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A Genetic Neuroscience Approach to Human Cognition

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A large gap exists between behavior genetics and cognitive neuroscience, although psychologists feature prominently in both fields. Behavior genetics focuses on individual differences and, through sophisticated statistical modeling in twin and family studies, addresses the genetic and environmental contribution to variation in cognitive ability. Cognitive neuroscience tends to focus on species universals in brain function during specific cognitive operations, which are isolated by clever experimental design, and located in the time and (brain) space by modern imaging techniques. This paper describes the complementary approach of "genetic neuroscience" that integrates the study of cognition as an individual trait and the study of cognition as an universal process. It is argued that the intermediate phenotypes or "endophenotypes" of brain function and structure from neuroscience will boost the power of geneticists' association and linkage approaches to find the genes underlying differences in cognitive ability. Neuroscience, in turn, will profit greatly from successfully identified gene functions. Genes can provide insight in the "black box" between molecular events and cognition. They offer many opportunities to lay bare gene by environment interactions in the psychological laboratory. By reviewing some of the main issues in each field and summarizing the mutual advantages of collaboration between geneticists and neuroscientists we hope to mount further support for a complementary approach.

Keywords: Endophenotypes, genomic searches, genotype by environment interaction, twin studies.

Introduction

Two different approaches to human cognition stand out in the field of psychology: cognition as a process and cognition as a trait. The study of cognition as the universal processes of human information processing has a long experimental research tradition known as cognitive psychology. This tradition recently received a major boost by its integration with new neuroscientific approaches to the brain yielding the integrated field of cognitive neuroscience (Gazzaniga, 2000). Cognition as a trait has traditionally been part of the psychometric approach to individual differences in mental capacities (Jensen, 1998) that, even at its conception, was strongly linked to genetics (Galton, 1869). The ties between research on cognitive (dis)ability and genetics have been strengthened even more with the recent progress in molecular genetic approaches (Flint, 1999). The major mission of this paper is to argue that a complementary approach, combining process-oriented cognitive neuroscience with trait-oriented molecular and behavior genetics, will further our understanding of cognition as a trait *and* as a process.

The authors of this paper are a psychophysiologist and behavior geneticist, respectively. In psychophysiology—a discipline effectively swallowed up by the broader field of neuroscience—physiological indices like electrical brain potentials, brain blood flow distribution, eye movements, or heart rate deceleration are used to index brain processes during cognition. By experimental design, complex cognitive operations are cut-up in smaller sub-units that are more amenable to experimentation. Memory operations, for instance, can be divided into short-term (or "working") memory and "im-

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plicit" or "explicit" long-term memory. Psychophysiological tools are then used to further unravel each of these cognitive processes. For instance, viewing words or pictures elicits electrical brain potentials that clearly differ between words/pictures that are remembered during a later recognition task and words/pictures that are not recognized or are new (Wilding & Rugg, 1997). These brain potentials show that the processes critical to successful encoding take place about 400–600 ms after stimulus presentation. When this experiment is repeated during brain blood flow imaging, the location of these processes can be pinpointed in the prefrontal and the medial temporal lobe (e. g., hippocampus) of the brain. Ideally, brain imaging results converge with animal and patient findings. In this example, they do because the (para)hippocampal brain region is known from neuropsychological and animal lesion studies to be required for formation of durable memories.

In behavioral genetics, individual variation in the ability to perform various cognitive operations, of which the IQ test is an often used "summary measure," is examined in subjects with different degrees of genetic relatedness. The workhorse of human behavioral genetics has been the twin study. A twin study compares the resemblance between genetically identical, monozygotic (MZ) twins to the resemblance between fraternal or dizygotic (DZ) twins. MZ twins share all of their genes, whereas DZ twins share, on average, 50% of their segregating genes. Hence, the demonstration that MZ twins are more similar than DZ twins for a certain trait points to a genetic contribution to the variation in this trait (Martin, Boomsma, & Machin, 1997). Efficient use of the information available in the variances and covariances of genetically related subjects can be made with a statistical technique called structural equation modeling (SEM). Basically, the total variance in a trait is decomposed into several contributing factors: [1] additive genetic variance (A), which results from the additive effects of the alleles of all contributing genetic loci; [2] dominance genetic variance (D), which results from the nonadditive effects of the alleles at all loci showing a dominance effect; [3] shared (common) environmental variance (C), which results from environmental events shared by both members of the twin pair (e. g., growing up in the same family); [4] unique environmental variance (E), which results from nonshared environmental effects and also includes measurement error (Neale & Cardon, 1992). The influence of observed confounders like age or socio-economic status can be incorporated in the model, as can the influence of measured genotypes, which may be genes of known function or anonymous chromosomal markers.

A strong boost to genetic approaches to the major themes in psychology, including cognition, can be expected with the publication of the near-finished maps of the human genome. Broadly speaking, two separate phases of research can be outlined, although their timetable will show large or complete overlap (or even reversed order for some topics). The first phase is geared toward finding genes (genomics) for cognition and characterizing the proteins they code for (proteomics). The second phase brings understanding about how genes are expressed during cognitive operations and how the expression of these genes in turn affects the ongoing cognition (functional genomics).

This paper addresses psychologists with an interest in neuroscience or in behavioral genetics. First, we present an overview of the main gene finding strategies currently in use. Second, we examine the available endophenotypes of behavior that could boost the power of gene finding. We then sketch how future genetic knowledge can improve research on cognition (1) as a process, focusing on protein-based understanding of nerve cells and genetic engineering in animals, and (2) as a trait, focusing on genotype by environment experiments. We conclude with an example of a collaborative research effort that, from its outset, was conceived of as a genetic neuroscience program.

Finding Genes with the Help of Cognitive Neuroscience

Humans show striking individual differences in the full spectrum of their cognitive abilities. Extensive research based on twin, family, and adoption data has documented that more than half of the variability in cognitive ability is due to genetic factors (Bouchard & McGue, 1981; Plomin, 1999). Highest heritability is found for broad indices of cognition, such as psychometric IQ, but heritability of specific cognitive processes such as verbal fluency, working memory operations or speed of processing is also extensive (Wright et al., 2001). In our longitudinal sample of 209 Dutch twin pairs, IQ was moderately heritable at age 5 (25%) but gradually increased to adult levels of 80%. These percentages—there is much misunderstanding about this—are population statistics and deal with effects on variance, *not* means. A heritability of 80% for IQ does not mean that parental care, education, or food availability do not strongly influence

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IQ; it just means that the variation between individuals in the examined population is due to genetic variation, for instance, because living conditions and the educational system are above the minimum level required to maximize genetic potential. Formally speaking, interindividual variance in an outbred population in an extremely homogeneous environment is due mainly to genetic variation, but interindividual variance in the same trait may be completely environmental in an inbred strain in an extremely heterogeneous environment. There is no contradiction here, rather it just shows that heritability estimates are about explained variance, not about predestination.

Gene-Finding Strategies

Linkage

Studies in the field of behavioral genetics have established the *presence* of genetic influences on cognitive traits. The genes themselves, however, have remained largely elusive with the exception of some neurological mutations with rather severe cognitive effects (e. g., Pick disease, X-linked mental retardation, Huntington) as reviewed by Flint (1999). Like the many rare diseases and disorders listed in full in the "Mendelian Inheritance in Man" (McKusick, 1998) and its online version (www.ncbi.nlm.nih.gov/omim; updated every day), these genetic defects of cognition are Mendelian in nature. A single gene is responsible for the disorder, there are only a few rare alleles that cause problems, and they do so mostly only when the person is homozygote for that allele (i.e., has no compensatory "good" allele). As a general strategy to find such Mendelian genes, a number of DNA markers of known location, evenly dispersed throughout the entire genome, are measured in individuals from multiple generations. DNA markers can be mutations in a single base pair (single nucleotide polymorphisms, SNPs) or a variable number of repeats of two or more base pairs (microsatellites). They need not be part of a functional gene—they are just landmarks in the genome. For each DNA marker, evidence for linkage is derived using statistical procedures that trace the cosegregation of the trait (and thus in many instances the gene) and a specific variant of the DNA marker along familial lineages in extended pedigrees. Put simply, if two children resemble each other for a certain trait, and if they both received exactly the same variant of a DNA marker from the same parent, that marker is probably close to the gene influencing the trait. Excellent summaries on the biometrical model underlying linkage, and many other fundaments of quantitative genetics, can be found in Lynch and Walsh (1998).

Linkage analysis assigns a numerical probability value (LOD score) to all markers, and a LOD-score profile is obtained for each chromosome. Evidence for linkage is said to be present when the maximal LOD-score exceeds a predefined threshold, which depends on the size of the genome and the number of markers. The chromosomal region surrounding a marker with a significantly high LOD-score will be selected for finemapping, which is essentially a repetition of the same procedure but now with all markers concentrated in the area of interest on a single chromosome. If the region containing the putative gene is sufficiently small, the DNA in the entire region is sequenced in full for a few persons. Comparing all base pairs in the genes in a number of different persons identifies the sites of allelic variation, also-called polymorphisms, within these genes (mutational analysis). If the trait is a disease or disorder, comparison of the polymorphisms between patients and controls without the disease ultimately reveals which allelic variant is responsible for the disease. The entire process from significant LOD scores to the actual allelic variants is usually summarized as "positional cloning." The circa 1500 disease genes now listed in the Online Mendelian Inheritance in Mancatalog have largely been detected by this process.

Nonparametric Linkage

It is uncertain to what extent the genetic mutations leading to brain pathology also explain variation in normal cognition. Most cognitive traits have polygenic determination, i. e., they are influenced by a number of different genes, environmental factors, and their possible interactions. Traits influenced by the developmental interplay of many genes and environmental factors are usually quantitative traits, and each of the genes that influence such quantitative traits is called a polygene. The chromosomal region (or locus) where such a polygene can be found is called a quantitative trait locus (QTL). To detect QTLs for polygenetic traits, full genomic searches use a similar linkage concept as described above, but apply *nonparametric linkage* analysis, such as sib-pair analysis. In sib-pair analysis, several hundred DNA markers are obtained from siblings and (optimally) their parents. By definition, the differences between two siblings for a trait will be smaller if they share the same variant of a QTL for that trait. Linkage of a marker to a QTL implies that the differences in the trait between the siblings will also be smaller if they share the same variant of the

marker, obtained from the same parent—they are identical-by-descent (IBD) for the marker. In a regression procedure originally derived by Haseman and Elston (1972), the evidence that a marker is in linkage with the trait is obtained by regressing the trait difference between siblings on the proportion of marker alleles shared identical-by-descent. A major drawback of this method is that it requires large numbers of sibs to detect significant evidence for linkage: it has very low power to detect QTL with reasonable effect sizes, i. e., that explain 3–5% of variance in a trait.

Allelic Association

A second strategy for genomic searches is the *allelic association* study, which aims to detect linkage disequilibrium. Linkage disequilibrium occurs when a marker allele (which may, but need not, be in a functional gene) and the QTL are so close on the chromosome that they remain linked over many generations of meiotic recombination. Association studies are similar in design to classic case-control studies in epidemiology. DNA is collected from all participants, and the cognitive trait is compared across the various allelic variants of the DNA marker. Vice versa, frequencies of the various allelic variants may be compared in subjects with a particular deviation in cognition, to detect an association between a particular allele and the occurrence of the cognitive deviation. The advantage over sib-pair analysis is that linkage disequilibrium mapping can detect the region of a QTL with only very small effects on the trait. Provided either that the selection of cases does not introduce population stratification or that the analyses properly control for such stratification, it provides a good complement to the linkage strategy. Association works best if the chromosomal region of interest is already known (for instance, by linkage or because there is a candidate gene). Screening the entire genome with association, however, requires huge numbers of markers (linkage requires only a few hundred markers) and is not currently feasible.

Candidate Genes

In some cases, good theoretical reasons exist to focus on *candidate genes*. The ideal candidate gene has been shown to be functional: It influences the concentration of the (iso)form of a protein, its functionality or efficiency, or perhaps most importantly, its responsiveness to environmental factors triggering the expression of the gene. Because neurotransmission is crucial to virtually any behavior, all known genes for receptors, transporters, or synthesis elements for neurotransmitters are usable as candidate genes. The problem with a candidate gene approach to cognition is the huge proportion of human genes involved in constructing, wiring up, and maintaining the nervous system. Even at a conservative estimate of "40% of all genes in the genome are expressed in the brain," thousands of genes can be considered functional candidate genes for cognition.

Several strategies are possible to select an optimal set of candidate genes. First, genes that are part of neurophysiological systems known to influence human memory and cognition from pharmacological or ligand-based brain imaging studies can be tested as candidates. Second, syntenic genes (or chromosomal regions) in animals known to influence performance in tests of animal learning and memory can be tested as candidate genes (or regions) in humans. These strategies cannot, alas, undo a fundamental problem inherent in the candidate gene approach. By looking for candidates among the pathways that we already know to matter we may still overlook the essential genes, precisely because of our large ignorance of the biology of cognition. For this reason, whole genome approaches remain a major strength as long as we can deal with the main factor impeding its detection of polygenes so far: low statistical power.

Boosting the Power of Linkage Analyses with Endophenotypes

To reiterate, the largest problem facing gene hunters is not the sheer number of possible genes that need to be examined (of which, despite the recent completion of the Human Genome Project, the largest part is as yet unidentified), but the relatively small contribution each gene may have to the relevant trait. The contribution of a single polygene to the population variance in most complex behaviors is likely to be very small. Statistical power for the detection of such QTLs remains the major concern to date. In fact, only a single gene (explaining 30% of the variation in fruit size in tomatoes) has been identified using these methods, although it must be assumed that a number of valuable linkage results are still tied up with industry.

To boost power of genomic searches, cognitive neuroscience can critically assist geneticists by yielding endophenotypes of cognition. Endophenotypes are exactly the kind of measures already used by neuroscientists to get closer to the actual biological systems involved in the specific cognitive process, i. e., time-locked electrical brain potentials or localized brain blood flow changes. Genetic influences on cognition are likely to be deter-

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mined by a complex interaction of multiple subcortical and cortical structures, each influenced by its own set of genes. The primary idea behind endophenotypes is that by studying confined aspects of human brain functioning it may be easier to isolate and identify the effects of each of these subsets of genes (Boomsma, Anokhin, & De Geus, 1997). Although these genes may explain only a small part of the entire cognitive task performance, they explain a large part of the variance in the endophenotype itself. As psychologists, with their solid background in methodology are well aware, "explaining a larger part of the variance in a measurable trait" immediately implies that there is more power to detect these genes. In short, the use of endophenotypes to find genes influencing complex behaviors fully obeys Caesar's adage of "divide et impera."

Behavioral and Biological Endophenotypes

A first obvious strategy—obtaining statistical linkage between genes and the "g" factor of cognition as summarized in the various "paper-and-pencil tests" of psychometric IQ (e. g., WAIS-III, RAVEN)—completely bypasses the neurophysiological pathways from genes to actual cognitive function. A divide-and-conquer strategy would introduce at least two additional levels in this "black box" between gene and cognition. In addition to psychometric IQ tests, many neuropsychological and cognitive function tests are available in psychology that test specific cognitive abilities. Table 1 lists only a fraction of the tests and task paradigms in use. All these tests assess the response speed and the response accuracy in order to evaluate the targeted cognitive operation.

Brain structure and function form a second source of endophenotypes for cognition. The advances in the neurosciences have provided a variety of techniques for the detailed assessment of brain function and structure, including neurophysiological techniques like EEG/ERP and hemodynamic neuroimaging methods like functional MRI-scans (fMRI). EEG depicts the spontaneous electrical activity of synchronously active populations of neurons in the cerebral cortex and is recorded from electrodes placed onto the scalp. Event-related potentials (ERPs) are changes in the amplitude or topography of the EEG in response to the occurrence of a specific event, which may be external (e. g., stimulus)

Table 1
Behavioral endophenotypes of cognition.

Type	Tasks/Paradigm	Cognitive function measured
Executive function	Tower of Hanoi	Planning & reasoning
	Wisconsin Card Sorting Task	Perseveration
Inhibitory control	Eriksen flanker task	Distractor repression
	Stop signal paradigm	Motor inhibition
	Stroop Color Word Test	Interference
	Anti-saccade task	Top-down repression of automated processing
Attention	Spatial cueing paradigm	Automatic vs. voluntary attentional orienting
Perception	Inspection Time (IT) task	Perceptual speed
	Posner letter matching	Physical vs. phonetic vs. category representation
	Conjunction vs. pop-out searches	Parallel vs. serial visual search
Working memory	N-backwards task	Executive (attentional) control
	Word or digit span tasks (e. g., Sternberg task)	Phonological loop
	Delayed match to sample test	Visuospatial sketchpad
Long-term memory	Item list learning	Explicit memory & primacy and recency effects
	Word-priming task	Implicit memory
Language	Dichotic listening	Lateralization
	Semantic priming	Lexical decision task
	Semantic interference	Word picture task

Table 2
Electrophysiological endophenotypes of cognition.

Type	"Component"	Tasks/Paradigm	Cognitive function measured
Executive function	ERN	Go-NoGo tasks	Error processing
	N200	Eriksen Flanker task	Inhibitory control
Attention	N100	Dichotic listening tasks	Auditory attention
	P100	Spatial-selective visual attention tests	Visual attention
Perceptual speed	VEP latency	Checkerboard reversal	Nerve conduction velocity
	N200 latency	Odd-ball task	Feature discrimination
	P300 latency	Odd-ball task	Cognitive slowing
Working memory	MMN	Odd-ball task	Sensory (echoic) memory
	P300	N-back task	Attentional focusing during working memory
	SW	Delayed response task	Working memory load
	EEG coherence	Delayed response task	Fronto-parietal connectivity during rehearsal
Long term memory	ERD	Item list learning	Memory encoding
	"old-new" 600	Old vs. new words	Recognition memory
Motor	CNV	Forewarned RT task	Motor preparation
	LRP	Eriksen Flanker task	Response selection
Language	N400	Word congruence tests	Semantic processing
	SPS	Correct/incorrect syntax	Syntactic processing

Abbreviations: ERN = error related negativity, VEP = visual evoked potential, MMN = mismatch negativity, SW = slow wave, ERD = event related desynchronization, CNV = contingent negative variation, LRP = lateralized readiness potential, SPS = syntactic positive shift.

or internal (e.g., the subject's movement). Since the event-related changes in electric brain activity are small, they can be extracted from the background activity only by time-locked averaging of EEG fragments across many repeated trials. Hemodynamic methods measure neural activity indirectly by relying on its coupling to regional changes in cerebral blood flow (rCBF) or blood oxygenation level (BOLD fMRI). fMRI, currently the dominant method, can localize brain activity to a spatial resolution of a few millimeters. To perform this same feat, EEG measurements would need a dense set of electrodes and parallel magnetic field recording (MEG) —and would still be able to localize only cortical, not subcortical, sources. fMRI, on the other hand, does not come near the high temporal resolution of ERPs. Thus, EEG and fMRI are widely perceived to be complementary.

Genetic research, however, imposes specific requirements on electrophysiological and neuroimaging methods, the most important being reliability, noninvasiveness, and the availability for the study of large samples (the full set of criteria defining a useful endophenotype are given below). The major method of investigating brain function that meets these criteria is through event-related brain potentials (ERPs), which are often classified into two broad categories of exogenous and endogenous components. Early exogenous components (auditory, visual, and somatosensory evoked potentials, N100, P200) are used, among others, to study the projection pathways to primary sensory cortices, selective attention, early object recognition, and processing perceptual mismatch. Later endogenous components (P300, N400, SPS, SW, ERN, CNV, LRP, see Table 2) are used to tackle many higher-order cognitive operations like working memory, uttering semantically and syntactically correct language, memory rehearsal, error processing, inhibitory executive control, or preparing for action (Fabiani, Gratton, & Coles, 2000; Rugg & Coles, 1995). In addition, event-related changes in EEG power—not necessarily phase locked to a stimulus—also appear to index specific aspects of human information processing. Indices of "event-relat-

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ed (de)synchronization (ERS/ERD)" in different frequency bands have been shown to be differentially sensitive to attention, working memory and long-term memory storage. An overview of some often used ERP/EEG measures is presented in Table 2.

What Constitutes a Good Endophenotype?

Tables 1 and 2 present only a small part of the endophenotypes available, with new additions flowing from the booming field of neuroscience almost monthly. Which criteria do we have to select the optimal endophenotypes from such a sea of possibilities? To hold promise in the hunt for genes affecting cognitive ability, endophenotypes must meet the following criteria:

1. They must be reliable traits (reliability).
2. They must show evidence of genetic influences (heritability).
3. They must be associated with the cognitive trait of interest (phenotypic correlation).
4. The association between endophenotype and cognition must derive partly from the same genetic source (genetic correlation).

To elucidate the biological pathways from the genes to cognition, ideally a fifth criteria also applies:

5. The association between endophenotype and cognition must be theoretical meaningful (causality).

The first two criteria are necessary because all genetic approaches are based on interindividual variance, which must be stable and genetic in origin. The latter three criteria simply aim at selecting an endophenotype—or indexes—that is a functional or structural trait truly "intermediate" between genes and cognition such that genes cause variance in the trait and the trait causes variance in the cognitive operation of interest. The theoretical sensibility of criterion 5 is most difficult to establish with certainty. Although it is quite reasonable to suggest that appropriate attention or high working memory capacity cause good task performance, good task performance itself may improve attention or allow the more efficient use of working memory. Furthermore, attention and working memory are latent theoretical constructs that are indexed by, but do not overlap with, the ERP/fMRI and behavioral indices used to probe them. Only a fundamental theory of brain and behavior can be used to guide genetic neuroscience here.

Learning About Cognition with the Help of Genes

Animal Experimentation

Having made a case for the usefulness of neuroscience in gene finding, we now turn to a second thesis of this paper: that cognitive neuroscience will be the first and foremost beneficiary of gene finding. This is not really a daunting task, in view of the huge contingent of "animal" researchers in the neuroscience community. They already use (neuro)genetics as one of their primary tools to understand the basic functional anatomy of brain cells and, consequently, their role in animal cognitive performance. Neurogenetics has its own bottom-up approach to finding genes that is in many ways a mirror image of the top-down association and linkage approach for human genes outlined above. Rather than searching for the genes that go together with certain behaviors, the neurogenetics approach searches for the behavior that goes with certain genes. In a process called mutagenesis, random mutations are created chemically or through X-irradiation in a number of organisms including bacteria *(Escherichia coli)*, round worms *(Caenorhabditis elegans)*, zebrafish *(Brachydanio rerio)*, frogs *(Xenopus)*, the fruit fly *(Drosophila melanogaster)*, and mice. Random mutagenesis kills many, but (because many are available) many also stay alive with selective changes in basic behavioral functions. The mutated genes are then concluded to be of relevance for those behaviors that are affected. Using this approach, more than a dozen genes have been identified that disrupt memory, with specific mutations blocking specific phases of memory (Dubnau & Tully, 2001).

One of the first ways to learn about cognition with the help of genes identified by linkage and association in humans is to compare them to—or even equate them with—the genes already found in these simple organisms. Their behaviors—slithering away from cold or flying toward the smell of rotting apple, may not be the type of behaviors that enchant most scholars of human behavior. Some of the genes for the rudimentary behaviors in these organisms, however, may prove to code for a more complex but still recognizable variant of that behavior in humans. Memory genes provide good evidence for evolutionary conservation of neuronal organization across species. In the sea hare *(California aplysia)* activation of ApCREB1 and inactivation of ApCREB2 are crucial events in the creation of memory traces. Very similar CREB gene families with very similar functions are involved in mouse and human memory pathways,

too (Flint, 1999; Mayford & Kandel, 1999). Many other genes identified in humans will have such meaningful animal homologs. Meaningful homology here means that there is synteny at the location of the gene between the human and animal chromosome, that there is large overlap in gene structure and protein product, and that the gene serves more or less the same function. Such homolog genes can be tested and manipulated by a number of powerful recent techniques described below that, although devised for genes found in animals, can also be put to work for genes found in humans.

Anatomy of Pathways

Anatomy always has been, and remains to date, a powerful approach to further our understanding of human physiology. The huge current investments in brain imaging capacity reflect a widespread belief in the explanatory power of functional anatomy. Once a gene has been identified, the first obvious question is therefore where that gene is expressed in the brain. To detect such locations, the basic strategy is to dissect animal brains into specific regions and to extract mRNA samples from each of these regions. The nucleotide coding of the pooled mRNA from each region is than tested against the nucleotide coding of the newly identified gene to see if a match occurs (hybridization). If so, that gene was expressed in the region that provided the mRNA sample. Using this hybridization technique, it was shown, for example, that a pair-association task selectively increased the expression of brain-derived neurotrophic factor (BDNF) in a specific area of the brain (area 36 of the inferotemporal cortex) in primates (Tokuyama, Okuno, Hashimoto, Xin Li, & Miyashita, 2000). Since BDNF is involved in activity-dependent changes in synaptic connections, such a mRNA expression pattern supports the hypothesis that visual long-term memory of objects is maintained in the visual association cortex.

Protein Function

By far the most important step after gene finding is to characterize the form and function of the protein(s) coded for by the gene. A powerful way to do this is by understanding the protein's interactions with other proteins (proteomics) by using expression micro-arrays or "gene-chips." With expression micro-arrays, the mRNA of the nervous tissues is obtained in a comparable manner as described above, but now the aim is to examine covariance patterns in gene expression under a variety of experimental conditions (Watson & Akil, 1999). The basic strategy is to collect mRNA from various brain regions in animals subjected to a control or an experimental condition. For instance, animals reared in an enriched and animals reared in an impoverished environment could be sacrificed, the brains dissected into specific regions and mRNA extracted from, say, the hippocampus, the basal ganglia, the visual cortex, and the frontal cortex. Now the pooled mRNA from these regions, with a unique fluorescent label for controls and experimental animals, is simultaneously tested against many DNA fragments that have been put onto a single micro-array. To assess which genes are expressed together, i. e., which are activated in the same region by the same difference in experimental conditions, the fluorescence of each gene on the micro-array or chip is tested. The unique fluorescent label for control and experimental animals now indicates which genes are selectively activated by the experimental manipulation. Because thousands of genes can be put on a single array, an automated laser microscopic system is usually needed, as is software for intelligent analysis and interpretation of the large amount of signals. When molecular biologists sigh that they are in need of good biostatisticians—and they do so often nowadays—it is not just multivariate association and linkage analysis or nucleotide sequence comparisons they have in mind, but also the clever analysis of these micro-array data.

Micro-arrays are a complex but extremely powerful tool and will facilitate the precise determination of when and where new proteins are called upon in the brain. This can be used, as in the example above, to detect effects of impoverished or enriched environments on an inbred (genetically homogeneous) strain, but it can also be used in cross-strain comparisons. For instance, employing gene chip technology the activities of approximately 13,000 genes were compared in two inbred strains of mice, C57BL/6 and 129SvEv, that show marked difference in the recovery from drug-induced epileptic seizures (Sandberg et al., 2000). The sensitive 129SvEvs experience extensive cell death in the hippocampus. The more robust C57BL/6s show little cell death. Across six distinct regions of the brain, 73 genes of the more than 13,000 genes canvassed were found to vary between the two strains in one or more brain areas. Almost 50 of these genes were turned on in the temporal lobe of the resistant strain versus only a dozen in the sensitive strain, confirming the well-known role of this part of the brain in epilepsy.

Genetic Engineering

Genetic engineering provides a third route to uncovering gene action other than through protein function or

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the anatomical distribution of the gene's expression. The first knock-outs of cognition genes in mice were the destruction of the alpha-CaMKII and tyrosine kinase *fyn* genes (Mayford & Kandel, 1999), which code for kinases involved in long-term potentiation (LTP). LTP was first observed in the hippocampus and conventionally elicited by a 25–100 Hz electrical stimulus for 1–1.5 s to hippocampal neurons that increase the strength of their synaptic connections with neurons further on in the hippocampal pathway. Such activity-dependent changes in synaptic strength were thought the most likely mechanism to explain associative learning in any organism. Indeed, the CaMKII knock-out mice did not just show signs of impaired LTP, but also failed to find their way in mazes, including the famous (among rodents) Morris milk maze. The use of CaMKII knock-out mice came about after a 30-year-long neurophysiological struggle with the about 20,000 neurons of the sea snail *Aplysia california*. One main promise of genetic neuroscience is to speed up such research programs substantially.

The most well-known forms of LTP involve the *N*-methyl-*D*-aspartate (NMDA) receptor for glutamate. The NMDA receptor was the site of a recent major advance in genetic engineering. Traditional knockouts like the CaMKII knock-out mouse are constitutive, i.e., they lack the gene in every cell and tissue and do so from conception onward. This means in practice that one cannot study the effects of genes that, on the one hand, affect complex traits, but that are also essential for normal development. Such knockouts simply die at or before birth. These problems are neatly circumvented in conditional, or regionally restricted, knockouts. Conditional knockout mice were made to lack a subunit of the NMDA-receptor only in a specific section of their hippocampus, termed the CA1 region, and nowhere else in the body (Tsien, 2000). Because of the importance of the hippocampus for memory formation, these mice lacked an essential "memory" gene. As expected, these animals not only demonstrated decreased LTP, but also poor spatial and nonspatial memory (Rampon et al., 2000). Interestingly, this was true only when raised under normal laboratory conditions. When they are exposed to an enriched environment each day for an extended period, they improve markedly and did as well as normal mice in various tasks. This behavioral enhancement is reflected anatomically: The number of connections between hippocampal cells was actually increased. Hence, in these mice the enriched environment "repaired" a genetically engineered memory defect.

Genetic engineering can be used not only to knock out genes, but also to insert extra copies of a gene (transgenic animals). One of the more convincing behavioral examples comes from the same laboratory that developed the conditional NMDA subunit knock-outs. Instead of inactivating a gene, they inserted an extra copy of another "memory" gene. This gene codes for an NMDA subunit called NR2B, which is more strongly expressed in young mice and stays open longer than the NR2A, which is more strongly expressed in older mice. This age-dependent expression of the different subunits might explain the age-related differences in learning and memory. Indeed, transgenic mice that had an extra copy of the gene for this receptor learned better in certain tasks than normal mice, and the older transgenic mice did as well as the younger ones (Tsien, 2000).

Another important addition to the genetic engineer's toolbox is the combination of gene deletion with the subsequent gene replacement to demonstrate reacquisition of function. After deletion of a gene that influenced a protein involved in the detection threshold of olfactory neurons, mice could not smell an odor unless it was presented in 50-fold concentrations (Ivic et al., 2000). An adenoviral vector was then used to reintroduce the deleted olfactory marker protein (OMP) gene. The mice demonstrated full restoration of the functionality of olfactory receptors neurons and their sense of smell. Thus, genetic engineering techniques have come full circle.

Human Experimentation

Knowledge of anatomical distribution and function of brain proteins and the development of both knockout and transgenic animals has already deepened our knowledge of the neuron and its signaling to other neurons. Nonetheless, many human cognition genes may have no clear animal homologs and yet prove to be of paramount importance to human cognition, specifically individual differences in cognition. These genes are likely to be found only through association/linkage studies in humans. To understand these genes at a functional level, all (animal) techniques outlined above may still work. In some genes, however, regulation and transcription may be very specific to human cells, and they may have developed a specific function in human cognition which they did not yet have in lower organisms. To understand the pathways by which such genes influence human cognition, the effects of natural variation in these genes must be tested in experimentation performed in human subjects. Such experiments are in everything identical to the usual experiments done in the psychological laboratory, save that subjects are now either

selected for a particular genotype or more broadly their genotype is one of the measured independent variables.

Genotype by Environment Testing

Genotype by environment studies will probably shape the best part of genetic neuroscience in the coming decade. "Environment" can be read in three ways: experimental condition (task structure, task demands), intervention/therapy, or the person's living environment in the classical sense (family, peers, work). In genotype by experimental condition studies, the interaction is tested between a genotype and task performance/brain activity under different experimental conditions. The idea is that the individual differences related to the genotype appear only under certain conditions, for instance, when memory systems are engaged, when attentional load is high, when subjects are fatigued, when distractors are present, etc. Genotype by condition testing can be used to test many exciting questions on individual differences in cognitive ability. Even purist scholars of universal processes, who consider individual differences entirely as a nuisance variable, might be helped by stratifying their subjects by genotype. By reducing the error variance they might find subtle task effects with more ease.

Genotype by condition experiments have already been performed for the best known example of allelic association in human cognition—that between the apolipoprotein ε4 allele and Alzheimer disease risk. Subjects with "early-onset sporadic," "late-onset familial," and "late-onset sporadic" Alzheimer disease have a substantially higher percentage of apolipoprotein ε4 alleles (40%) compared to healthy controls (15%). Results from brain imaging studies have shown a prominent volume loss of the hippocampus and amygdala in AD patients with two ε4 alleles as compared to AD patients with genotypes ε3/ε4, ε3/ε3, ε3/ε2. Most importantly, genotype by task interaction showed that unaffected subjects who had at least one ε4 allele, had selective impairment in memory related tasks, but not in other cognitive abilities (Feskens et al., 1994; O'Hara et al., 1998).

Reading Disorder

Dyslexia has been known to be heritable for a long time, and biological explanations include defects in the magnocellular pathway in early visual processing and disconnection syndromes within the left hemisphere. The best replicated linkage results on a typical human cognitive trait is the linkage on the short arm of chromosome 6 for developmental dyslexia (Grigorenko, 2001). A striking aspect of this linkage success is that it depends largely on the use of endophenotypes for dyslexia. The usual measure of dyslexia is the discrepancy between a composite reading performance score and the IQ. Linkage was not found on such global measures, but rather on specific dyslexia-related cognitive processes like phonemic awareness (of spoken words), phonological decoding (of printed nonwords), rapid automatized naming (of colored squares or object drawings), single-word reading (orally, of printed real words), vocabulary, and spelling (of dictated words).

As soon as these robust linkage results lead to the actual genes, two potential gene-by-environment experiments can be performed. First, dyslexia is one of the many common disorders suggested to be the quantitative extreme of the distribution of brain functions underlying cognitive ability—in this case reading ability—in the population at large. When the actual genes are available, their effects in unaffected subjects who do carry some (or all) of the risk alleles, but are not dyslectic, can be tested. Also, subjects with very high reading abilities can be tested for their genotype at the reading disability genes to critically test whether or not some "good" alleles of these genes actually contribute to reading ability.

A second experiment, involving a much broader view on environment, is suggested by the well-known but poorly understood finding that the prevalence of dyslexia sharply differs across languages. Word recognition accuracy, for instance, is twice as bad in dyslectics in the United States and France as it is in Italy. Do the Italians have different dyslexia genes? A controlled cross-cultural comparison of brain activation clearly showed that dyslexia in these countries has an identical biological basis (Paulesu et al., 2001). In comparison to English or French, however, Italian maps all letters of the alphabet unambiguously to speech sounds. Italian orthography is less deep. Do the dyslexia genotypes interact with the depth of the orthography? In that case the higher incidence of dyslexia in French or English speakers would constitute a true genotype by environment interaction.

Development

Perhaps the most powerful experiment allowed by gene discovery is a test of the interplay of a gene and "its" environment in the developing organism. Although there is a huge impact of early brain development on later cognitive function, heritability of IQ scores gradually increases from childhood to young adulthood. This suggests that the effect of some genes on adult IQ may not show in childhood, or that the effect of some genes

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increases with aging (genetic amplification). The two current longitudinal studies on changes in genetic architecture of IQ are undecided whether the increase in heritability of IQ is due to new genetic factors or to genetic amplification (Boomsma & van Baal, 1998; Cherny & Cardon, 1994) let alone what environmental factors could influence either. When actual genotypes can be measured, the differential impact of factors like SES, child exercise behavior or its educational system can be assessed over time. Ideally, such longitudinal studies will reveal the full pattern of age-dependent and/or environment triggered gene-expression.

An Example: Collaboration of the Dutch, Australian, and Japanese Twin Registries

In summary: A promising strategy for gene finding in humans is to collect endophenotypes of cognition in large-scale family samples across different populations. In these samples, linkage analyses, sequence-maps based discovery, and candidate gene approaches must be freely alternated—and when appropriate combined. Once genes have been found, rapid progress in animal engineering and protein/gene databases can be used as a first attempt to understand their exact role in cognition. Furthermore, genotype by environment research in selected genotypes can be used to refine our understanding of what types of tasks are affected under what conditions. A final unmentioned strategy arises out of the endophenotypes themselves that—if well-chosen—they can yield crucial information on the pathway from gene to actual cognition.

To implement this double strategy of gene finding followed by gene usage, the Dutch, Australian, and Japanese Twin Registries currently run a collaborative study with a common protocol that targets genes underlying individual differences in cognitive ability (Wright et al., 2001). In this effort, endophenotypes of cognition were measured in 2129 participants, including 378 MZ males, 540 MZ females, 208 DZ males, 312 DZ females, 368 DZ opposite-sex twin pairs, and 290 singleton siblings of twins. Apart from extensive psychometric IQ testing, behavioral and electrophysiological indices from two major domains were measured in all participants: speed of information processing and working memory capacity. Speed of information processing is the speed with which one can perform basic cognitive operations. Reaction time (RT) has been the most studied behavioral correlate of processing speed, but encompasses a number of serial and parallel cognitive processes that lead up to the final motor response. We aimed at measuring these processes by separate indices. First, inspection time (IT) was used as an index of early perceptual speed or visual search/scanning speed. This simple measure has long been known to be a powerful predictor of IQ and the IQ-IT relation was fully replicated in the large Dutch and Australian twin samples (–0.28 and –0.37 respectively). Second, the latencies of the N100, P300, LRP event-related potentials were used to probe higher-order processing speed of the engagement of attention, working memory and decisional processes.

Working memory refers to the limited capacity system that integrates incoming information, storing it temporarily for decision-making, judgment, and response, and allowing us to attend to events, maintain them, integrate them with past experience, and monitor our actions. Baddeley and Hitch (in Baddeley, 1986) propose a model with a frontal lobe executive that selects the main processing goals, selectively focuses sensory attention, plans the overall strategy, and, most importantly, controls two slave systems responsible for the encoding and temporary storage of either visual material (the visuospatial sketchpad), or verbal material (the phonological loop). Much evidence suggest that (the frontal executive of) working memory overlaps with general intelligence or "*g*." In order to probe the phonological loop of working memory, we use performance measures (accuracy and reaction time) during a reading span and a digit span task. Operation of the spatiovisual sketchpad is examined by the EEG slow wave during the delay interval of a spatiovisual delayed response task. In addition, cortico-cortical connectivity of frontal regions to the parietal cortices (spatiovisual processing) are examined by task-related shifts in EEG power and coherence.

Endophenotypes at Multiple Levels

The first combined analyses of the behavioral and electrophysiological measures of speed of information processing, working memory task performance, and IQ show evidence of significant genetic covariation between these elementary and more complex measures of cognition (Wright et al., 2001). This covariation could derive from two different sources. Genes coding for basic structural aspects of neural wiring like myelin-sheathing, number of ion-channels, efficiency of synaptic transmission, etc.—through their effect on processing speed—could affect working memory capacity. Working memory capacity, in turn, would influence virtually all

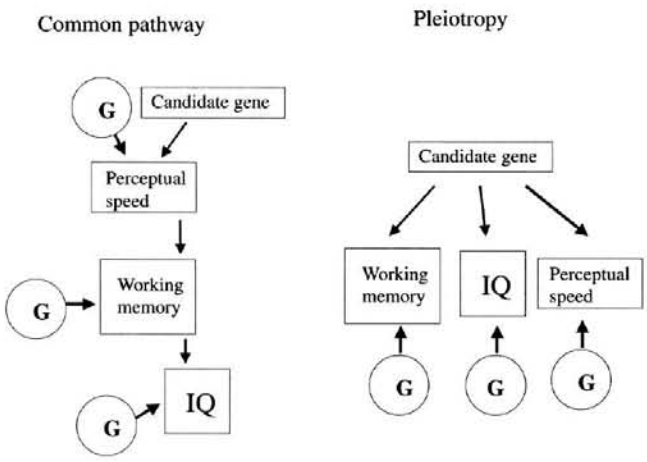

Figure 1
Simple example of two of the multivariate models that can be tested for a candidate gene. The principal tool for data analysis is structural equation modeling (SEM) as implemented, for instance, in the Mx program (Neale, 1997). SEM enables maximum likelihood analysis of raw observations, in which models for expected values can be written in terms of measured covariates such as age and sex, but also measured genotypes, so that genotypic associations are given their correct significance allowing for covariates and the relatedness between twin subjects. Existing quantitative genetic models that have been developed to address the comorbidity/correlation between measures can be extended to include effects of measured genotypes (the candidate genes). Pathways are modeled as in the left panel of the figure, in which the effect of a gene on IQ is through a more basic measure such as perceptual speed. This pathway is tested against the alternative model of pleiotropy, in which the candidate gene has direct effects on perceptual speed and IQ, but where perceptual speed and IQ need not correlate through effects of this particular candidate gene. Background genetic influences (G) are modeled throughout by using the known difference in the amount of shared genes of MZ (1) and DZ (0.5) twins.

attentional cognitive processing, including (sub)tests of intelligence. Alternatively, the covariation could point to the existence of pleiotropic genes, i. e., genes that affect cognition independently at multiple levels, for instance, genes (growth factors) that influence general brain development. Explicitly modeling the multivariate genetic covariance of speed and working memory measures allow for a direct test of whether the candidate genes show pleiotropic effects on multiple systems, or whether gene effects over elementary processes affect "downstream" cognition. This illustrates the large advantage of endophenotypes at multiple levels—going from inspection time and early ERPs through late ERPs, task-related EEG (de)synchronization, and reaction times all the way up to actual spatial and verbal memory performance and full psychometric IQ. It ensures that we can explore its functional cause, once an association of candidate genes with complex abilities has been demonstrated.

Figure 1 demonstrates, in very simplified form, how the analysis of the pathways between genes and cognition can be examined simultaneously at the molecular biological level, the neuroscience level of the brain, and the psychological level of cognitive performance itself. Existing quantitative genetic models developed to address the correlation between multiple measures can be extended to include effects of measured genotypes (the candidate genes). Pathways can then be modeled as in the left panel of Figure 1, where the effect of a gene on IQ is through a more basic measure such as perceptual speed. This pathway is tested against the alternative model of pleiotropy, where the candidate gene has direct effects on perceptual speed and IQ, but where perceptual speed and IQ need not correlate through effects of this particular candidate gene (right panel of Figure 1). The great strength of analyzing random *twin* samples is that we can obtain a direct estimate of the population variance accounted for by each candidate gene *and* an estimate of the polygenic background variance remaining because of unidentified genes ("G"). In other words, (twin) family studies can model both observed and unobserved genes.

Concluding Remarks

The genetic neuroscience approach is essentially a reductionistic approach. All valid arguments against a reductionistic approach must be kept in mind and apply fully here. Also, there are great complexities in actual gene finding and the understanding of the phenotype from the genotype both of which have been portrayed here far more optimistically than the true state of affairs. Finally, our newly found genetic knowledge, alongside its well-rehearsed benefits for future health care, may also bring ethical dilemma's. We have, throughout, deliberately sidestepped these important issues. This is not because we fail to see them or to take them seriously, but because we choose to focus on the positive. Genetic neuroscience simply has too many opportunities not to get excited. Here is that much needed tool to further our understanding of the exact cell assemblies in which complex cognitive operations must ultimately take

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place. The first crucial mission is to intensify the collaboration between cognitive neuroscientists and behavioral geneticists. The discipline of psychology seems an obvious meeting place.

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