Genes and the parsing of cognitive processes

Terry E. Goldberg and Daniel R. Weinberger

Clinical Brain Disorders Branch, GCAPP, IRP, NIMH, NIH, Bethesda, MD 20892, USA

Now that the human genome has been sequenced there exists the possibility of identifying specific genes that affect human cognition. In this article, recent studies that have found associations between common gene variants and specific cognitive processes are reviewed. Several principles for evaluating this new field are also discussed. The interpretation of results is far from simple because a single gene can affect multiple processes, multiple genes can impact on a single process, and multiple cognitive processes are intercorrelated. In general, functional neuroimaging has been a more sensitive assay of cognitive processing than behavioral measures used alone, although there are important caveats regarding its use. Replicated findings so far involve associations between a *COMT* polymorphism and prefrontally-based executive functions and neurophysiology, and a *BDNF* polymorphism and medial-temporal-cortex based declarative memory processes. Implicit in this review is a concern that many of the cognitive paradigms used evolved for purposes well outside those described here. As such it may be necessary to view cognition in novel ways, based on constraints imposed by genomics and neurobiology, in order to increase the effect size of genotypic influences on cognition.

With the sequencing of the human genome, it has become possible to begin to identify which of the myriad genes expressed in the CNS have an impact on human cognition. Of approximately 35 000 genes, upwards of 20 000 can be considered to play a role in the development, plasticity and maintenance of the CNS, although many of these will also play roles in other organ systems as well. Approximately 6 million single nucleotide polymorphisms (SNPs; see Glossary) are believed to characterize the genetic variability in worldwide populations, and it is likely that a minority of the common variations (perhaps fewer than five per gene) will be functional in nature, that is, result in changes in the expression or behavior of proteins. Most of these functional mutations will affect either the regulation of TRANSCRIPTION, via so-called PROMOTER polymorphisms, the organization of transcription, via so called SPLICE-SITE polymorphisms, or variations in the protein coding sequences, which themselves can result in changes that range from SYNONYMOUS, in which the function of the protein is unchanged, to NON-SYNONYMOUS or MISSENSE, in

which the function of the protein may be altered [1,2]. It is, of course, unclear how many of these variations in genes may affect cognitive information processing to a measurable degree in normal individuals. In theory, given the importance of gene regulation and protein function for brain development and learning in general, each gene might have an effect on information processing, if the cognitive PHENOTYPE were parsed correctly and the sample afforded adequate power. On the other hand, variation in normal human cognition is related to many factors, and the sum of all genetic effects is not likely to be greater than 50% for many types of cognition [3]. Thus, individual gene effects are expected to be small. Moreover,

---

Glossary

Allele: a variant of a gene

Association: the strength of a relationship between a polymorphic marker or SNP and a phenotype; that is, the strength of the co-occurence of allele and phenotype in sets of individuals

Candidate gene: a gene whose function is thought to influence a neurobiological process, cognitive ability, or diagnostic susceptibility

Exons: the sequences in the gene that comprise the code for the mature protein

Genotype: the combination of alleles at a locus (often expressed as the homozygote aa, the heterozygote Aa, and the homozygote AA)

Introns: sequences in genes that are not included in the protein

Linkage: the degree to which a marker is in close enough proximity to the causative mutation (even in the face of recombinations, i.e. events that occur when paired chromosomal regions cross over) to segregate with the trait of interest within a family pedigree

Linkage disequilibrium: correlation between a specific allele at one locus to another allele at a second locus

Penetrance: the probability that an individual with a given allele will manifest a given phenotype

Phenocopy: an individual who manifests a similar phenotype to another individual but does not share the genotype; it is usually thought to reflect environmental causes

Phenotype: cognition, behavior, anatomy, physiology, diagnosis, etc. that are associated with genes or segregate with polymorphic markers

Promoter: a region in the gene that signals the gene to begin protein synthesis

SNP (single nucleotide polymorphism): A variant in a single nucleotide at a specific location in the genomic sequence that may or may not have functional consequences for the protein, depending on type of substitution and the context. If a SNP is not functional (i.e. is silent or is in a non-coding area of the gene) it may still be in a monitoring relation with a functional mutation (i.e. if it is physically close, and in linkage disequilibrium)

Splicing: intronic RNAs are snipped and discarded; exonic RNAs joined

Splice variant: variation in the combination of exons that are used to synthesize the protein

Transcription: the process by which mRNA is synthesized from chromosomal DNA sequences; mRNA is then used to produce a protein via a process called translation

Synonymous polymorphism: a variant that does not change the amino acid sequence of a protein

Non-synonymous/Missense polymorphism: a variant that specifies a different amino acid; it can have a significant effect on the biological actions of the protein

---

Corresponding author: Terry E. Goldberg (goldbert@intra.nimh.nih.gov).

some polymorphisms might be quite rare and so offer little in the way of power for accounting for variability at the phenotypic or trait level in the general population. Certainly, a more complete and necessarily complex account of gene-cognition relations will also take into consideration interactions among genes, gene–environment interactions, and stochastic factors.

Many genetic mutations that have been associated with brain development and disease impact on cognition and can produce dementia or mental retardation. Rare mutations that cause mental retardation syndromes will not be covered herein (e.g. Velo Cardial Facial Syndrome, Williams syndrome, Down's syndrome), nor will disease specific mutations (e.g. polyglutamine repeats in Huntington's disease; the presenilins in Alzheimer's disease; synuclein in Parkinson's disease) [4–7]. The role of *APOE* in cognition is not reviewed, as it is not altogether clear whether the effects of the *APOE* polymorphism can be used to parse normal cognition, or whether they represent very early signs of Alzheimer's disease [8,9]. This review will focus on common gene variants that affect cognitive performance within or overlapping with the normal range by highlighting CANDIDATE GENES and evidence of allelic ASSOCIATION as opposed to LINKAGE findings, although when relevant, these too will be discussed. The candidate genes under consideration here are listed in Table 1. Linkage studies assess whether a polymorphic genetic marker from a specific chromosomal region can be linked to a trait. Because specific genes are not identified by this approach, linkage studies are not emphasized herein. Heritabilities of various cognitive functions will also not be discussed as these have been reviewed in detail recently [3].

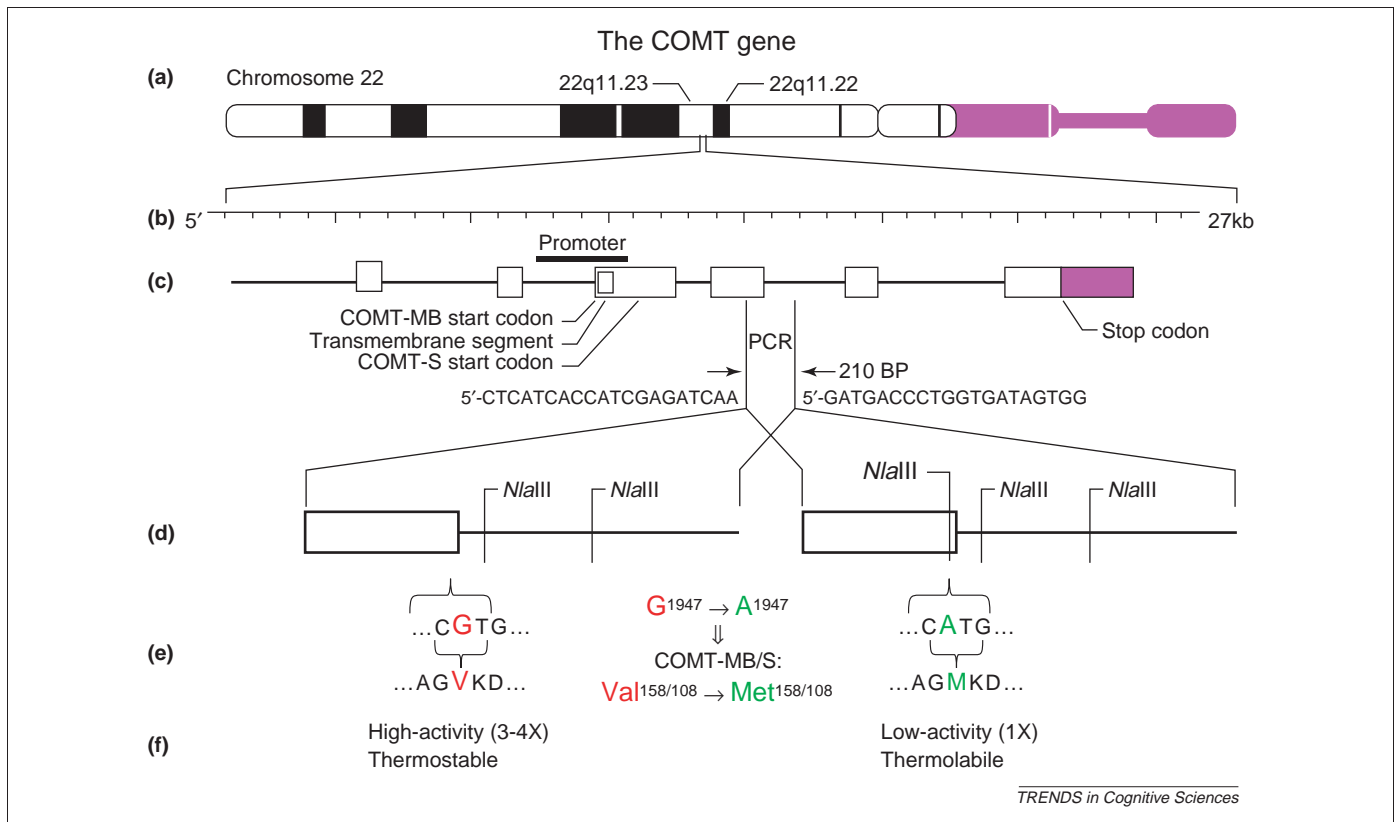### The search for links between single genes and cognition
To evaluate the potential role of individual genes in cognitive processes, it is necessary to consider several basic principles of genetic analysis. In association studies (which are emphasized in this review) the strength of the relationship between the variants of a specific candidate gene and the phenotype (here cognition) is tested. If a particular sequence variant (ALLELE) is enriched in frequency in a population characterized by a categorical phenotype (e.g. a clinical diagnosis) or is statistically associated with variation in a quantitative phenotype (e.g. a cognitive test score), the allele is said to be associated with that phenotype, and presumably relates to its genetic origins. Selection of the candidate gene and of the phenotype are obviously crucial. In the best of all

possible worlds one would start with well-defined functional polymorphisms, which by definition result in physiological effects at the cellular and/or systems level that bear on the biology of the phenotype of interest and a phenotype that is heritable and well-characterized (see Figure 1 for a schematic of one such candidate gene). When genetic variants are used without such established relationships, greater caution is required in accepting the results, as it is not clear how or if the genetic variation impacts on brain function. A positive association between an allele and a phenotype means one of three things: (1) the allele is a causative factor in the phenotype; (2) the association results because another allele, not recognized, is in so-called 'linkage disequilibrium' with the allele tested; (3) the association is an artifact. In any association analysis, one allele is being tested, but it is possible that other nearby alleles, which are not directly tested but might actually account for the finding, are enriched in one of the tested GENOTYPE groups. This phenomenon is LINKAGE DISEQUILIBRIUM and reflects the fact that much of the human genetic sequence has existed in relatively uninterrupted blocks during evolution. Thus, a given allele actually serves as a proxy for other neighboring alleles that have traveled together across generations on the same chromosome. For example, another SNP up to hundreds of thousands of nucleotide bases away from the genotyped SNP may actually be the causative mutation accounting for the phenotype variation, but because this SNP was not identified, its association is unknown. Artifacts can arise from several sources, including genotype errors, which are not uncommon, and from multiple testing. Another important and probably common source of artifact is so-called population stratification. Population stratification refers to ethnic group differences in allele frequency, due primarily to effects of population of origin and geographical isolation, which tend to concentrate certain alleles in different populations. Thus, if two ethnically (i.e. genetically) different groups score differently on a cognitive test because of cultural or sociological factors, the intrinsic population genetic structural differences could be spuriously held responsible for the cognitive differences.

It is also important to remember that the contribution of any single gene to a given cognitive process is likely to be small. Valid associations, therefore, can easily be obscured by differences in age, education, gender, and IQ, all of which can influence a variety of cognitive processes. Systemic illness, brain injury, psychiatric status, and drug and alcohol abuse can also influence cognition. These

Table 1. Candidate genes used in association studies with cognition

Gene name	Abbrev.	Location	Function
Alpha 7 nicotinic receptor	*CHRNA7*	15q	Cholinergic receptor;attentional gating
Brain derived neurotrophic factor	*BDNF*	11p	Role in LTP; episodic memory
Catechol-O-methyltransferase	*COMT*	22q	Involved in degradation of dopamine, notably in prefrontal cortex; executive subprocesses
Dopamine receptor type 4	*DRD4*	11p	Dopamine receptor with a limbic distribution; attention
Dopamine transporter	*DAT1*	5p	Reuptake of dopamine at or near the synapse; attention
Monoamine oxidase A	*MAOA*	Xp	Degradation of dopamine, norepinephrine, serotonin; attention
	OTX1	2p	Transcription factor involved in forebrain development
Semaphorin	*SEMA4F*	2p	Axonal growth cone guidance
Serotonin 2A receptor	*5HT2A*	13q	Serotonin receptor with wide forebrain distribution; episodic memory

The COMT gene

(a) Chromosome 22   22q11.23 —— —— 22q11.22

(b) 5′   27kb

(c)   Promoter

COMT-MB start codon
Transmembrane segment
COMT-S start codon
PCR
—— 210 BP
Stop codon

5′-CTCATCACCATCGAGATCAA   5′-GATGACCCTGGTGATAGTGG

(d)   *Nla*III   *Nla*III   *Nla*III   *Nla*III   *Nla*III

(e)   ...C**G**TG... $G^{1947} \rightarrow A^{1947}$ ...C**A**TG...

...AG**V**KD...   COMT-MB/S: ...AG**M**KD...

$Val^{158/108} \rightarrow Met^{158/108}$

(f)   High-activity (3-4X)   Low-activity (1X)
Thermostable   Thermolabile

TRENDS in Cognitive Sciences

Figure 1. Schematic of the *COMT* gene, which is involved in the degradation of dopamine, illustrating several important features about functional SNPs. **(a)** The locus of the gene is on the long arm ('q') of chromosome 22. **(b)** The size of the gene is 27 000 base pairs. **(c)** Six exons are shown, two of which are not translated into protein. **(d)** The alleles in question can be identified by PCR-based restriction fragment length polymorphism analysis using the restriction enzyme NlaIII because each allele differs in the location of recognition sites for this enzyme and thus in the pattern of DNA fragments. **(e)** The polymorphism is identified as a single nucleotide G to A substitution in exon 4. Several other SNPs thoroughout the gene, including one in the promoter, are also functional (not shown). An amino acid is changed from Valine (Val) to Methionine (Met) at codon 158. **(f)** The protein variants of the G−A substitution have differing neurobiological properties; one is more thermolabile than the other. The stable Val allele is more active enzymatically than the less stable Met allele.

factors should be controlled across genotype groups, to maximize the genotype effect. Furthermore, all tasks are not created equal. Care should be taken so that the tasks selected as phenotypes bear some appropriate relationship to the biology of the gene. Last, genotype–phenotype associations are phenomenological and do not imply causation. Only by placing the association in a neurobiological context can plausible and mechanistic models be constructed.

Another caveat has to do with the issue of multiple comparisons. A variety of tasks from multiple cognitive domains may have to be used because of doubt about which measures might be most sensitive to the putative genetic effects, thus increasing the number of statistical contrasts. It also may be necessary to oversample a given cognitive domain with multiple instruments, given psychometric differences among tasks, cohort effects, and an incomplete understanding of the neurobiological effects of the gene of interest. These may then be examined in relation to multiple SNPs within a gene. These procedures increase the probability of type I statistical error (see Box 1). This being said, several of the tasks may be inter-correlated, in essence, reducing the number of independent comparisons. Similarly, each SNP is not independent from every other SNP. Some are in linkage disequilibrium with nearby SNPs. Again, this may somewhat attenuate the problem of multiple comparisons, albeit not completely,

and probably not in a straightforward manner. Nevertheless, the problems of multiple comparisons are real and it remains possible that some of the results described here are spurious and should be accepted with caution until they are independently replicated.

Functional neural imaging may offer a more powerful method to examine genotypic effects on cognitive processing in brain [10]. There are perhaps three reasons for this. First, neurophysiology at the systems level as measured by PET ^{15}O or BOLD fMRI may be closer to the neurobiological effects of the gene than is overt behavior. Second, it may be more difficult for an individual to compensate for genetically determined neurophysiological aberrations as opposed to compensating at the behavioral level where such factors as test-taking attitude, motivation, strategy, persistence, and response monitoring can influence performance and obscure a genotype association in a way that may not directly reflect ability level. Last, the time series statistical analysis of fMRI data increases statistical power and hence sensitivity to small differences. However, there are also caveats associated with neuroimaging approaches that are important to appreciate. Methodological factors unrelated to genotype (machine type, drift, movement correction, etc.) might decrease reliability in large-scale multi-site studies. Of course, use of fMRI also introduces issues of multiple comparisons, although

Box 1. Confounds, pitfalls, and contributing factors in genetic association studies

Type I Error

Significant associations with non-functional SNPs might require more convergent evidence than functional SNPs (in promoter or exonic regions or in splice sites) to reduce 'false positives'.

Differences in allele frequency among populations (usually due to geographic isolation, but also to factors such as genetic drift, assortative mating, and founder effects) can be spuriously associated with any phenotypic differences that exist among the groups (including those determined environmentally). For instance, differences in the frequency of an allele between Asian and Caucasian populations could be spuriously associated with use of chopsticks.

Case–control association studies may be prone to gross or subtle stratification.

Type II Error

Genetic heterogeneity, such that multiple genes affect the same cognitive trait, reduces the variance that any one gene can explain.

Phenocopies are non-genetically determined phenotypes with features similar to the genetically determined phenotype (e.g. resulting from drug or alcohol abuse, head injury, systemic illness, birth complications, CNS infections, etc.) that will reduce the power of association studies by introducing random genetic variation

Loss of power can result from categorical classification of the phenotype.

Box 2. Intermediate phenotypes

Many cognitive abilities, traits, or psychiatric symptoms are complex and could be emergent, depending on the actions or interactions of multiple genes that affect basic component biological functions. Intermediate phenotypes, that is, less complex biological phenotypes, might have a simpler genetic architecture and be closer to the neurobiology of a gene or small panel of genes, and thus show greater PENETRANCE (see Glossary) of their gene effects. In other words the phenotypes reflect more elementary phenomena and the number of genes needed to produce variations in these traits can be fewer than those involved in producing a complex trait (e.g. a clinical diagnostic entity). Thus, intermediate phenotypes provide a means for identifying some of the more basic components of the clinical trait as well as the consequences of gene actions [55]. A strong form of the argument for use of intermediate phenotypes can be applied to schizophrenia. In this version of the argument, schizophrenia qua schizophrenia is not inherited. Rather multiple alleles disadvantageous for information processing are inherited and complex psychiatric symptoms such as hallucinations or delusions are emergent phenomena. This would be akin to geotaxia in drosophila, where several genes, none of which would have been predicted to have a relationship to geotaxia on the basis of prior notions about their function, significantly influence the trait in question [56].

Criteria for considering a cognition-based intermediate phenotype

(i) Evidence for heritability
(ii) Can be reliably measured (e.g. test–retest reliability)
(iii) High frequency of impaired scores in index cases; increased frequency of impaired scores in relatives
(iv) Has a known neurobiology that can be related to candidate gene effects

analysis programs such as SPM provide corrections for the interrogation of large numbers of voxels.

The following sections review recent studies that have found associations between common gene variants and specific cognitive processes.

Attentional processes and cognitive control

Attentional gating and CHRNA7

Variability in a specific type of early attentional processing is thought to involve sensory gating or inhibition, and has recently been associated with allelic variations of the α7 nicotinic subunit receptor gene (*CHRNA7*) located on chromosome 15q14 [11]. The attentional process has been indexed by an electrophysiological event, the so-called P50 ERP, which is thought to originate in the temporal-limbic cortex. In this paradigm, the amplitude of a response to a second auditory stimulus presented 500 ms after an initial and identical auditory stimulus is diminished in most normal individuals by 50% or more. The P50 response appears to be heritable and is therefore a phenotype with likely genetic determinants. Loss of the P50 response has been produced by pharmacological blockade of the α7 receptor and lesions of septal-hippocampal cholinergic afferents; nicotine normalizes P50 sensory gating abnormalities through stimulation of α7 receptors. P50 has been used as an intermediate phenotype in schizophrenia research because of a possible role for failures in gating in the development of symptoms such as hallucinations and disorganization (see Box 2).

Leonard *et al.* [12] reported evidence in humans that a variety of polymorphisms in the promoter region of *CHRNA7*, which have been shown in cell-expression models to affect *CHRNA7* transcription (i.e. mRNA expression), were associated with a failure to inhibit the P50 auditory evoked potential response in both normal controls and schizophrenic subjects. This finding suggests

that variations in the *CHRNA7* promoter sequence affect the abundance of *CHNRA7* protein and thereby affect nicotinic processing in human hippocampus and related cortices, which in turn affects processing in this cognitive paradigm. The P50 phenotype demonstrated stronger linkage to markers at 15q than did clinical diagnosis to these markers in schizophrenia enriched pedigrees [13]. One unresolved technical question about P50 deserves comment. It is often the case that a minority of subjects (20–30%) do not show a response to the conditioning stimulus during any given testing session, thus precluding evaluation of P50. It is unclear what the meaning of these failures is, although they raise questions about test–retest reliability.

Attentional networks and aminergic genes

Catecholamines have long been implicated in various components of attentional processing, and catecholamimetic drugs are mainstays of treatment for disorders of arousal and attention. Recently, Fan, Posner and colleagues [14] have examined various aspects of attention in relationship to common polymorphisms in catecholeamine-related candidate genes, including those encoding the dopamine type-4 receptor (*DRD4*), dopamine transporter (*DAT*), catechol-O-methyltransferase (*COMT*) and monoamine oxidase-A (*MAOA*) These genes are involved in diverse aspects of aminergic signaling in brain (i.e. dopamine, norepinephrine, serotonin). Fan and colleagues measured alertness to incoming stimuli (thought to engage right frontal and parietal cortical areas during processing); orienting and selecting stimuli for further

processing (thought to engage posterior parietal lobe, the pulvinar, and superior colliculus); and executive control involved in resolving conflicts among various inputs (thought to engage dorsolateral prefrontal cortex and the anterior cingulate). All attentional targets involved left-ward or rightward pointing arrowheads flanked either by arrowheads pointing in the same direction (congruent) or in the opposite direction (incongruent); various cue conditions identified the location of the targets with varying probability. The heritability of these specific cognitive assays has not been established, however. A more crucial limitation of this study is that the ethnic or racial backgrounds of the New York metro area sample were not reported; nor were other demographic differences. Thus stratification effects and potential pheno-copies related to educational or other intellectual effects are unknown, but likely to be important, as all of these genes have shown considerable population variation in their genotype frequencies.

A mixed set of findings was reported with common alleles in these genes, some of which appear to be functional. For example, no positive findings were reported for genotypes based on the presence or absence of a marker in an untranslated region of *DAT* or for variants in a coding region (exon iii) of *DRD4*. However, a *DRD4* SNP at nucleotide position -521 known to affect transcription (the C allele results in considerably more transcription than the T allele) was associated with executive attention in the expected direction, that is, presumably more transcription allows for greater D4 signaling with consequent efficient responses to stimulus incongruity. *MAOA* genotypes derived from a polymorphism in the promoter region of the gene involving short or long repeated sequences of nucleotides had a significant impact on both alerting and executive function. With regard to executive cognition, subjects in the long 4-repeat class demonstrated more efficient management of incongruity effects, although this allele has previously been associated with greater tran-scription and presumably greater enzymatic catalysis of biogenic amines, including dopamine, norepinephrine, and serotonin [15]. Thus the biological plausibility of this relationship is somewhat problematic. With regard to *COMT*, a trend towards a significant overall effect of a functional EXONIC SNP was observed, as individuals with the so called Val/Val genotype were most efficient in managing incongruity. However, other work suggests that Val alleles of *COMT* are associated with poorer perform-ance in executive tasks that engage prefrontal cortex, and whether this would translate into the association found in the Fan *et al.* study is unclear (see section below, Executive Function, for a more complete discussion of *COMT*'s neurobiology and genotypic associations).

In a companion fMRI study, Fan *et al.* [16] examined the effects of polymorphisms in the *DRD4* gene (an insertion/deletion SNP in the 'upstream' region of the gene with unknown functional effects) and the aforementioned functional polymorphism in the promoter region of the *MAOA* gene using the congruent and incongruent task conditions described above. Again, the basic premise of the experiment was that greater dopaminergic availability should result in more efficiency in managing incongruent

or conflicting stimuli resulting in smaller reaction time (RT) differences between conditions (congruent and incon-gruent). Genotypic effects were predicted to be significant in the anterior cingulate, a region thought to play an important role in conflict monitoring or conflict resolution in cortical information processing. An fMRI study based on 8 subjects with each of the *MAOA* genotypes (4-repeat vs. 3-repeat) showed large differences in the cingulate in favor of the 4-repeat group, implying that more efficient behavior is associated with greater activation. This is somewhat counterintuitive, given the putative effects of the variant on aminergic degradation. For the *DRD4* receptor polymorphism, the insertion group demon-strated less conflict in terms of RT ratio than the deletion group and also demonstrated greater activity in the cingulate, although this could be attributed to relatively lower activation for the insertion group in the congruent condition.

ADHD and dopamine-related genes

Many studies have attempted to find associations between attention deficit hyperactivity disorder (ADHD) and polymorphisms in dopamine candidate genes including *DAT* and *DRD4*. Dopamine function has long been implicated in ADHD because of the efficacy of stimulant drugs in ameliorating symptoms of impulsivity. The *DAT* gene has been the target of a gene knockout animal model of ADHD and associations of *DRD4* with novelty seeking and risk taking behavior [17,18] have been observed. Based on a meta analysis [19] an association to the *DAT* gene was considered significant (but see [20] for a con-trasting view).

Although children with ADHD also have various cognitive impairments that can be measured with psycho-metric tasks, nearly all studies have used a diagnosis-based phenotype (usually derived from the Diagnostic and Statistical Manual-IV), with exceptions described below. Those studies using cognitive measures of attention restricted their samples to ADHD probands, although the range of performance of index cases overlaps with that of normal individuals. Eisenberg *et al.* [21] found that the *COMT*'s Val allele was strongly associated with a variable from a Continuous Performance Test (CPT) thought to measure impulsivity within a group of nearly 50 subjects. Loo *et al.* [22] found that children with ADHD who were homozygous for a functional allele in the DAT gene (the '10-repeat sequence' in an untranslated region of the gene's 3′ end) exhibited poor performance on a vigilance task (the CPT) in comparison with children who carried other allelic variants at this locus. The allele is thought to result in significantly higher transporter availability than the alternate version of the allele, in principle translating into less synaptic dopamine. The CPT used high-target probabilities to generate commission errors, considered to be a surrogate measure of impulsivity. This finding is at least biologically consistent with the observation that DAT inhibitor drugs, which increase synaptic dopamine, improve performance on this task. Swanson *et al.* [23] examined a putatively functional allele of the DRD4 gene ('7-repeat' variant) which as noted, has been proposed to be a susceptibility factor in ADHD. Children with clinically

diagnosed ADHD were assessed using an attentional network task similar to that used by Fan and colleagues so that various orienting, selection, and control processes were measured. Contrary to predictions, the 7-repeat 'absent' group performed more slowly and variably; neither group demonstrated selective impairments. Taken together, these results in children with ADHD suggest, albeit weakly, that variants in dopamine related genes may have an impact on some aspects of the severity of impulsivity in ADHD.

Executive subprocesses and COMT

Executive cognition and cognitive control processing involve complex cellular and circuit interactions centered around the prefrontal cortex [24]. Dopamine has been prominently studied as a crucial neurotransmitter for tuning neuronal and circuit responses during executive processes, and recent studies indicate that genetic factors affect dopamine flux in prefrontal cortex. In particular, a common variant in the COMT gene appears to account for significant variance in prefrontal cognitive function. The variant is a SNP in exon 4 that results in an amino acid substitution of valine (Val) for methionine (Met). The two different amino acids cause differences in enzyme activity and, ultimately, thermolability of the protein and thereby its functional ability to catabolize dopamine. The more stable Val allele is associated with greater enzymatic activity and hence greater dopamine degradation than the Met allele [25]. The role of COMT is surprisingly regional and may be greatest in frontal cortex [26], perhaps because the dopamine transporter, crucially involved in regulating dopamine in the striatum, is expressed in low abundance in cortex and has little role in regulating cortical dopamine levels [27].

Given the extensive animal and human literature suggesting that dopamine plays an important role in working memory function, such as maintenance and set shifting [24,28]. Egan *et al.* sought to determine the association of COMT genotype with prefrontally mediated cognition and prefrontal cortical physiology in a sample that comprised 175 patients with schizophrenia, 219 unaffected siblings, and 55 controls [29]. COMT genotype was related in allele dose fashion to performance on the Wisconsin Card Sorting Test, a task that demands a complex combination of set shifting, abstraction, and response to feedback and reliably engages prefrontal cortex [30]. They found that individuals with two Met alleles performed best and individuals with no Met alleles (i.e. those with two Val alleles) performed worst. Approximately 4% of variance in perseverative errors was explained by COMT Val/Met genotype. In summary, consistent with other evidence that dopamine signaling enhances prefrontal neural function, the low activity Met allele, which presumably allows more dopamine to become available at the synapse, was associated with better performance, whereas the high activity Val allele was associated with worse performance.

The COMT findings in the WCST have been replicated in independent samples of healthy adult controls [31,32]. COMT effects were also observable in children in performing a prefrontal type task (namely, Delayed Response). COMT

effects were not observed on another prefrontal task (Self-Ordered Pointing), thought not to be dependent on dopamine function [33]. However, ceiling effects on the latter task, as well as unknown covariance between the tasks, preclude strong interpretations about specificity. Another study found that COMT genotype had significant effects on a factor score considered to reflect speed of processing and attention, but not executive function, in a sample of medicated schizophrenic patients [34]. These results might not be contradictory, as cognitive control functions that are implemented at least in part by prefrontal regions can also play a role be manifested in specific tests of speed and attention, and executive functions may be altered by antipsychotic medication, thus obscuring the genetic effect.

In the same cohort studied by Egan *et al.*, Goldberg *et al.* [35] explored the association of COMT genotype with performance on the N-Back task, a more specific assay of working memory and executive processing. In this task a number between 1 and 4 was displayed every 1.8 s on a computer screen. In the One-Back condition in which a working memory load is imposed above and beyond instructional context, the subject views the first stimulus, but does not respond; the subject then views the second stimulus and responds by pressing a button corresponding to the first stimuli, and so on. Thus, the subject must continuously recall information that was 'one back' in a sequence. In the Two-Back condition, the subject must continuously recall the stimulus that was 'two back'. N-Back performance was scored as the percentage of correct responses. This task was used because it permits a parsing of subcomponents of executive cognition and working memory, including load, delay, and updating. A significant COMT genotype effect was found again: Val/Val individuals had the lowest N-Back performance (and slowest reaction time) and Met/Met individuals had the highest performance, with similar effects across the three clinical groups. Moreover, effects were similar in the One-Back and Two-Back tasks, suggesting that genotype was not affecting working memory subprocesses related to load or delay. Rather, a prefrontal cognitive mechanism common to the One-Back and Two-Back conditions, probably executive processes involved in information updating and temporal indexing, was implicated. These genotypic effects indicate that both the N-Back and WCST might demand processes that rapidly stabilize a representation in working memory buffer and then allow its deselection. In the N-Back, failures in this process result in updating errors; in the WCST in perseverative errors. Considering that the three groups (normal, sibling, index) were impacted more or less linearly by COMT genotype in this study and the earlier study using the WCST, an additive genetic model in which allele load is similar in its influence on prefrontally based working memory irrespective of the genetic or environmental background in which it is expressed is suggested (see Figure 2). Allele load here refers to the number of Val alleles an individual carries (zero, one or two).

COMT genotype did not significantly influence attention on the CPT and intelligence using a Wechsler Adult Intelligence Scale-Revised derived measure of *'g'*.
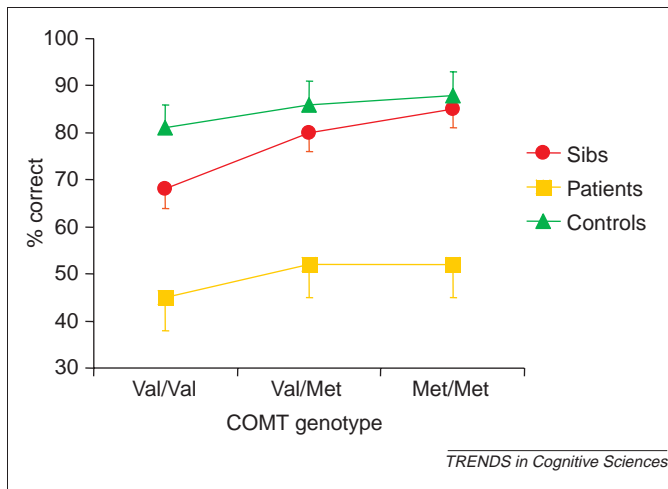
Figure 2. An additive effect of *COMT* genotype on the 'N-Back test' of working memory and executive processing is observed. Genotypic effects are relatively similar irrespective of group (healthy, schizophrenia patients, unaffected siblings of patients). This was demonstrated in a random effects ANOVA in which main effects of group and *COMT* genotype were significant, but a genotype x group interaction was not significant [35].

However, it is important to note that the negative findings on the CPT and IQ should not be considered conclusive. *COMT* effects on IQ, although not significant, were present and consistent in allele load, suggesting that in a larger sample with greater power an effect might have been found. The results also suggest that not every CNS gene will inevitably have associations to 'g' that are greater than those to subprocesses of cognition; relationships may be of degrees and not be absolute. Second, separating N-Back performance from attentional control might be somewhat artificial and is likely to depend on a complex interplay between the neurobiology of the gene in question and psychometric and demand characteristics of the task itself. Hence, for another gene, *G72* (thought to play an indirect modulatory role in glutamate receptor function), a strong association between a non-functional SNP and both N-Back and CPT performance has been found (Goldberg *et al.*, unpublished).

Egan *et al.* also examined the effects of *COMT* genotype on prefrontal physiology measured with fMRI while individuals performed the N-Back task in groups matched on performance [29]. Met allele load predicted a more efficient physiological response (i.e. less BOLD activation) in prefrontal cortex in the Two-Back condition of the N-Back (see Figure 3a). In other words, the group with relatively more cortical dopamine available at the synapse (i.e. Met/Met) had relatively greater behavioral 'bang' for its physiological 'buck'. Gallinat *et al.* [36] found that an ERP during a P300 'oddball' task was impacted by *COMT* genotype in a large sample of healthy controls and schizophrenic patients of European descent. Specifically, amplitude in frontal regions (thought not to be related to crucial target-related attentional processing) was lower in individuals with Met/Met genotypes than Val carriers, consistent with the notion that the Met allele is associated with less physiological 'noise'. (Note that the groups in the studies illustrated in Figure 3 are relatively small as genotype-based groups generally had fewer than 15 subjects [29,37]. By contrast, some behavioral findings were based on groups an order of magnitude larger. This suggests that fMRI might have greater sensitivity in detecting genotype-based differences in physiology.)

Mattay *et al.* [37] explored the effects of this functional *COMT* polymorphism on the actions of amphetamine in prefrontal cortex. They reasoned that because *COMT* genotype appears to play a role in determining the set point or baseline of dopaminergic tone in prefrontal cortex, it should interact with amphetamine induced increases in synaptic dopamine. Because evidence also indicates that dopamine impacts cortical function in an inverted U-shaped curve within a narrow range, it was predicted that amphetamine might improve the performance of normal individuals with lower dopaminergic tone and worsen the performance of individuals with higher levels of dopaminergic tone [38,39]. Mattay *et al.* found that amphetamine (0.25 mgs kg^{-1} dextroamphetamine) enhanced the physiological efficiency assayed by fMRI BOLD response in prefrontal cortex of individuals who were Val homozygotes and who had presumably less synaptic dopamine at all levels of working memory load. By contrast, healthy subjects who were Met homozygotes showed deterioration in cortical function under amphetamine at high working memory loads. Figure 3b illustrates this interaction between drug, genotype and load. These pharmacogenetic results might shed light on the variable clinical effects of amphetamine treatment, in which some individuals demonstrate improvements in mood and information processing, whereas others become dysphoric, irritable or lose mental acuity. They also support the link between *COMT* genotype and dopamine mediated prefrontal function.

Episodic memory
BDNF
Basic studies in slice preparations and in animals have shown that brain-derived neurotrophic factor (BDNF) plays an important and direct role in LTP and hippocampal function during memory processing. Thus, it might be expected that a genetic alteration in BDNF function could have implications for hippocampal based learning and memory. Egan *et al.* [39] investigated the functional implications of a common missense polymorphism in the human *BDNF* gene producing a Val to Met substitution in the signal sequence region of the gene upstream of the mature BDNF protein itself. Rodent hippocampal neurons in culture transfected with Val-*BDNF* or with Met-BDNF cDNA constructs were studied to determine how the polymorphism would affect BDNF trafficking within the cell. Val allele peptides exhibited a punctate distribution pattern throughout the soma and neuronal processes, whereas Met peptides showed reduced expression in dendrites and large clusters in the perinuclear region, suggesting differences in intracellular trafficking. Differences in activity dependent secretion of BDNF favoring the Val cells were also observed. These cellular effects suggested that Met alleles will be less effective in mediating BDNF-modulated changes in neural plasticity.

In a cohort of 641 human subjects (including normal individuals, schizophrenic patients and their non-psychotic siblings), levels of *n*-acetyl asparatate (NAA), a putative
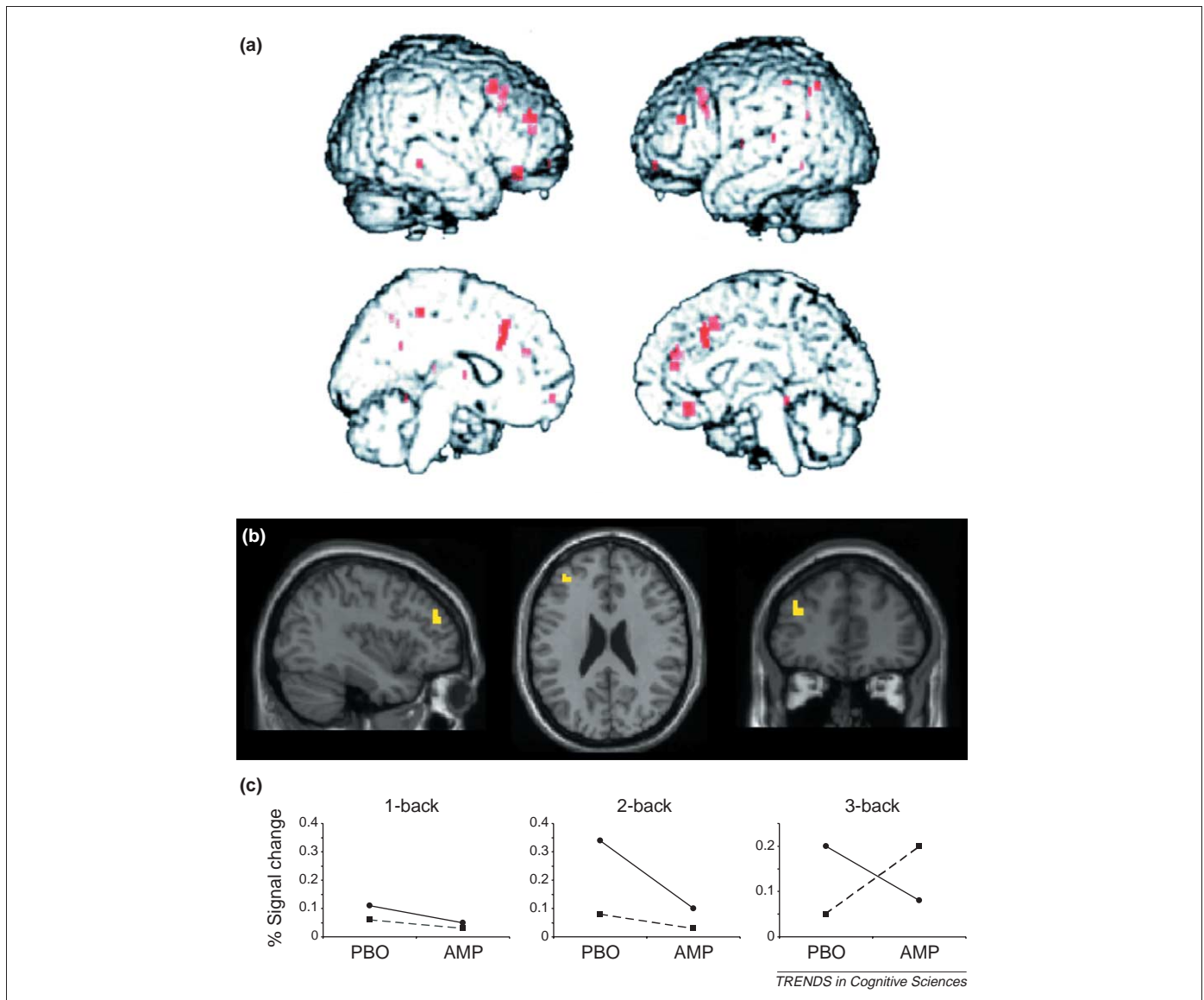
Figure 3. The NIMH version of the '*N*-Back' task reliably engages a network that includes dorsolateral prefrontal cortex. In groups known to have reduced dopaminergic input to prefrontal cortex and in groups in which there is evidence of reduced dopaminergic 'tone' in prefrontal cortex, *N*-Back engagement results in overactivation of the network for a fixed level of performance, a physiological circumstance characterized as inefficiency. **(a)** shows that normal individuals with the *COMT* Val/Val allele demonstrated greater activation in dorsolateral prefrontal cortex during the Two-Back task compared with Val/Met individuals, who in turn demonstrated greater activation than Met/Met individuals [29]. This finding is consistent with the concept of inefficiency caused by genotypically reduced dopaminergic tone. Importantly, groups were matched for performance, so physiology could be examined without confounding it with performance related factors. **(b)** shows the prefrontal locus of a complex interaction between amphetamine status and *COMT* genotype [35]. **(c)** Val homozygote individuals demonstrated greater physiological efficiency across all working memory loads while receiving amphetamine; that is, they benefited, whereas Met homozygote individuals demonstrated greater activation and hence inefficiency at high working memory loads while receiving amphetamine.

in vivo measure of neuronal integrity and synaptic abundance, were assayed with magnetic resonance spectroscopic imaging and found to be lower in the hippocampus of subjects with Met alleles; no differences were found in other regions between genotype groups. Additionally, the Met/Met genotype group exhibited impaired verbal episodic memory in contrast to the Val/Val genotype in a task involving memory for semantically structured stories (the finding was mildly amplified over a thirty minute delay). Surprisingly, these effects were not found in memory for word lists, perhaps because the latter requires more strategy driven semantic processing and is therefore a less pure test of memory function. Consistent with this notion was a factor analysis in which list-learning loaded moderately on multiple cognitive factors, and memory for stories loaded strongly on a single factor. Interestingly, memory for stories but not lists has been shown to be more strongly correlated with hippocampal atrophy in elderly subjects [40]. Thus, subtle differences in task demands can interact with genotype in unexpected but not implausible ways to increase or decrease power.

In a related fMRI paradigm (see Figure 4) in normal subjects that measured BOLD signal during encoding of visual scenes (indoor vs. outdoor) and then again during recognition of these scenes mixed with foils (old vs. new), Hariri *et al.* [41] found that Met carriers exhibited diminished hippocampal engagement in comparison with Val homozygotes during both encoding and retrieval processes. Crucially, the interaction of genotype and
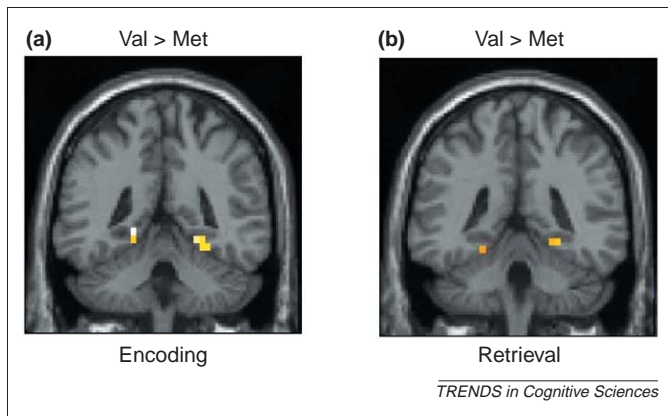
Figure 4. In a translational study [39] involving an amino acid altering polymorphism in the BDNF gene, it was shown that this SNP (i) affects intracellular trafficking and regulated secretion of BDNF, (ii) has an impact on NAA (measured by NMR spectroscopy), a measure of neuronal integrity in the hippocampus, and (iii) affects verbal episodic memory in behavioral testing. In a further study of the effect of this BDNF polymorphsim on hippocampal memory processing, Hariri *et al.* [41] using fMRI, showed a direct neurophysiological effect on MTL function that was modulated by BDNF genotype while subjects encoded **(a)** and recognized **(b)** novel visually presented scenes. BDNF Met carriers demonstrated less activation in MTL during encoding and retrieval than Val/Val homozygotes. The interaction of genotype and hippocampal BOLD response during encoding, but neither main effect, predicted a large share (25%) of the behavioral variance on the task in normal subjects. This implies that although genotypic effects on variance might be small, interaction effects (here genotypic modulation of a neurophysiological response) might help improve prediction of behavioral variance.

hippocampal BOLD response during encoding (but not genotype alone or hippocampal BOLD encoding alone) accounted for a large and significant proportion of the variance in recognition accuracy (Figure 4). This study linked genotype, hippocampal physiology, and performance, thus completing the conceptual loop running through the argument for BDNF's role in human mnemonic function. These translational findings represent a demonstration of a role for BDNF in human memory and hippocampal function and suggest that the mechanism by which the polymorphism initiates these effects relates to an alteration in intracellular trafficking and secretion of BDNF.

5-HT2A

The gene for the 5-HT2A receptor (*HTR2A*) was recently found to be associated with variation in verbal episodic memory in a group of 349 healthy European subjects [42]. An infrequent (9%) missense mutation in an exonic region of the gene results in attenuated receptor function upon stimulation. Individuals who were homozygous for the common histine allele (N = 279) performed significantly better than carriers of the less frequent tyrosine allele (N = 70) on a verbal episodic memory task involving recall of short lists of words at five and 30 min. Recall of visually presented figures after delays was significantly different across genotypes only in males. An association of memory to genetic variation in a serotonin receptor gene is somewhat surprising in that although the serotonin system has been implicated in learning and memory in simple organisms (e.g. aplysia [43]), memory changes have generally not been apparent in humans administered serotonin reuptake inhibitors or 5-HT2A antagonists (e.g. cyproheptadine, ritanserin, MDL 100907). This being said, the human studies generally did not focus on

episodic memory and often came in the context of clinical trials; subtle findings may have been overlooked. It also might be considered that the 5HT2A effect is mediated by a signaling partner of serotonin, for example, BDNF. This complexity illustrates the uncertainties that befall genetic associations when the biology of the gene and the biology of the phenotype are not clearly related.

Language

Language impairment

The results of linkage studies of specific forms of language ability using large family datasets have identified several chromosomal regions that segregate with 'impairment,' using categorical and quantitative definitions of the phenotype [44–46]. It is not known whether the loci in these chromosomal regions will be relevant to variance in the normal range. No candidate gene studies have yet been published based on these results. A very rare mutation in the *FOXP2* gene has recently been shown to severely disrupt the development of speech and language in a single extended pedigree in the UK [47]; a translocation in the gene also resulted in speech and language abnormalities in another unrelated individual [48]. It is not known if there are other functional polymorphisms in the *FOXP2* gene that have subtle effects on language ability or other cognitive abilities within the normal range; all identified SNPs to date have been in noncoding regions of the gene (www.Ncbi.nlm.nih.gov/SNP/snp_ref.cgi).

Reading

Reading is presumably a skill based on the elaboration of processing circuitry used in language. This conclusion is justified because alphabetic reading is a recent addition to the language repertoire; it was invented ~4000 years ago by the Phoenicians. Thus, reading *per se* is unlikely to be under genetic control, but it can serve as a measurable proxy of this basic linguistic circuitry. Thus, reading and its impairments in dyslexia can be considered relevant to the current discussion because many studies have also used reading subprocesses involving phonological segmentation, 'word attack' skills in pseudoword reading, and orthographic knowledge (e.g. as measured by reading 'exception' words) as intermediate phenotypes. The underlying assumption of this approach is that subprocesses vary along a normal distribution and that genes associated with their regulation have effects that become cumulative in the presence of other genes that play a role in other reading subprocesses.

Genetic linkage analyses have identified regions of the genome that might contain polymorphisms that play a role in reading and disabilities in reading. Recent reviews of linkage studies related to reading suggest that loci on chromosomes 2, 3, 6, 15 and 18 showed positive and replicable effects in independent samples [49,50]. However important methodological concerns about phenotypes and their relation to linkage regions have been raised. In a study involving two sets of families in which at least one sibling was affected by dyslexia and a twin sample in which at least one twin was affected. Fisher *et al.* [51] found that different combinations of cognitive phenotypes demonstrated linkage, which varied depending on region

and sample. Superficially, a locus on chromosome 6 influenced phonological decoding and orthographic processing whereas a locus on chromosome 18 influenced word reading and phoneme awareness. However, the investigators pointed out that conclusions about cognitive specificity are unwarranted because of limitations in linkage mapping using multiple correlated measures with possibly different psychometric sensitivities. Using multivariate analysis and principle components analysis, Marlow *et al.* [52] formally demonstrated that effects of multiple reading subprocesses, including nonword reading and phonologic manipulation, irregular word reading, and lexical decision, as well as single word reading and spelling themselves, contributed to the two linkage findings. This work strongly implies that a single gene might impact multiple cognitive domains; it is also almost certainly the case that multiple genes impact a single cognitive domain, given the relatively small proportion of the variance accounted for by any single gene in association studies. Even given problems resulting from covariance among measures, it is important to note that at least some of the markers in linkage studies have been strongly and reliably associated with intermediate phenotypes of reading ability (e.g. phonologic awareness in pre-readers, nonsense word reading, rapid reading or automatized reading). This supports the attempt to assess subprocesses or intermediate phenotypes that may have stronger genetic associations.

Association studies of candidate genes located in a region of chromosome 2p in which positive linkage was observed (i.e. *SEMA4F* and *OTX1* [53]) have been negative. Nevertheless, reading ability and disability provide a model for identifying replicable quantitative trait loci in linkage studies. Use of functional neuroimaging to discern differences in the effect of candidate gene polymorphisms may ultimately be helpful. Obviously, choice of an activation task and brain region upon which to focus, as well as issues of sample size and heterogeneity, will be key.

Summary

Several intriguing findings have emerged in this very early stage of research on discovering relationships between gene variants and variation in cognitive phenotypes. These come in the context of the following:

(1) Gene effects on brain function in normal individuals are small and so sample sizes must be large in behavioral studies. Functional neuroimaging might offer a way to improve power.

(2) Some of the work appears robust and might already have yielded fundamental insights. The impact of *COMT* genotype on prefrontal-based cognition has been replicated across multiple cohorts using a variety of cognitive, pharmacological, and fMRI paradigms. The impact of BDNF genotype on episodic memory also appears to be replicable.

(3) Some important cognitive domains have been understudied, including basic aspects of working memory (e.g. subprocesses as maintenance and set size), semantic memory, and visual processing (although see work on Williams syndrome for severe spatial impairment [54]).

Box 3. Some directions for future research

• Further genetic sequencing to identify SNPs; molecular biological assays to assess their functionality
• Novel statistical techniques to address issues of multiple comparisons
• Large scale multi-site studies to identify genes of small effect
• Assessment of genotypic effects on drug response to cognitive enhancing agents

---

(4) Cognitive intermediate phenotypes at the very least provide information that is not redundant with diagnostic based phenotypes (e.g. phonologic awareness in dyslexia linkage studies, P50 and *CHRN7* in schizophrenia, *N*-Back and *G72* in schizophrenia) and in some cases they appear to have superior power in identifying associations or linkage.

(5) Perhaps the most important question raised in this review has been implicit; it has to do with how cognition is parsed. It will become increasingly important to use genetic information to constrain, refine and decompose tasks, so that subprocesses are identified that are closer to neurobiology and in principle yield stronger associations with genotype, yet remain cognitive in nature. This process will, of course, be iterative, and can be done in conjunction with a variety of neuroimaging techniques. Many familiar tasks are historical accidents, designed as army selection tests or educational tracking tests, or based on various sequential information processing stages (so-called boxology), with little consideration given to neurobiology. Psychometric parameters such as test–retest reliability, skewness of distribution, ceiling and floor effects, and factor analysis have gone unreported for many of the tests discussed here. All could influence findings. In short, new approaches to parsing cognition will need to capitalize on constraints imposed by genomics.

(6) Finally, it is important to appreciate that a report of an association between a genotype and a variation in a cognitive function is not proof that genetic variation impacts on brain information processing. As in any case–control comparison, many occult factors could account for the association. Indeed, whereas the studies cited invariably look at the effect of one gene, the subsamples might differ at many untested loci in the genome, which could account for the observed effects, not to mention the role of environmental factors. The sets of associations between single genes and single cognitive processes reviewed here are clearly simplifications of genetic, neurobiological and cognitive subsystems that interact in complex ways. Ultimately, an association between gene and cognitive phenotype will require convergent evidence from other areas of biology and a variety of sophisticated bioinformatic approaches (see also Box 3).

References

1 Botstein, D. and Risch, N. (2003) Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease. *Nat. Genet.* 33, 228–237
2 Grantham, R. (1974) Amino acid difference formula to help explain protein evolution. *Science* 185, 862–864
3 Bouchard, T.J. and McGue, M. (2003) Genetic and environmental influences on human psychological differences. *J. Neurobiol.* 54, 4–45

4 Battaglia, A. and Carey, J.C. (2003) Diagnostic evaluation of developmental delay/mental retardation: an overview. *Am. J. Med. Genet.* 117C, 3–14

5 Nussbaum, R.L. and Ellis, C.E. (2003) Alzheimer's disease and Parkinson's disease. *Eng. J. Med.* 14, 1356–1364

6 Ross, C.A. (2002) Polyglutamine pathogenesis: emergence of unifying mechanisms for Huntington's disease and related disorders. *Neuron* 35, 819–822

7 Xu, J. and Chen, Z. (2003) Advances in molecular cytogenetics for the evaluation of mental retardation. *Am. J. Med. Genet.* 117C, 15–24

8 Bennett, D.A. *et al.* (2003) Apolipoprotein E epsilon4 allele, AD pathology, and the clinical expression of Alzheimer's disease. *Neurology* 60, 246–252

9 Dik, M.G. *et al.* (2000) APOE-epsilon4 is associated with memory decline in cognitively impaired elderly. *Neurology* 54, 1492–1497

10 Hariri, A.R. and Weinberger, D.R. (2003) Imaging genomics. *Br. Med. Bull.* 65, 259–270

11 Freedman, R. *et al.* (2000) Inhibitory neurophysiological deficit as a phenotype for genetic investigation of schizophrenia. *Am. J. Med. Genet.* 97, 58–64

12 Leonard, S. *et al.* (2002) Association of promoter variants in the α7 nicotinic acetylcholine receptor subunit gene with an inhibitory deficit found in schizophrenia. *Arch. Gen. Psychiatry* 59, 1085–1096

13 Freedman, R. *et al.* (1997) Linkage of a neurophysiological deficit in schizophrenia to chromosome 15 locus. *Proc. Natl. Acad. Sci. U. S. A.* 94, 587–592

14 Fossella, J. *et al.* (2002) Assessing the molecular genetics of attention networks. *BMC Neurosci.* 3, 14

15 Carson, R.P. and Robertson, D. (2002) Genetic manipulation of noradrenergic neurons. *J. Pharmacol. Exp. Ther.* 301, 410–417

16 Fan, J. *et al.* (2003) Mapping the genetic variation of executive attention onto brain activity. *Proc. Natl. Acad. Sci. U. S. A.* 100, 7406–7411

17 Gainetdinov, R.R. and Caron, M.G. (2003) Monoamine transporters: from genes to behavior. *Annu. Rev. Pharmacol. Toxicol.* 43, 261–284

18 Kluger, A.N. *et al.* (2002) A meta-analysis of the association between DRD4 polymorphism and novelty seeking. *Mol. Psychiatry* 7, 712–717

19 Faraone, S.V. *et al.* (2001) Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *Am. J. Psychiatry* 158, 1052–1057

20 Maher, B.S. *et al.* (2002) Dopamine system genes and attention deficit hyperactivity disorder: a meta-analysis. *Psychiatr. Genet.* 12, 207–215

21 Eisenberg, J. *et al.* (1999) Haplotype relative risk study of catechol-O-methyltransferase (COMT) and attention deficit hyperactivity disorder (ADHD): association of the high-enzyme activity val allele with ADHD impulsive-hyperactive phenotype. *Am. J. Med. Genet.* 88, 497–502

22 Loo, S.K. *et al.* (2003) Functional effects of the DAT1 polymorphism on EEG measures in ADHD. *J. Am. Acad. Child Adolesc. Psychiatry* 42, 986–993

23 Swanson, J. *et al.* (2000) Attention deficit/hyperactivity disorder with a 7-repeat allele of the dopamine D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention. *Proc. Natl. Acad. Sci. U. S. A.* 97, 4754–4759

24 Robbins, T. (2000) Chemical neuromodulation of frontal-executive functions in humans and other animals. *Exp. Brain Res.* 133, 130–138

25 Weinshilboum, R.M. *et al.* (1999) Methylation pharmacogenetics: catechol O-methyltransferase, thiopurine methyltransferase, and histamine N-methyltransferase. *Annu. Rev. Pharmacol. Toxicol.* 39, 19–52

26 Gogos, J.A. *et al.* (1998) Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. *Proc. Natl. Acad. Sci. U. S. A.* 95, 9991–9996

27 Sesack, S.R. *et al.* (1998) Dopamine axon varicosities in the prelimbic division of the rat prefrontal cortex exhibit sparse immunoreactivty for the dopamine transporter. *J. Neurosci.* 18, 2697–2708

28 Levy, R. and Goldman-Rakic, P.S. (2002) Segregation of working memory functions within dorsolateral prefrontal cortex. *Exp. Brain Res.* 133, 23–32

29 Egan, M.F. *et al.* (2001) Effect of COMT val[108/158] met genotype on frontal lobe function and risk for schizophrenia. *Proc. Natl. Acad. Sci. U. S. A.* 98, 6917–6922

30 Berman, K.F. *et al.* (1995) Physiological activation of a cortical network during performance of the Wisconsin Card Sorting Test: a positron emission tomography study. *Neuropsychologia* 33, 1027–1046

31 Malhotra, A.K. *et al.* (2002) A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. *Am. J. Psychiatry* 159, 652–654

32 Joober, R. *et al.* (2002) Catechol-O-Methyltransferase val-108/158-met gene variants associated with Wisconsin Card Sorting Test. *Arch. Gen. Psychiatry* 59, 662–663

33 Diamond, A. *et al.* (2004) Genetic and neurochemical modulation of prefrontal cognitive functions in children. *Am. J. Psychiatry* 16, 125–132

34 Bilder, R.M. *et al.* (2002) Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. *Biol. Psychiatry* 52, 701–707

35 Goldberg, T.E. *et al.* (2003) Executive subprocesses in working memory: relationship to catechol-O-methyltransferase Val158Met genotype and schizophrenia. *Arch. Gen. Psychiatry* 60, 889–896

36 Gallinat, J. *et al.* (2003) Assoiation of the G1947A COMT (Val 108/158Met) gene polymorphism with prefrontal P300 duing information processing. *Biol. Psychiatry* 54, 40–48

37 Mattay, V.S. *et al.* (2003) Catechol O-methyltransferase val[158]-met genotype and individual variation in the brain response to amphetamine. *Proc. Natl. Acad. Sci. U. S. A.* 100, 6186–6191

38 Williams, G. and Goldman-Rakic, P.S. (1995) Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. *Nature* 376, 572–575

39 Egan, M.F. *et al.* (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 112, 257–269

40 Wilson, R.S. *et al.* (1996) Association of memory and cognition in Alzheimer's disease with volumetric estimates of temporal lobe structures. *Neuropsychology* 10, 459–463

41 Hariri, A.R. *et al.* (2003) Brain-derived neurotrophic factor val[66]met polymorphism affects human memory-related hippocampal activity and predicts memory performance. *J. Neurosci.* 23, 6690–6694

42 Quervain, D.J-F. *et al.* (2003) A functional genetic variation of the 5HT2a receptor affects human memory. *Nat. Neurosci.* 6, 1141–1142

43 Bailey, C.H. *et al.* (2000) A novel function for serotonin mediated short term facilitation in Aplysia. *Proc. Natl. Acad. Sci. U. S. A.* 97, 11581–11586

44 Consortium, S.L.I. (2002) A genome wide scan identifies two novel loci involved in specific language impairment. *Am. J. Hum. Genet.* 70, 384–398

45 Bartlett, C.W. *et al.* (2002) A major susceptibility locus for specific language impairment is located on 13q21. *Am. J. Hum. Genet.* 71, 45–55

46 Stein, C.M. *et al.* (2004) Pleiotropic effects of a chromosome 3 locus on speech-sound disorder and reading. *Am. J. Hum. Genet.* 74, 283–297

47 Lai, C.S. *et al.* (2001) A forkhead-domain gene is mutated in a severe speech and language disorder. *Nature* 413, 519–523

48 Marcus, G.F. and Fisher, S.E. (2003) FOXP2 in focus: what can genes tell us about speech and language? *Trends Cogn. Sci.* 7, 257–262

49 Fisher, S.E. and DeFries, J.C. (2002) Developmental dyslexia: genetic dissection of a complex cognitive trait. *Nat. Rev. Neurosci.* 3, 767–780

50 Francks, C. *et al.* (2002) The genetic basis of dyslexia. *Lancet Neurol.* 1, 483–490

51 Fisher, S.E. *et al.* (2002) Independent genome-wide scans identify a chromosome 18 quantitative-trait locus influencing dyslexia. *Nat. Genet.* 30, 86–91

52 Marlow, A.J. *et al.* (2003) Use of multivariate linkage analysis for dissection of a complex cognitive trait. *Am. J. Hum. Genet.* 72, 561–570

53 Francks, C. *et al.* (2002) Fine mapping of the chromosome 2p12-16 dyslexia susceptibility locus: quantitative association analysis and positional candidate genes SEMA4F and OTX1. *Psychiatr. Genet.* 12, 35–41

54 Mervis, C.B. (2003) Williams syndrome. *Dev. Neuropsychol.* 23, 1–12

55 Gottesman, I.I. and Gould, T.D. (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. *Am. J. Psychiatry* 160, 636–645

56 Toma, D.T. *et al.* (2002) Identification of genes involved in *Drosophila melanogaster* geotaxis, a complex behavioral trait. *Nat. Genet.* 31, 349–353