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Quantitative genetics in the era of molecular genetics: Learning abilities and disabilities as an example

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Abstract

Objective—To consider recent findings from quantitative genetic research in the context of molecular genetic research, especially genome-wide association studies. We focus on findings that go beyond merely estimating heritability. We use learning abilities and disabilities as examples.

Method—Recent twin research in the area of learning abilities and disabilities was reviewed.

Results—Three findings from quantitative genetic research stand out for their far-reaching implications for child and adolescent psychiatry. First, common disorders such as learning difficulties are the quantitative extreme of the same genetic factors responsible for genetic influence throughout the normal distribution (the Common Disorders are Quantitative Traits Hypothesis). Second, the same set of genes is largely responsible for genetic influence across diverse learning and cognitive abilities and disabilities (the Generalist Genes Hypothesis). Third, experiences are just as influenced genetically as are behaviors and genetic factors mediate associations between widely used measures of the environment and behavioural outcomes (the Nature of Nurture Hypothesis).

Conclusions—Quantitative genetics can go far beyond the rudimentary 'how much' question about nature versus nurture, and can continue to provide important findings in the era of molecular genetics.

Keywords

Quantitative genetics; molecular genetics; twin studies; learning abilities; disabilities

Quantitative genetic research--strain and selection studies in nonhuman animals and twin and adoption studies in our species--has demonstrated the ubiquitous importance of genetic influence on behavioral dimensions and disorders[1]. For learning disabilities, MZ and DZ twin concordances are about 85% and 50% respectively for reading; 75% and 45% for language; and 70% and 50% for mathematics[2]. These results indicate substantial genetic influence on learning difficulties, which is greater than for most other common psychiatric

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This article represents one of several articles published in the xxx issue of the Journal of the American Academy of Child and Adolescent Psychiatry that explores the intersection of genetics and mental health disorders in children and adolescents. The editors invite the reader to investigate the additional articles on this burgeoning area of developmental psychopathology.

disorders. Figure 1 compares results for learning difficulties to those for three psychiatric disorders: schizophrenia (MZ=50%; DZ=20%); depression (45%; 30%); and alcoholism (50%; 35%)[1]. For the entire range of learning abilities rather than disabilities, heritability estimates are typically about 50%, meaning that about half of the variance in learning abilities can be attributed to genetic differences3. In terms of public acceptance of these findings, a large UK survey indicated that more than 90% of teachers and parents say that they believe genetics to be at least as important as the environment for learning abilities and disabilities4.

Quantitative genetic methods estimate the cumulative effect of genetic influence regardless of the number of genes involved or the magnitude or complexity of their effects. If we could find the genes responsible for heritability there would be no more need for quantitative genetic designs because genetic influence could be assessed directly from each individual's DNA rather than implied indirectly by genetic relatedness as in twin and adoption studies. However, although genome-wide association (GWA) research has had many successes[5], it seems highly unlikely that most of the genes responsible for the heritability for any complex trait will be identified in the foreseeable future. The reason is that the largest effect sizes found in GWA efforts to date are very small, which means that many such genes of even smaller effect size will be needed to account for heritability6.

The largest effect sizes of replicable associations from GWA studies are odds-ratios of about 1.2 for case-control studies of disorders and less than 1% of the population variance for quantitative traits. These effect sizes are so small that samples in the thousands are needed to identify replicable associations, for example, in case-control studies of schizophrenia[7], type 2 diabetes[8] and obesity[9], and in studies of quantitative traits such as lipids[10] and height[11]. For this reason, it is not surprising that the first GWA study of reading ability that was powered to detect effect sizes of about 1% of the variance was unable to detect reliable associations of this magnitude with a sample of 4000[12]. Similarly, GWA studies of cognitive abilities were unable to detect reliable associations in studies with 700 subjects[13] and 3000 subjects[14]. Significant associations with cognition and memory reported in one GWA study with 350 subjects[15,16] have not been replicated[17].

If the largest effect sizes of replicable associations are so small, hundreds of genes of very small effect size will be needed to account for heritability which is typically about 50%. Moreover, finding the rest of the associations with even smaller effect sizes seems a daunting task--this has been called 'the missing heritability' problem[18]. For this reason, molecular genetics seems unlikely to replace quantitative genetics in the foreseeable future. Nonetheless, we hope that our prediction about GWA research is wrong and that it will be possible to identify most of the missing heritability, which coupled with decreasing genotyping costs, would put quantitative genetics out of business. This hope is not unrealistic in the long term: GWA research only began in 2007 and has only searched the genome for common single-nucleotide polymorphisms (SNPs). Hope for finding the missing heritability springs from the rapid pace of developments in GWA research which includes other types of polymorphisms such as copy-number variants (CNVs), other rare variants, non-coding RNA and the entire genome sequence which will capture variants of any type[19]. Moreover, finding *any* replicable associations between DNA variants and behavior is useful for research purposes as in the case of the *FTO* gene which is associated with body weight and obesity, and is a highly replicated finding across multiple studies[20].

The GWA finding that many genes of small effect size are responsible for heritability should not have been a surprise because quantitative genetic research on complex traits in nonhuman animals using the selection design has for decades provided evidence that many genes of small effect are involved. If only a few genes were responsible for the heritability

of a trait, selected lines would separate after a few generations and would not diverge any further in later generations. In contrast, selection studies of behavioral phenotypes as well as other complex traits show a linear response to selection even after dozens of generations of selection. For example, in one of the largest and longest selection studies of behavior, mice were selected for activity in a brightly lit box called an open field, where lower activity scores are presumed to index fearfulness[21]. As shown in Figure 2, strong evidence of genetic influence can be seen by the successful response to selection. After 30 generations of such selective breeding, a 30-fold average difference in activity was achieved–indeed, there was no overlap between the activity of the low and high lines. Moreover, the difference between the high and low lines steadily increases each generation, indicating that many genes contribute to variation in this behavior.

Our goal is not to denigrate GWA research–indeed, GWA is the focus of much of our own research[12,14,22]. Instead, our goal is to point to the bright future of quantitative genetic research, especially when its potential is exploited to go beyond merely estimating heritabilities. The main point of our paper is that quantitative genetic methods can go far beyond the rudimentary nature-nurture questions about *whether* and *how much* genes influence behavior to investigate *how* genes influence behavior. In this paper, we describe three examples of such quantitative genetic findings in relation to learning abilities and disabilities, before highlighting additional quantitative genetic methodologies that we predict will provide important biological and environmental findings as we enter the era of molecular genetics.

Common disorders are quantitative traits

Quantitative genetic research supports the conclusion that learning disabilities are the quantitative extremes of the genes responsible for the normal distribution of learning abilities3,[23]. DeFries-Fulker (DF) extremes analysis[24] assesses genetic links between the extreme and the normal range by bringing together the dichotomous classification of learning disability and the quantitative trait of learning ability. Rather than assessing twin similarity in terms of concordance for a diagnostic cut-off (i.e. the disorder as *qualitatively* distinct from the normal range of controls), DF extremes analysis assesses twin similarity as the extent to which the mean standardized quantitative trait score of co-twins of the selected extreme probands is similar to the mean standardized score of those probands. This measure of twin similarity is called a group twin correlation (or transformed co-twin mean) in DF extremes analysis because it focuses on the mean quantitative trait score of co-twins rather than individual differences. Doubling the difference between MZ and DZ group twin correlations estimates the genetic contribution to the average phenotypic difference between the probands and the population. The ratio between this genetic estimate and the phenotypic difference between the probands and the population is called *group heritability*, the extent to which the phenotypic difference between the probands and the population can be explained by genetic differences. It should be noted that group heritability does not refer to individual differences among the probands—the question is not why one learning-disabled proband has slightly worse learning difficulties than another, but rather why probands as a group have more learning problems than the rest of the population. Finding group heritability implies that both learning disability and learning ability are heritable and, most importantly, that there are genetic links between learning disability and normal variation in learning ability. If a measure of extremes (or a diagnosis) were not linked genetically to a quantitative trait, group heritability would be zero. Research using this DF extremes method consistently show that group heritabilities are substantial for reading, language, mathematical disabilities as well as general learning disability[2]. These results suggest that common learning difficulties are the quantitative extreme of the same genetic factors responsible for the normal distribution of learning abilities.

This conclusion–that the polygenic distribution underlying behavioral traits, like learning disabilities, is normally distributed–has far-reaching conceptual and practical implications, especially for studies of qualitatively diagnosed common disorders, diseases and disabilities. Although there are a few GWA studies of quantitative traits, most notably height[11], nearly all current GWA studies are based on qualitative diagnoses of cases and controls[5,25]. Fisher showed how quantitative traits can be explained by qualitative Mendelian inheritance if multiple genes are involved[26], but what about the converse–common complex disorders that are diagnosed qualitatively? If, as GWA research indicates, multiple genes affect these disorders, their genetic liability is distributed quantitatively not qualitatively. Thus, there is a disconnect between qualitatively diagnosed disorders that are the focus of GWA studies and their quantitatively distributed polygenic liabilities. The resolution lies in recognizing that common disorders are the extremes of quantitative traits[27]. In other words, what we call common disorders such as learning disabilities are the quantitative extremes of continuous distributions of genetic risk. The obvious test of this hypothesis is that genes found for disorders in case-control studies will be associated, not just with differences between cases and controls, but with individual differences throughout the entire range of variation. For example, genes found to be associated with reading disability in case-control studies are predicted to be associated with reading ability for the entire range of variation, including good readers.

Several implications follow from thinking quantitatively about disorders, especially when some of the many genes are identified that are responsible for their heritability[27]. Independent of genetics, this trend towards thinking quantitatively can already be seen in the area of mental disorders[28,29], although debates about diagnoses versus dimensions span the entire breadth of medicine[30]. The most novel implication of thinking quantitatively is that it leads to thinking positively. Thinking positively suggests that we should investigate mechanisms that push beyond normality; for example, not just fixing poor reading but promoting good reading. In the area of learning disabilities and abilities, quantitative genetic research has begun to address high cognitive abilities[31].

Generalist genes

Quantitative genetic research has shown that the same genes affect different learning abilities and disabilities[2,32,33]. In other words, when genes are found that predict reading disability or ability, the same genes are also highly likely to predict mathematics disability or ability. Because these results suggest that a single set of genes has general effects across diverse learning abilities and disabilities, this is called the Generalist Genes Hypothesis.

These surprising findings derive from multivariate genetic analysis which investigates not only the variance of traits considered one at a time but also the covariance among traits[1,34]. Multivariate genetic analysis estimates the extent to which genetic and environmental factors that affect one trait also affect another trait. It yields a statistic called the *genetic correlation* which indexes the correlation between genetic effects on the two traits independent of the heritabilities of the two traits. That is, the genetic correlation between two traits can be 1.0 even when the heritabilities of the two traits are modest. The genetic correlation can be roughly interpreted as the likelihood that genes found to be associated with one trait will also be associated with the other trait.

In a review of a dozen multivariate genetic studies of learning abilities and difficulties, the average genetic correlation was 0.70 between reading and language, reading and mathematics, and language and mathematics[2]. Similar results emerge from more recent research in middle childhood[35,36] and early adolescence[37]. Figure 3 shows the results of the latest multivariate genetic test of the General Genes Hypothesis[37]. The genetic correlations

among the latent variables range from 0.75 to 0.91. Results similarly supportive of the General Genes Hypothesis have been found using this same dataset for low ability[38] and high ability[39].

The good news is that if the same set of genes is largely associated with most learning disabilities it should be easier to find these genes. However, because the genetic correlations are less than 1.0, genes also contribute to making children better at some abilities than others. That is, when genes are identified that are responsible for genetic influence on reading ability, most of these genes will also be associated with mathematics ability, but some will not[40].

If genetic correlations are so high between learning abilities, it makes sense to expect that components within each learning domain are even more highly correlated genetically, and that is the case. Genetic correlations range between 0.60 and 0.90 within the domains of language, reading, and mathematics[2]. For example, in a recent study, five components of mathematics including computation, interpretation, and non-numerical processes were assessed via the Internet in a study of more than 1000 10-year-old twin pairs[41]. The average genetic correlation between the five components of mathematics was 0.91.

Moreover, the general effects of genes appear to extend beyond specific learning abilities such as reading and mathematics to other cognitive abilities such as verbal abilities (e.g. vocabulary and word fluency) and non-verbal abilities (e.g. spatial and memory). Multivariate genetic research on diverse cognitive abilities consistently finds genetic correlations greater than 0.50 and often near 1.0 across diverse cognitive abilities[42]. Similar results suggesting substantial genetic overlap have been found for more basic information processing measures such as speed of processing as well as measures of brain volume42.

Phenotypic correlations among diverse tests of cognitive abilities led Charles Spearman in 1904 to call this general factor *g* in order to avoid the many connotations of the word intelligence[43]. To what extent do generalist genes for *g* overlap with generalist genes for learning abilities? A review of about a dozen such studies concludes that genetic correlations between *g* and learning abilities are substantial but somewhat lower than the genetic correlations among learning abilities[2]. This result suggests that most (but not all) generalist genes that affect learning abilities are even more general in that they also affect other sorts of cognitive abilities included in the *g* factor.

The Generalist Genes Hypothesis suggests that genetic nosology differs from current diagnoses which are based on symptoms rather than etiology. Because genetic effects are general, they dissolve distinctions between diverse learning difficulties that ostensibly differ so much in terms of the cognitive processes involved. When these generalist genes are identified, they will greatly accelerate research on general mechanisms at all levels of analysis from genes to brain to behavior[44].

Multivariate genetic research also has an interesting story to tell about environmental influences on learning abilities. Genetic research distinguishes two types of environmental influences. Environmental influences that make family members similar are called shared environment. And environmental influences that do not contribute to resemblance among family members are called non-shared environment, which also includes error of measurement. Multivariate genetic analyses indicate that shared environmental influences are generalists: Shared environmental correlations among learning and cognitive abilities are as high as genetic correlations. For example, in two recent studies, the shared environmental correlation was 0.74 between reading and mathematics at 7 years[45] and the average shared environmental correlation was 0.86 between five components of mathematics at 10 years[41]. An obvious hypothesis that has not yet been rigorously tested is that some monolithic factors

such as the socioeconomic status of the family or school quality might be responsible for these generalist shared environmental effects.

In contrast to these generalist effects of shared environment, non-shared environmental effects are specialists: Non-shared environmental correlations are low. For example, in the same two studies, the non-shared environmental correlation was 0.39 between reading and mathematics at 7 years[45] and the average non-shared environmental correlation was 0.24 between five components of mathematics at 10 years[41]. Little is known about specific non-shared environmental influences that are the source of specialist environments largely because most environmental research focuses on shared environmental factors such as family background. Further investigation is needed to identify these specialist non-shared environmental influences which are specific to each trait and each age. This is particularly important, as quantitative genetics has highlighted that non-shared environmental influences are the main source of environmental influences on traits, and that the effect of shared environmental factors is low and decreases with age.

The nature of nurture

The great strength of quantitative genetic methods is that they investigate the net effect of genetic and environmental influences simultaneously which means that quantitative genetic studies are as much studies of the environment controlling for genetic effects as they are genetic studies controlling for environmental effects, as illustrated in the previous section. It is also possible to use quantitative genetic designs to explore the interplay between nature and nurture, especially when measures of the environment are included46,47. Quantitative genetic theory includes two concepts at the genotype-environment (GE) interface-GE interaction and GE correlation-although there are other ways to address the interplay between nature and nurture[48,49]. GE interaction refers to genetic sensitivity to environments in the sense that the effects of the environment can depend on genetics and the effects of genetics can depend on the environment48. In contrast, GE correlation refers to genetic exposure to the environment in that experiences can be correlated with genotype; for this reason GE correlation has been called the *nature of nurture*[50]. In other words, genetic effects on behavior do not stop at the skin; genetic effects need to be considered in relation to an 'extended phenotype' that includes effects on individuals' environments[51,52]. Although GE interaction is currently the focus of much molecular genetic research[53–55], our reading of the quantitative genetic literature suggests that GE correlation is a more widespread phenomenon[47].

Investigating GE correlation in quantitative genetic research involves treating environmental measures as dependent measures to assess the extent to which these measures, which ostensibly assess the environment, in fact show genetic influence. Beginning with the pioneering work of Rowe[56,57], dozens of twin and adoption studies have shown ubiquitous genetic influence on widely used measures of the environment[58]. A recent review of 55 independent genetic studies that included measures of the environment reported an average heritability of 0.27 across 35 different environmental measures, including not just measures of the family environment, such as parenting, but also measures outside the family such as peer groups, classroom environments, and life events[59]. For example, one recent developmental study of 1800 twin pairs interviewed retrospectively about peer group deviance showed heritabilities from 0.40 to 0.50 from childhood to young adulthood[60].

Evidence for the heritability of environmental measures led to the first GWA study of an environmental measure[61], a measure called CHAOS[62] which assesses 'environmental confusion' in the home and which is more strongly associated with cognitive development in childhood than any other proximal measure of the environment[63,64]. Similar to other GWA

studies described earlier, no replicable associations were found, but the point is that heritable variation in environmental measures implies that variation in DNA sequence is ultimately responsible for their heritability. Other molecular genetic studies have begun to focus on GE correlation, rather than just considering GE correlation as a confounding factor in research on GE interaction[65].

Of course, finding genetic influence on environmental measures does not mean that environments are inherited any more than the heritability of reading means that words are inherited. What these findings mean is that genetic factors affect children's experiences, mediated for example by genetic influences on the children's personality. Three types of GE correlation have been described[66,67]. Passive GE correlation occurs because genetically related family members provide an environment correlated with a child's genetic propensities. Evocative GE correlation happens because children evoke reactions from others based on the child's genetic propensities. Active GE correlation involves children's selection, modification and creation of environments correlated with their genetic propensities. A developmental theory of GE correlation proposes that during childhood, the influence of passive GE correlation declines and the importance of the active kind increases as children begin to make their way in the world beyond their families[67].

Genetic influence on experience suggests a new perspective on the environment, as illustrated in Figure 4. The traditional model of the environment makes the reasonable assumption that an environmental measure indexes the environmental contribution to behavior. In contrast, the GE correlation model takes into account the interface with genetics in two ways: (1) an environmental measure can be influenced genetically and (2) the association between an environmental measure and a behavioral phenotype can be mediated genetically. Multivariate genetic analysis, described in the previous section, can be applied to investigate the genetic and environmental etiology of the association between an environmental measure and a behavioral phenotype. The first such multivariate genetic analysis found that the phenotypic correlation of 0.61 between maternal negativity and adolescent antisocial behavior was more than half mediated by genetic factors[46]. Subsequent multivariate genetic studies have reported similar results–for example, between measures of the environment such as parenting, peer deviance, and life events and measures of behavior such as psychopathology, academic achievement and cognitive ability1. A general rule of thumb is that the size of the genetic influence on an environmental measure is a good indication of the extent of the genetic links between that environment and the behavioral outcome measure.

The GE correlation model of the environment predicts not only that DNA variants can be found that are associated with measures of the environment but also that these DNA variants will mediate associations between environmental measures and behavioral measures. This will be the definitive test of the GE correlation model. As is the case with all quantitative genetic research, more precise questions can be asked when we are able to include specific genes in addition to specific measures of the environment. For example, it will be possible to test the extent to which GE correlation arises for passive, evocative or active reasons and to test the hypothesis that genetic effects become less passive and more active during childhood and adolescence. An early study using a composite of SNPs associated with general cognitive ability in a sample of 7000 7-year-old children found GE correlations with preschool proximal measures of the family environment (chaos and discipline) rather than distal measures (maternal education and father's occupational class), suggesting evocative rather than passive GE correlation[68].

The GE correlation model points to a radically different view of the way the environment works. Instead of a child being a passive recipient of environmental events, which is a

holdover from the days of stimulus-response learning theory, the GE correlation model supports an active view of experience in which children make their own environments in part on the basis of their genetic proclivities[58]. That is, children select, modify, construct and even re-construct experiences for genetic reasons, creating correlations between their genotypes and their environments. Where do parents and policy makers fit in this GE correlation model? Sandra Scarr, who has done much of the seminal research in this area, concluded that "Parents' most important job is to provide support and opportunities, not to try to shape children's enduring characteristics. Policy makers' most important role is to help parents provide support and opportunities for their children" [69],p.204.

Future directions for quantitative genetics

As summarized above, quantitative genetic research continues to contribute clinically relevant findings, as well as charting the direction for future molecular genetic research. In addition to the three findings outlined above, there are several other quantitative genetic methodologies that we predict will continue to be informative during, and beyond the era of molecular genetics, and which we highlight here.

The first and most notable contribution that quantitative genetics makes over molecular genetics is that quantitative genetics is as much about the environment, as it is about genetics. Although some molecular genetic studies have begun to include environmental measures[54,55,61,70], the majority of these do so at a candidate gene level and not genome-wide. In addition, just as genetic influences are typically of small effect size, the same is likely true for environmental influences, making environmental influences as difficult to detect as DNA variants. The benefit of quantitative genetics is that we do not need to know specifically what these environmental influences are, just as we do not need to know which specific genes are involved. This means that quantitative genetics can investigate how environmental influences function, even before specific factors are identified, and can also help to chart the direction for future environmental research that focuses on identifying these environmental measures. The ideal situation would be to know what the specific genetic and environmental influences are, and quantitative genetics will be influential in identifying these. Quantitative genetic research has provided some of the best evidence for the role of the environment in complex traits, most notably indicating that environmental influences typically operate on an individual-by-individual basis and not generally on a family-by-family basis[71]. Quantitative genetics also provides a valuable method for identifying specific environmental factors while controlling for genetic influence: the MZ differences design[72]. The MZ differences design can also be extended to investigate longitudinal and multivariate pathways[73].

Molecular genetic research currently focuses on univariate analyses, although some multivariate GWA studies are underway, the methods for multivariate and longitudinal GWA studies are in their infancy, whereas such models for quantitative genetic research have been extensively developed and are widely used[34]. In addition, twin studies are typically cohort studies that have collected a variety of phenotypes during development. In contrast, most GWA studies are focused on one particular disorder, so few can be extended to investigate multivariate and longitudinal research questions. Molecular genetic research in complex traits will really come into its own when we have GWA data on large population-representative cohort studies with multiple phenotypes and environmental data, and once we have determined optimal statistical techniques for analyzing the millions of data points that would come out of such molecular genetic studies. But for the time-being, quantitative genetics provides the only validated method for assessing multivariate and longitudinal etiological questions.

Finally, just as quantitative genetic methodologies can be used to study environmental measures as the dependent variable, they can also be applied to biological data. Recent studies have highlighted the utility of applying the twin design to gene expression, methylation (epigenetics), and copy-number variant data[74,75,76], especially in relation to understanding the genetic and environmental origins of these biological traits77

Conclusion

Genome-wide association studies are struggling to identify a few of the many genes responsible for the ubiquitous heritability of common disorders and complex dimensions such as learning disabilities and abilities because the largest effect sizes are so small. In contrast, we hope that these three examples of findings from quantitative genetics, as well as the future uses of quantitative genetic research highlighted here, illustrate the potential of quantitative genetics to continue to make discoveries with far-reaching ramifications for child and adolescent psychiatry.

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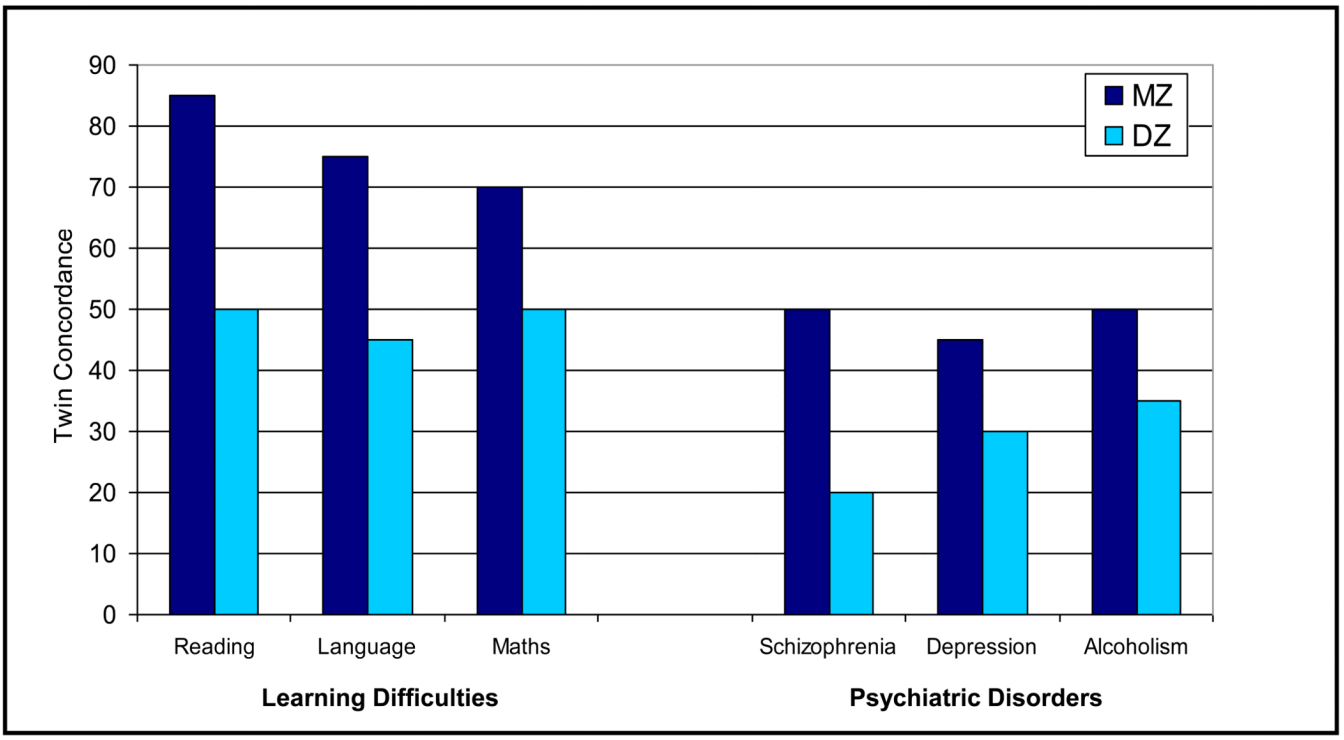

Figure 1.
MZ and DZ twin concordances of learning disabilities and for psychiatric disorders. Data extracted from review by Plomin et al.,[1].
Note: DZ = Dizygotic; MZ = Monozygotic

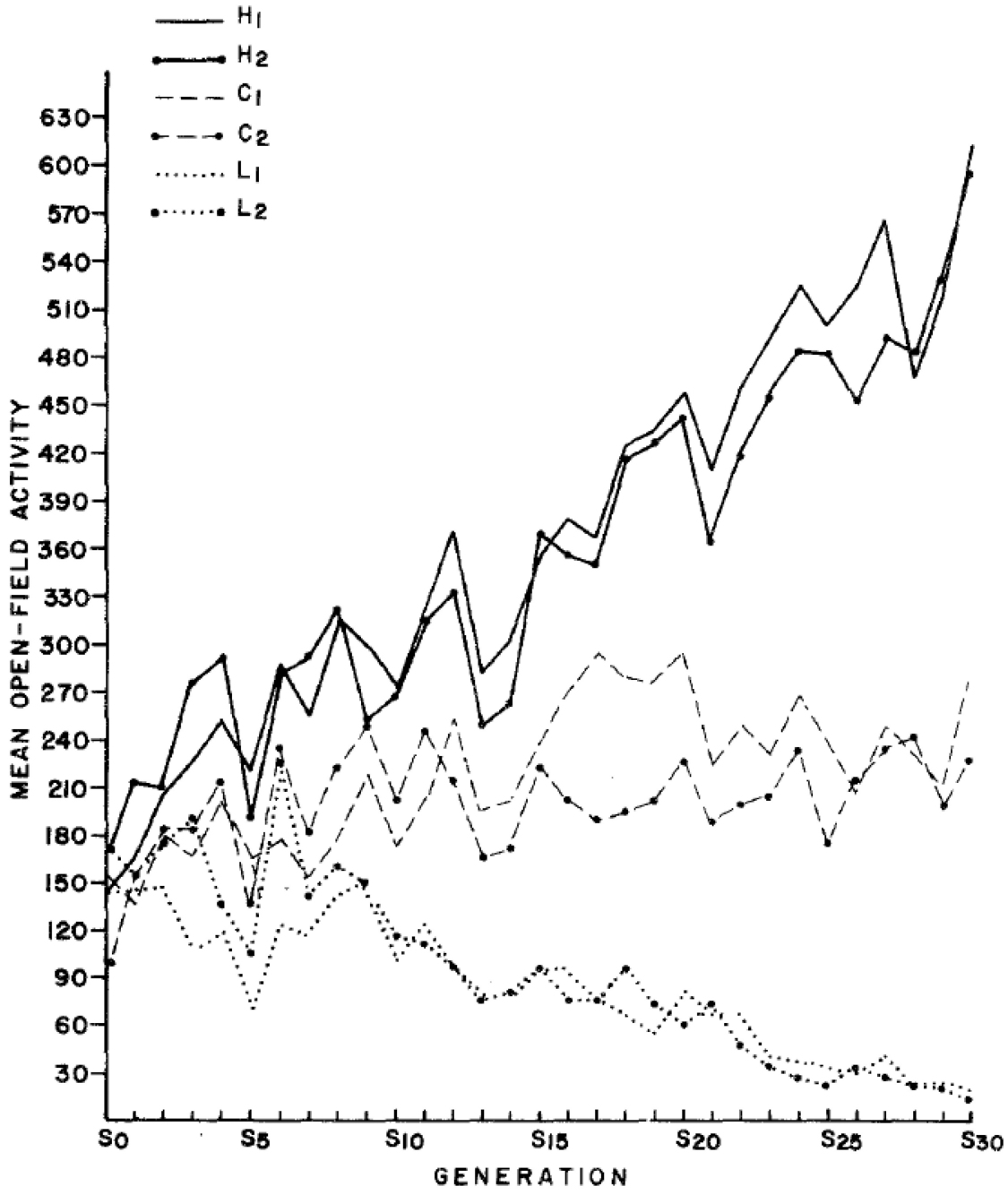

Figure 2.

Results of a selection study of open-field activity. Note: Beginning with an F3 cross between two inbred strains of mice, two lines were selected for high open-field activity (H1 and H2) in which the most active (lease fearful) mice were selected and mated with other high-active mice. Similarly, two lines were selected for low open-field activity (L1 and L2), and two lines were randomly mated within each line to sever as controls (C1 and C2). (With kind permission from Springer Science+Business Media: *Behavior Genetics*, Response to 30 generations of selection for open-field activity in laboratory mice, volume 8, 1978, page 3–13, J. C. DeFries, M. C. Gervais, & E. A. Thomas, figure 2, ©1978 by Plenum Publishing Corporation. All rights reserved.)

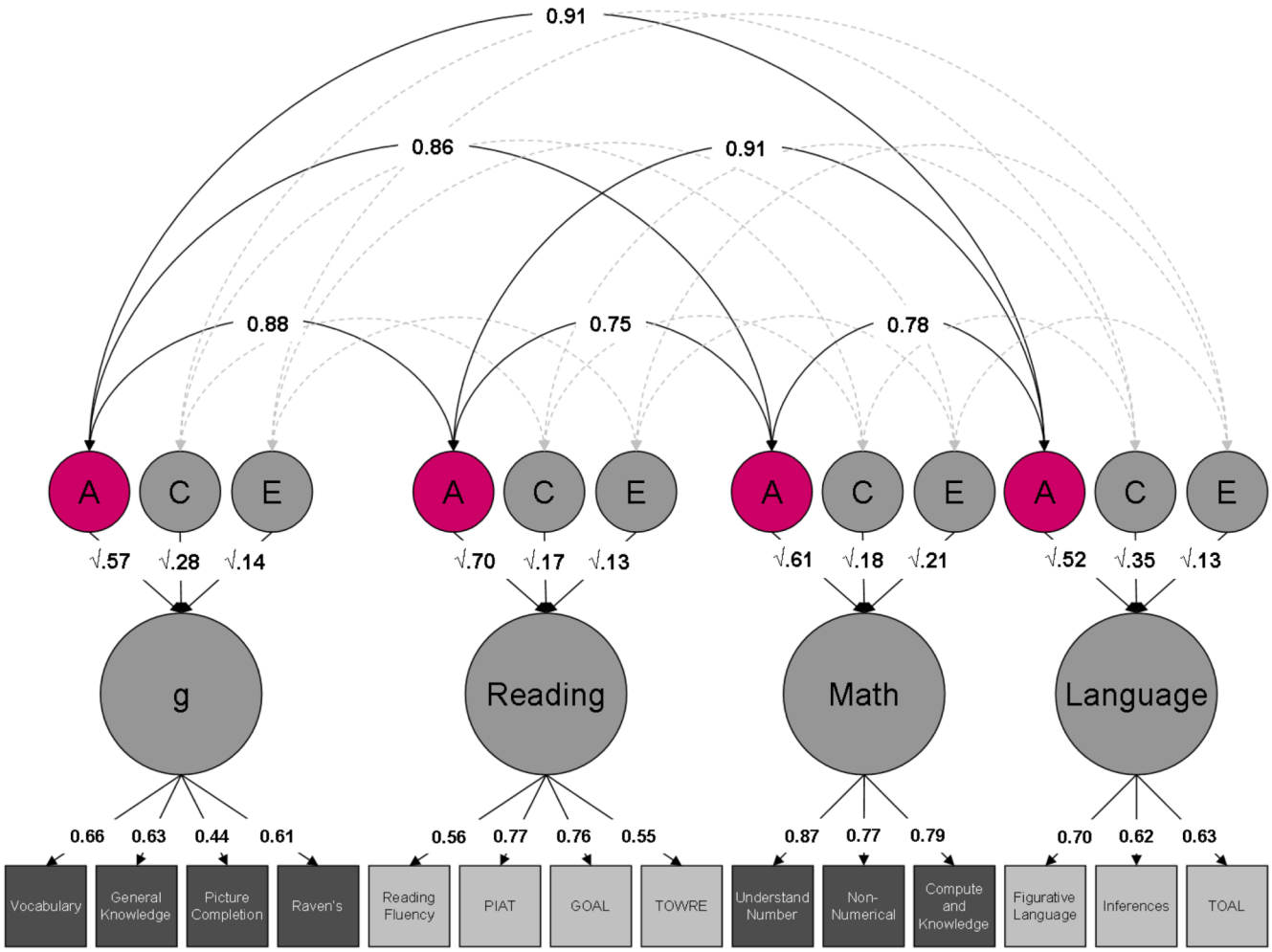

Figure 3.

Multivariate genetic common pathway model for 14 cognitive tests for more than 5000 pairs of twins at 12 years of age. Note: Squares represent measured traits; circles represent latent factors. The lower tier of arrows represents factor loadings; the middle tier represents genetic and environmental path coefficients; the curved arrows at the top represent correlations between genetic latent factors. Estimates of cross-trait additive genetic effects (A) are highlighted. Reprinted by permission of the publisher (Taylor & Francis Ltd, http://www.tandf.co.uk/journals) from Davis, Haworth & Plomin. Learning abilities and disabilities: generalist genes in early adolescence. *Cognitive Neuropsychiatry* 2009;14(4): 312-31.) A=Additive genetic effects; C=Shared (common) environmental effects; E=non-shared environmental effects; g = general cognitive ability; GOAL = Global Online Assessment for Learning, Formative Assessment in Literacy for Key Stage 3; PIAT = Peabody Individual Achievement Test (reading comprehension); TOAL = Test of Adolescent and Adult Language; TOWRE = Test of Word Reading Efficiency.

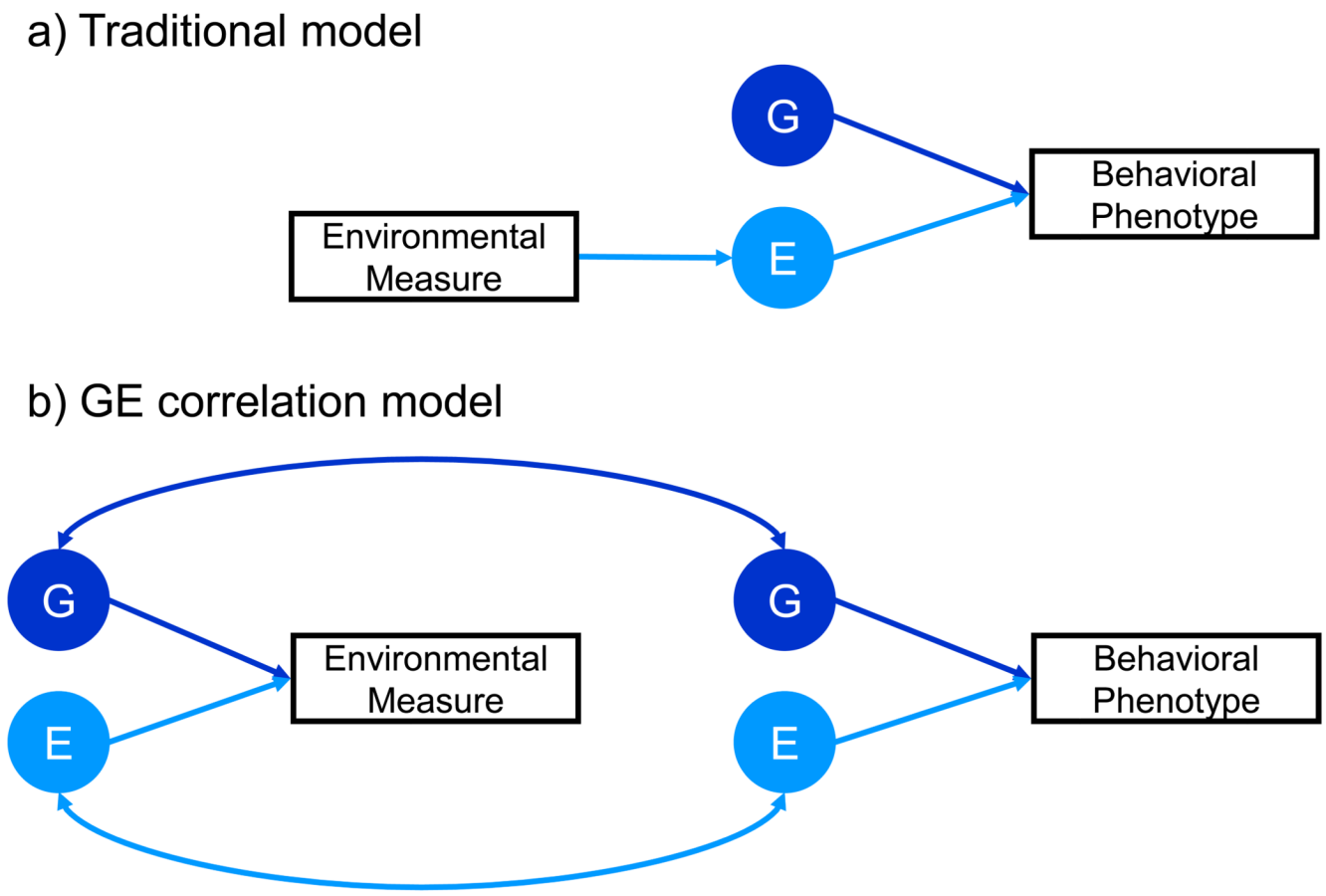

Figure 4.
The relationship between environmental measures and behavioral phenotypes: a) Traditional model and b) genotype-environment (GE) correlation model.