and common mild disorders, called 'complex disorders' because they are influenced by multiple genes and environmental factors. Many researchers now believe that common mild disorders are often merely the quantitative extreme of the same factors that create normal variation. In other words, there may be no common disorders, just dimensions of normal variation. Genes in such multiple-gene (polygenic) systems are called quantitative trait loci (QTLs) because they are likely to result in dimensions (quantitative continua) rather than disorders (qualitative dichotomies)[15].

The second important feature of the new study[1] is that it shows an association between individual differences in gray matter volume in the frontal cortex and '*g*' or general cognitive ability. The concept of '*g*' is controversial; not all researchers are comfortable with the idea that a single factor may influence all types of intelligence[6]. Although '*g*' is not the whole story of cognitive abilities—group factors representing specific abilities are also important level of analysis—trying to tell the story without '*g*' loses the plot entirely. The Thompson *et al.* results suggest that '*g*' is not simply a statistical abstraction that emerges from factor analyses of psychometric tests; it also has a biological substrate in the brain. Dozens of studies, including more than 8,000 parent–offspring pairs, 25,000 pairs of siblings, 10,000 twin pairs and hundreds of adoptive families, all converge on the conclusion that genetic factors contribute substantially to '*g*'[7]. Moreover, multivariate genetic analysis, which investigates the extent of genetic basis for associations between variables, shows that most of the genetic action on diverse cognitive abilities involves '*g*'[8]. A key issue for neuroscience is to understand the brain mechanisms that mediate this genetic effect.

Studies of total brain volume anticipated the interesting finding by Thompson *et al.* of an association between gray matter volume and '*g*'. In 14 studies of about 700 individuals, correlations between brain volume and '*g*' are about 0.40 (ref. 4), indicating that individuals with larger brain volumes have higher 'g' scores. These correlations are similar in magnitude to the correlations found for frontal gray matter volume in the new study[1]. However, Thompson *et al.* underestimate the extent to which gray matter volume in each brain region correlates with '*g*'. They report partial regressions or correlations that indicate the association between each brain region and '*g*' independent of other brain regions. Such analysis will miss associations with '*g*' to the extent that gray matter volumes in different brain regions are intercorrelated, as is likely. For example, an MRI study of total volume of 13 brain regions found that the brain regions intercorrelated substantially and that a general factor (first unrotated principal component in a factor analysis) accounted for 48% of the variance[5]. Thus the simple correlations between gray matter volume in different brain regions and '*g*' should be considerably higher than suggested by Thompson *et al.* Moreover, simple correlations would probably show that all brain regions correlate with '*g*', not just the frontal region. Further analyses of these data could also examine whether gray matter density correlates positively with different cognitive abilities, not just with a composite '*g*' score. That is, the correlation between gray matter volume and the '*g*' composite could be due to certain abilities (such as verbal abilities) correlating highly and other abilities (such as spatial abilities) correlating less well. In contrast, the hypothesis of 'genetic *g*'—that the same genetic factors affect diverse cognitive abilities—leads to the prediction that gray matter volume should correlate not just with a '*g*' composite but with all cognitive abilities.

The old workhorse of the twin design (comparing MZ and DZ twins) can be used to ask questions that go beyond estimating heritability. For example, the twin design can trace the developmental course of genetic and environmental influences. One of the most fascinating findings about '*g*' is that its heritability increases almost linearly from infancy (about 20%) to childhood (about 40%) to adulthood and old age (about 60%)[9]. Does the heritability of gray matter follow a similar developmental course?

In addition, a multivariate genetic analysis suggests that the association between total brain volume and intelligence is substantially mediated genetically[5]. Although the extent to which correlations between brain and cognition are genetic must be assessed rather than

assumed, given the high heritability of gray matter volume in the new paper[1], it seems likely that its association with '*g*' is also mediated genetically rather than environmentally. Multivariate analysis can also help with the next step: discovering what underlies this association and what other aspects of brain anatomy and physiology give rise to individual differences in '*g*'. For example, could differences in the number of specific types of receptors or the density of neuromodulatory pathways be responsible for the observed correlations with intelligence? Magnetic resonance spectroscopy provides measures of metabolic byproducts that can serve as markers for some of these variables.

Although it is possible that a single fundamental brain characteristics such as frontal gray matter volume is responsible for *g*, it seems more likely that many brain processes are involved. However, so far, the pickings are slim other than brain volume measures. For example, although EEG alpha peak frequency[10], EEG coherence (which has been taken as a measure of brain interconnectivity[11]) and peripheral nerve conduction velocity[12] are all highly heritable, these measures do not relate to '*g*'[13]. Thus, '*g*' does not seem to involve speedier brains, at least as assessed by these physiological measures. Although event-related brain potential (ERP) measures yield widely varying heritability estimates across cortical sites, measurement conditions and age, some researchers have reported that ERP (especially the P-300 component) is related to '*g*'[14]. Other researchers have reported correlations between '*g*' and brain functioning as assessed by positron emission tomography, single photon emission tomography and functional MRI[13], but we are not aware of genetic studies using these techniques.

Finding high heritability for '*g*'-related brain measures paves the way for molecular genetic studies to harvest the fruits of the Human Genome Project. Armed with such information, we are poised to identify the specific DNA variation responsible for high heritability. However, identifying specific genes associated with complex traits has proven more challenging than expected, largely because many genes are probably involved, each with small effects[7]. Nevertheless, finding specific genetic variation is a high priority for research because it will provide a very sharp scalpel for dissecting pathways relating genes, brain and cognition.

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Spreading synapsins

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Fluorescent synapsins were used to study the dissociation–reassociation cycle of this synaptic vesicle protein *in situ*, and how this process relates to regulation of exocytosis.

Three decades ago, Greengard and colleagues identified an abundant brain protein that is a substrate for the cAMP-dependent protein kinase[1]. In the ensuing years, this family of proteins, called synapsins, has been investigated intensely. Somewhat surprisingly, their precise role in synaptic transmission is still unclear. Now, Chi and colleagues[2] elegantly combine fluorescence microscopy with molecular biology to provide new insight into the involvement of synapsins in neurotransmitter release.

Synapsins are abundant at nerve terminals and are highly conserved, and their biochemical properties are regulated by activity. For this reason, investigators have anticipated that synapsins are critical in synaptic transmission. Synapsins have been implicated in a variety of functions—synaptic vesicle clustering, mobilization and even exocytosis—based on their dynamic affinity for synaptic vesicles[3–6]. Mice with two of the three synapsin genes knocked out are viable, but have abnormal synaptic transmission[4]. Although it remains to be seen whether removing all three synapsin genes has a more profound effect on survival, knockout mice alone may not reveal subtle regulatory roles; mechanistic studies are important in this regard.

Previous experiments using biochemical methods have suggested the following sequence of events. At rest, synapsins are associated with synaptic vesicles and, perhaps, with any actin filaments that may be present in presynaptic sites[1]. Synapsins do not have a membrane-spanning sequence; therefore, their observed association with synaptic vesicles must arise from binding to vesicle components. Synapsins also form homo- and heterodimers, which may assist in crosslinking neighboring vesicles. During action potential stimulation, synapsins dissociate from vesicles and disperse into the cytosol[7–9]. Synapsin dissociation from vesicles, controlled by phosphorylation, frees the vesicles to move toward the active zone to replenish spent vesicles. Upon termination of stimulation, synapsins are dephospho-

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