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Generalist genes and cognitive neuroscience

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Multivariate genetic research suggests that a single set of genes affects most cognitive abilities and disabilities. This finding already has far-reaching implications for cognitive neuroscience, and will become even more revealing when this — presumably large — set of generalist genes is identified. Similar to other complex disorders and dimensions, molecular genetic research on cognitive abilities and disabilities is adopting genome-wide association strategies. These strategies involve very large samples to detect DNA associations of small effect size using microarrays that simultaneously assess hundreds of thousands of DNA markers. When this set of generalist genes is identified, it can be used to provide solid footholds in the climb towards a systems-level understanding of how genetically driven brain processes work together to affect diverse cognitive abilities and disabilities.

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Current Opinion in Neurobiology 2006, **16**:145–151

This review comes from a themed issue on
Cognitive neuroscience
Edited by Paul W Glimcher and Nancy Kanwisher

Available online 24th March 2006

0959-4388/\$ – see front matter

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DOI 10.1016/j.conb.2006.03.004

Introduction

One of the most important findings to emerge from quantitative genetic research on cognitive abilities is that the genetic correlations (see glossary) among them are very high, suggesting that a single set of genes is responsible for most of the substantial genetic influence on diverse cognitive abilities. We begin with a brief introduction to the quantitative genetic evidence that points to the importance of generalist genes (see glossary). We then consider new approaches to finding such genes and review research on this topic to date, most of which has been published since 2003. We focus on cognitive abilities such as spatial, verbal and memory abilities rather than learning abilities such as reading. Our review is limited to research using direct measures of cognitive performance rather than measures of brain structure or function (see [1,2,3]). Ethical issues related to genetic

research on cognitive abilities are discussed elsewhere [4].

Generalist genes

Quantitative genetic research (see glossary) consistently shows substantial genetic influence on individual differences in cognitive abilities such as spatial, memory and verbal abilities [5]. Heritability estimates are typically about 40%, indicating that 40% of the total variance in these traits can be attributed to genetic variance. We also know that diverse cognitive abilities correlate moderately between individuals — this is the basis for Spearman's *g*, (see glossary) general cognitive ability, initially proposed a century ago [6]. A meta-analysis of 322 studies of cognitive abilities yielded an average correlation of about .30 among cognitive abilities, for example, among individuals' performance on spatial, verbal and memory tasks [7]. Studies using more representative samples and more reliable measures yield higher correlations [8].

To what extent do different sets of genes affect each of these cognitive abilities? An important advance in quantitative genetics that addresses this question is multivariate genetic analysis (see glossary), which goes beyond analysing the variance of each cognitive ability considered separately to analyse the covariance between them [9]. Multivariate genetic analysis yields a statistic called the 'genetic correlation', which indexes the extent to which genetic effects on one trait correlate with genetic effects on another trait, independent of the heritability of the two traits or the phenotypic correlation between them. The genetic correlation can be roughly interpreted as the extent to which the same genes affect the two traits: a genetic correlation of 1.0 indicates that the same genes affect both traits and a genetic correlation of 0.0 signifies that completely different genes are involved. However, quantitative genetic research cannot specify the generalist genes themselves nor the mechanisms by which they have their effect. For example, generalist genes could primarily affect a fundamental physical (e.g., neural density), physiological (e.g., synaptic plasticity), or psychological (e.g., working memory) process; these rudimentary genetic effects could then pervade all downstream cognitive functioning. In genetics, the word pleiotropy refers to such manifold effects of a gene. (See **Box 1** for more detail about multivariate genetic analysis and the genetic correlation.)

Multivariate genetic research on cognitive abilities consistently reveals that genetic correlations among diverse cognitive abilities are typically about .80. This suggests that mainly the same set of genes affects cognitive

Glossary

Allele: An alternative form of DNA sequence at a locus.

Association: A correlation between allelic frequencies and a phenotype in the population.

DNA marker: A polymorphism in DNA itself, such as single nucleotide polymorphism (SNP), in contrast to variations in a gene product, such as blood groups.

Generalist genes: Genes that affect multiple cognitive abilities, thus creating genetic correlations among the abilities.

Genetic correlation: A statistic from multivariate quantitative genetic analysis derived from the analysis of covariance between traits that indicates the extent to which genetic effects on one trait correlate with genetic effects on another trait.

Genome-wide: The entire 3-billion base pairs of DNA sequences across all of the chromosomes. Genome-wide linkage and association refers to using sufficient numbers of DNA markers (such as SNPs) to find linkage or association anywhere in the genome.

Linkage: Close proximity of loci on a chromosome so that the loci violate Mendel's second law of independent assortment, because closely linked loci are not inherited independently within families.

Linkage analysis: A technique that detects linkage between DNA markers and traits; used to map genes to chromosomes.

Locus (loci): A particular sequence of nucleotide base pairs of DNA.

Microarray: A highly miniaturised array, sometimes called a chip, that can genotype hundreds of thousands of SNPs simultaneously (and can also be used to detect tens of thousands of different RNA transcripts in gene expression studies). Several million strings of single-stranded nucleic acid fragments (probes) can be anchored to a glass or silicon slide the size of a postage stamp. Corresponding fluorescently labelled DNA sequences of interest can hybridize to these probes if there is an exact match in sequence. The fluorescent signal indicating a match can be detected by laser scanning.

Multivariate genetic analysis: Quantitative genetic analysis of the phenotypic covariance between traits (see Box 1).

Pleiotropy: Multiple effects of a gene.

Quantitative genetics: A theory and set of methods to decompose phenotypic variance into genetic and environmental components of variance by comparing relatives who differ in genetic and environmental relatedness. For example, the classical twin method estimates genetic and environmental components of variance by comparing the phenotypic resemblance of identical twins who are genetically identical and fraternal twins who are half as similar genetically.

Quantitative trait locus (QTL): DNA sequences that affect traits in multiple-gene systems, thus contributing to quantitative (continuous) variation in a phenotype.

Single nucleotide polymorphism (SNP): DNA polymorphisms in which the only difference is in a single nucleotide base pair of DNA.

Spearman's *g*: More than a century ago, Charles Spearman observed that diverse cognitive abilities are correlated across individuals. He coined the symbol *g* to refer to the general cognitive ability responsible for this covariance, in an attempt to avoid the use of the word 'intelligence', which even then had come to mean different things to different people.

abilities as diverse as memory and spatial in addition to information-processing measures [10,11]. Moreover, there is some evidence that the genetic overlap among cognitive abilities increases during development, with genetic correlations nearly reaching 1.0 in late adulthood [12]. Recent multivariate genetic analyses of learning abilities such as language, reading and mathematics yield similarly high genetic correlations of about .80, suggesting substantial genetic overlap among learning abilities; genetic correlations are also substantial (about .60) between learning abilities and cognitive abilities [13**].

These multivariate genetic results suggest that a single set of genes is largely responsible for genetic effects on cognitive abilities and learning abilities. It should be emphasized that not all genetic effects on cognitive abilities are general — some effects are specific — but what is interesting and unexpected from these results is the large extent of the general genetic effects. The 'generalist genes' hypothesis predicts that when genes are found that are associated with a particular cognitive ability, such as spatial ability, the same genes are also likely to be associated with other cognitive abilities, such as memory abilities, in addition to other learning abilities, such as reading and mathematics. This hypothesis also infers that attempts to identify these generalist genes will be facilitated by targeting what is in common among cognitive abilities rather than what is specific to each cognitive ability [14].

Quantitative trait loci

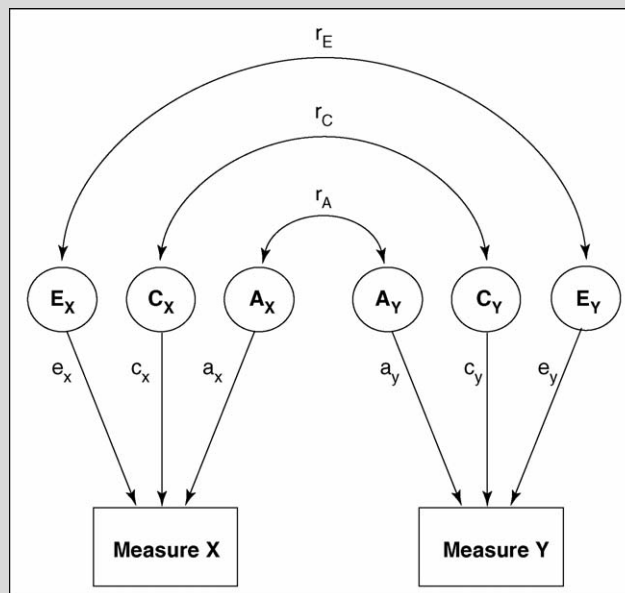
During the past three years, dozens of candidate gene association (see glossary) studies of specific and general cognitive abilities have been reported [15]. In 2005, the first studies were reported of genome-wide linkage (see glossary) [16] and genome-wide association [17**]. Much more linkage research has been conducted during the past decade on reading disability [18], but we focus here on more recent research on cognitive abilities.

This molecular genetic research is premised on the assumption that cognitive abilities, similar to other quantitative dimensions and common disorders, are influenced by many genes of small effect [19]. This view is referred to as the quantitative trait locus (QTL; see glossary) model because if many genes of small effect are involved a quantitative distribution is expected, not the qualitative dichotomy of a monogenic disorder. This assumption of the QTL model also applies to common disorders such as cognitive disabilities. That is, the QTL model assumes that common disorders (frequencies >0.01) are the quantitative extreme of the same genes responsible for normal variation, a hypothesis supported by quantitative genetic research that shows strong genetic links between learning disabilities and abilities [13**]. Although there are thousands of monogenic disorders in which a single mutation is necessary and sufficient for a disorder — many including cognitive effects among their symptoms — these disorders are rare and yield a combined frequency of only about 0.5%. For example, 282 monogenic disorders have been identified that include symptoms of mental retardation [20]; although these are often severe, they are rare (most 0.01%). Moreover, even these monogenic disorders involve highly pleiotropic (see glossary) effects across the brain so that their effects are likely to be general, which suggests that it will be difficult to track causal pathways.

Finding genes responsible for highly penetrant monogenic disorders is straightforward: genome-wide linkage

Box 1 Genetic correlation

Figure 1



Correlated factors model for one individual from a twin pair. Variance in each trait (X and Y) is divided into that due to latent additive genetic influences (A), shared environmental influences (C), and non-shared environmental influences (E). Paths, represented by lower case (a, c, and e), are the standardized regression coefficients which when squared indicate the proportion of variance accounted for. Correlations between the latent genetic, shared environmental, and non-shared environmental influences are denoted by r_A , r_C , and r_E .

How is it possible to estimate the genetic correlation between cognitive abilities? The essence of the method is simple [44]. Consider the classical twin design that compares resemblance for identical twins (monozygotic, MZ) who are genetically identical (clones) with the resemblance for fraternal twins (dizygotic, DZ) who, like other first-degree relatives, are 50% similar genetically. For a single trait X — for example, memory ability — genetic influence on the variance of the trait is estimated by the extent to which MZ twins are more similar than DZ twins. More specifically, doubling the difference between the MZ twin correlation and the DZ twin correlation estimates heritability, the proportion of the phenotypic variance of the trait that can be attributed to genetic variance. (The difference in MZ and DZ twin correlations is doubled because the difference represents half the genetic variance.) The same univariate approach can be applied in a multivariate context to estimate genetic influence on the covariance between traits X and Y — for example, the covariance between memory and spatial ability. Instead of using the twin method to decompose the variance of trait X into genetic and environmental components of variance, the cross-trait cross-twin (CTCT) correlations for MZ and DZ twins can be used to decompose the covariance between trait X and trait Y into genetic and environmental components of covariance. To the extent that CTCT correlations between X and Y are greater for MZ twins than DZ twins, the covariance between X and Y can be attributed to common genetic influences. More specifically, doubling the difference between the CTCT for MZ and DZ twins estimates bivariate heritability, the proportion of the phenotypic covariance between X and Y that can be attributed to genetic covariance. Multivariate genetic analysis uses maximum-likelihood model-fitting approaches that can be illustrated as path models of the sort shown in Figure 1 [9]. Doubling the difference between the CTCT for MZ and DZ twins represents the chain of paths $a_x \cdot r_A \cdot a_y$, which estimates the genetic contribution to the phenotypic correlation between X and Y. This chain of paths is the genetic correlation weighted by the product of the square roots of the heritabilities of X and Y. Because the heritabilities of X (a_x^2) and Y (a_y^2) are known, we can solve the chain of paths $a_x \cdot r_A \cdot a_y$ for r_A . An important feature of the genetic correlation is that it is independent of the heritabilities of X and Y and of the phenotypic correlation between X and Y: the genetic correlation can be high when the heritabilities are low (and vice versa) and the genetic correlation can be high when the phenotypic correlation is low (and vice versa). It is for this reason that the genetic correlation is an important guide for molecular genetic research. For example, if heritabilities are moderate (e.g. 0.40) and phenotypic correlations are moderate (e.g. 0.40), genetic correlations can be high (e.g. 0.80). This is the result that emerges from multivariate genetic research on cognitive abilities and disabilities. A genetic correlation of 0.80 between verbal ability and spatial ability can be interpreted roughly to mean that if a QTL is associated with verbal ability there is an 80% chance that the same QTL will be associated with spatial ability.

analysis using a few hundred DNA markers (see glossary) with large affected pedigrees will identify the chromosomal location of the mutation. QTL analysis, however, demands much greater power to detect the much smaller effect sizes that are expected if many QTLs are involved. QTL linkage designs accomplish this by studying many families of small size (usually parents and siblings or just

siblings) rather than a few large pedigrees. The first QTL linkage study of nonverbal cognitive ability reported linkages to chromosomes 2 and 6 in a study of 246 families [16]. QTL linkage provides much greater power to detect QTLs than traditional linkage designs do, although QTL linkage is nonetheless limited to detecting QTLs of rather large effect size (~10% of the total variance).

By contrast, association designs, which investigate correlations between allelic variation and traits, can detect QTLs of much smaller effect size [21]. QTL associations can be identified in an unselected sample (for example, comparing quantitative trait scores for genotypic groups) or by comparing allelic frequencies for phenotypically low and high groups (or cases and controls). QTL association research has primarily focused on a few candidate genes because genome-wide association scans require genotyping hundreds of thousands of DNA markers, which has only recently become possible with the advent of microarrays (see glossary) [22], as explained below.

Candidate genes

QTL research on cognitive abilities largely consists of association analyses of polymorphisms in genes that can be considered candidates for cognitive function, primarily genes involving synaptic transmission. These dozens of studies, too numerous to cite individually here, are reviewed in two recent papers [15,23]. Although the studies use diverse measures of cognitive function, most of the measures involve general cognitive ability and are, thus, likely to point to generalist genes. If any of these associations were solidly replicated, they could be used to test the generalist genes hypothesis by investigating the extent to which they are associated with a broad range of cognitive abilities. However, none of the candidate gene associations has been consistently replicated.

Eight studies have reported significant associations of cognitive abilities with the catechol-*O*-methyltransferase (*COMT*) gene. Eight other neurotransmitter genes have also been reported to show significant associations. Four genes related to brain development, and other genes including the apolipoprotein gene (*APOE*), which is most well known as a risk factor for Alzheimer's disease [15], have also shown significant associations with cognitive abilities.

As is typical with candidate gene association studies of complex traits [24,25], reports have also appeared that do not replicate these findings. For example, four studies have not found significant cognitive associations with *COMT* and six studies have not replicated associations with *APOE* [15]. An important factor in the poor replication record of candidate gene association studies is that most studies have been considerably underpowered to detect QTLs of small effect size [26,27]. For example, the eight studies reporting significant associations with *COMT* had sample sizes that averaged fewer than 100 control individuals [15]. Samples of 100 only provide 80% power to detect an association if it accounts for about 10% of the total variance of the quantitative trait. Detecting QTLs that account for 1% of the population variance with 80% power requires samples of about 1000 unselected individuals or case and control samples of about 500 each [28] for a single test, that is, before considering genome-wide

protection against false positive results and other complications [21].

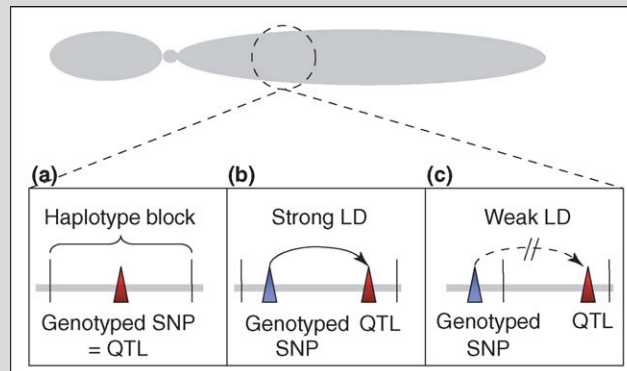
Another problem with candidate gene studies of cognitive abilities is that any of the thousands of genes expressed in the brain could conceivably be a candidate. Moreover, although the 25 000 genes in the human genome make the quest for QTLs challenging, 'genes' — defined as coding DNA that is transcribed into RNA and translated into proteins — represent only 2% of the genome. Non-coding DNA that is transcribed but not translated is also likely to be an important source of QTLs [29,30,31^{*}]. Because of the potential importance of non-coding DNA, the quest for QTLs for cognition needs to consider the whole genome rather than limiting the search to the 2% of the genome that involves protein-coding genes (see Box 2). Also for this reason, the acronym 'QTL' is more appropriate than 'gene' because QTL is neutral as to whether or not the functional DNA polymorphism is in a traditional protein-coding gene.

Genome-wide association scans

For an association scan to be truly genome-wide, hundreds of thousands of DNA markers are needed and the reasons for this are discussed in more detail in Box 2. Practical inconveniences of genotyping dense marker sets are now mostly resolved and genome-wide association scans are now possible, thanks to the development of microarrays and other high-throughput genotyping techniques that genotype simultaneously hundreds of thousands of single nucleotide polymorphisms (SNPs; see glossary) [32]. Microarrays have been most widely used to measure RNA expression throughout the genome, so-called gene expression profiling; we are referring here to microarrays that assess DNA polymorphisms of the two-allele SNP variety. This advance of SNP microarrays, however, also raises problems such as the need to balance false positive and false negative effects when testing hundreds of thousands of SNPs [33], especially in the search for QTLs of small effect size. The solution to detecting QTLs of small effect size is to study very large samples. A practical problem is that microarrays are expensive and can be used only once, which puts them out of reach of most budgets to study the very large samples required to attain the power needed to detect QTLs of small effect size. One promising way to greatly reduce the amount of genotyping for large samples is to pool DNA from many individuals into groups, such as cases versus controls or low versus high on a quantitative trait [34]. Estimates of allelic frequencies from pooled DNA appear to be reliable when compared between pools and valid when compared with individual genotyping. DNA pooling is best viewed as a tool to screen large numbers of SNPs for large samples to nominate a small number of candidate markers that can then be confirmed with individual genotyping. DNA pooling was used in a two-stage design to screen 432 SNPs in genes expressed

Box 2 Genome-wide association studies

Figure 2



Three scenarios that might arise in an association design using SNP genotyping. A section of a chromosome showing three possible relationships between a SNP and a functional QTL: **(a)** direct association involves genotyping the functional SNP (that is, the SNP is the QTL). **(b)** Indirect association relies on strong linkage disequilibrium (LD) between the genotyped SNP (blue) and the functional SNP (red). Linkage disequilibrium decreases as a function of distance between the genotyped SNP and the functional SNP. **(c)** When the genotyped SNP is not in LD with the functional SNP, the association is 'missed' because the association signal is not correlated.

Because genome-wide association designs require several hundredfold more markers than those for linkage studies, most association research to date has focused on candidate genes — driven by either biologically plausible hypotheses or previous QTL linkage signals. But as mentioned in the text, protein-coding regions account for only 2% of the genome, so what about the rest of the genome? Until recently, the remaining 98% was considered 'junk', but evidence suggests that the biological complexity of humans is correlated with the proportion of 'junk' or non-coding DNA (ncDNA) [31]. Therefore, it is likely that ncDNA regions harbour an untapped source of QTLs and genome-wide association designs are needed. Because high genotyping throughput is required for a genome-wide association study, current designs have capitalized on the simplest and most abundant form of genetic variation in the genome: single-nucleotide polymorphisms (SNPs). Throughout the human genome, SNPs close together on a chromosome are often correlated with each other. Correlated SNPs, in which the genotype of one predicts that of another marker, are said to be in 'linkage disequilibrium' (LD) with each other. These correlated markers cluster in chunks, called 'haplotype blocks', which are inherited together on the same chromosome. To find a significant association, a genotyped marker needs to either be the functional variant (direct association) or be in LD with the functional variant (indirect association) (see Figure 2). To conduct a direct genome-wide association study, one would need to genotype all functional SNPs [45]. Such functional SNPs are difficult to predict, but one likely class of SNP is non-synonymous SNPs (nsSNPs), which alter the amino acid sequence of a gene. For this reason, the Sanger Centre are conducting the Exon Resequencing Project that aims to identify all nsSNPs (<http://www.sanger.ac.uk/genetics/exon/>). Currently, our best chance of finding QTL associations in genome-wide scans is by indirect association. But given the incomplete knowledge of the patterns of LD throughout the genome, how many SNPs are needed for a 'genomewide' indirect study? It has been suggested that ~200 000 SNPs chosen on the basis of known LD patterns (i.e., haplotype blocks from the HapMap Project [47]) should be adequate [46**]. (Issues of correlated sequence structure [haplotype blocks] are being pursued and preliminary data have been made freely available by the HapMap Project [47].) One alternative and immediate solution is to use many more SNPs — which is quite feasible with the advent of microarrays — and hope that the high density of SNPs will capture functional SNPs (Figure 2a) and SNPs in the same haplotype as the functional QTL (Figure 2b), and avoid 'missed' associations (Figure 2c). This has been the ethos behind various genotyping platforms including the Affymetrix 500K GeneChip[®]. Digesting the genome using two restriction endonucleases then preferentially amplifying and labelling specific-length fragments, followed by hybridisation of these fragments to complementary oligonucleotides (containing flanking sequences around known SNPs) on microarrays permits a huge proportion of the genome to be interrogated in one pass. Of course both quantity and quality is desirable in the selection of SNPs; ultimately microarrays will be available with all functional DNA polymorphisms in the genome. Technologies such as SNP microarrays, designed with mass genotyping in mind, are driving down the cost to a level that would have been considered impossible just a few years ago: a genome-wide association study at less than \$.0025 per SNP.

in the brain for association with non-verbal cognitive ability in 4-year-old children, which identified a replicated association of very small effect size with the heat-shock cognate protein 8 gene (*HSPA8*) [35].

The strength of microarrays to genotype large numbers of SNPs and the strength of DNA pooling to genotype large samples can be combined by genotyping pooled DNA on microarrays, a technique dubbed 'SNP microarrays and DNA pooling' (SNP-MaP) [36,37]. SNP-MaP allele frequency estimates for groups such as cases and controls (or individuals with low or high quantitative trait scores) are

compared to nominate SNPs that show the greatest allele frequency differences; these nominated SNPs can then be confirmed with individual genotyping. The SNP-MaP method has been applied in a multistage design using a microarray that genotypes 10 000 SNPs, and it identified four SNPs associated with general cognitive ability in a sample of 6,000 children that were individually genotyped [17**]. The average effect size of these four SNPs was only 0.2%, but when aggregated into what has been called a 'QTL set' their effects add up to account for 0.8% of the variance. A microarray that genotypes 500 000 SNPs is now commercially available, which should greatly increase the

effect size of such QTL sets. The QTL set associated with general cognitive ability has been used as a multivariate genetic index in top-down behavioural genomic analyses including multivariate, development and gene–environment analyses [38*]. These multivariate analyses support the generalist genes hypothesis, in that the QTL set identified on the basis of associations with general cognitive ability was also associated with verbal and non-verbal cognitive abilities in addition to reading ability.

Conclusions

Multivariate genetic research consistently points to a single set of generalist genes that accounts for much genetic influence on diverse cognitive abilities and on reading and other learning abilities. Attempts to identify QTLs associated with cognitive abilities have focused on candidate genes, but genome-wide association scans with large samples that can detect QTLs of small effect size promise breakthroughs. Although each of the many generalist QTLs will involve different molecular mechanisms, a QTL set will be useful in tracing the pleiotropic pathways between genes and cognition through the brain to understand how generalist genes have their diffuse effects. These pathways will be complex and determining direct causation will be difficult [39–42]. Nonetheless, generalist QTLs will help to focus attention on how the brain functions as a system to solve cognitive problems and to accelerate research on the integration of mechanisms at all levels from gene expression and proteomics to brain, mind and behaviour [43].

Acknowledgements

Supported by a program grant from the UK Medical Research Council (G0500079) and a grant from the Wellcome Trust (GR075492MA).

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