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Editorial

Genetics of Brain Function and Cognition

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There is overwhelming evidence for the existence of substantial genetic influences on individual differences in general and specific cognitive abilities, especially in adults. The actual localization and identification of genes underlying variation in cognitive abilities and intelligence has only just started, however. Successes are currently limited to neurological mutations with rather severe cognitive effects. The current approaches to trace genes responsible for variation in the normal ranges of cognitive ability consist of large scale linkage and association studies. These are hampered by the usual problems of low statistical power to detect quantitative trait loci (QTLs) of small effect. One strategy to boost the power of genomic searches is to employ endophenotypes of cognition derived from the booming field of cognitive neuroscience.

This special issue of *Behavior Genetics* reports on one of the first genome-wide association studies for general IQ. A second paper summarizes candidate genes for cognition, based on animal studies. A series of papers then introduces two additional levels of analysis in the "black box" between genes and cognitive ability: (1) behavioral measures of information-processing speed (inspection time, reaction time, rapid naming) and working memory capacity (performance on on single or dual tasks of verbal and spatio-visual working memory), and (2) electrophyiosological derived measures of brain function (e.g., event-related potentials). The obvious way to assess the reliability and validity of these endophenotypes and their usefulness in the search for cognitive ability genes is through the examination of their genetic architecture in twin family studies. Papers in this special issue show that much of the association between intelligence and speed-of-information processing/brain function is due to a common gene or set of genes, and thereby demonstrate the usefulness of considering these measures in gene-hunting studies for IQ.

KEY WORDS: Genetics; twin studies; endophenotypes; processing speed; working memory; cognition.

If there is any truth in the allegation that behavior geneticists like behaviors best when they show high heritability, then surely filling out an IQ test is the human behavior that makes us most happy. Extensive research based on twin, family, and adoption data has documented that more than half of the striking individual differences in adult IQ test performance are due to genetic factors (Bouchard and McGue, 1981; Boomsma, 1993; Devlin *et al.*, 1997; McClearn *et al.*, 1997; Plomin, 1999; Wright *et al.*, 2001). This finding applies across many countries and across the entire adult age range.

In spite of the overwhelming evidence for the existence of "genes of cognitive ability," actual identification of such genes is limited to neurological mutations with rather severe cognitive effects (e.g., Pick's disease, X-linked mental retardation, Huntington's disease) as reviewed by Flint (1999). Like the many rare diseases and disorders listed in Online Mendelian Inheritance in Man (OMIM) (McKusick, 1998) these genetic defects of cognition are largely Mendelian in nature. True polygenes (or QTLs) that influence the normal range of cognitive ability have

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yet to be identified. In this special issue of *Behavior Genetics,* Plomin and co-workers report on their efforts to detect such polygenes of cognitive ability through association analysis in what are probably the world's most valuable samples of children selected for extremely high cognitive ability (*g*) as compared to average *g.* In a very stringent cascade of five replication stages, designed to reduce the false associations that notoriously haunt such an enterprise, pooled DNA of the high and average *g* participants was tested for group differences in the allele frequencies of simple sequence repeat (SSR) markers approximately evenly spaced at 2 cM throughout the genome. No markers survived the allele-specific directional test for all five stages, providing empirical support for the claim that a systematic genome scan for allelic association needs tens or hundreds of thousands of markers to detect polygenes for a complex trait (Kruglyak, 1999).

One solution to this problem, also advocated by Plomin *et al.* as their next step, is to choose markers in functional candidate genes, e.g., genes suspected to influence neurotransmission in the brain because they code for protein constituents of receptors, transporters, or enzymes involved in neurotransmitter synthesis and degradation. Ideally, the candidate gene has already been shown to be functional: It influences the concentration of the (iso)form of such a protein, its functionality or efficiency or, perhaps most important, its responsiveness to environmental factors triggering the expression of the gene (in terms of markers for allelic association this means cSNPs and SNPs in regulatory regions). The problem with a candidate gene approach to cognitive ability, however, is that a huge proportion of human genes may be 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 could be considered functional candidate genes. For the benefit of this special issue, Morley and Montgomery undertook an extensive search of the scientific literature to identify over 150 candidate genes (and chromosomal regions) which have already been found to influence some aspect of cognition in humans, or of learning and memory in mice or *Drosophila.* Despite millions of years of separation in evolution, the structural and functional homologies between human and mouse genomes are striking, and biological pathways are often highly conserved (Strachan and Read, 1999). A rational first choice for human candidate genes of cognition would be syntenic genes in mice. The promising animal model strategy 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, exactly because of our ignorance of the biology of cognition. Also, not all human genes need have clear animal homologs but may still prove to be of paramount importance to human cognition. For this reason, whole genome linkage approaches are attractive as long as we can deal with the main factor impeding its detection of polygenes so far—low statistical power. The remaining papers in this special issue largely deal with a strategy to boost power of genomic searches by employing endophenotypes of cognition derived from that other booming field—cognitive neuroscience.

The current approach to hunt cognitive ability genes—association/linkage studies using paper and pencil tests of psychometric IQ—completely bypasses the neurophysiological pathways from genes to actual cognitive function. However, genetic influences on cognitive ability are likely to be determined by a complex interaction of multiple subcortical and cortical structures, each influenced in part by its own set of genes. The primary idea behind endophenotypes is that studying confined aspects of human brain functioning may be a more powerful way to localize and identify each of these subsets of genes (Almasy and Blangero 2001; Boomsma *et al.,* 1997; de Geus and Boomsma, 2001; Lander, 1988; Leboyer *et al.,* 1998). Although each of these genes may explain only a small part of the variance in cognitive ability, they will explain a large part of the variance in the endophenotype itself. This boosts the statistical power to localize these genes in genomic searches. Localizing and identifying the genes of cognitive ability one by one, by means of a number of endophenotypes covering specific cognitive operations, should go a long way toward yielding the complete set. In short, the use of endophenotypes to find genes influencing a complex trait fully obeys Caesar's adage of "divide et impera."

At least two additional levels can be introduced in the "black box" between genes and cognitive ability. In addition to tests of general cognitive ability, a rich set of neuropsychological and cognitive function tests are available in psychology that test specific cognitive abilities. Examples in the papers of this special issue are various measures of information processing speed (inspection time, reaction time, rapid naming) and working memory capacity (performance on single and dual task verbal and spatiovisual short term memory tasks). Direct measures of brain structure and function

form a second source of endophenotypes for cognitive ability. The advances in the neurosciences have provided a variety of techniques for the detailed assessment of brain function and structure, including neurophysiological techniques like electroencephalographic (EEG) recordings and haemodynamic neuroimaging methods like functional magnetic resonance imaging scans (fMRI). Genetic research imposes specific requirements on these methods, the most important of which are reliability, stability, noninvasiveness, and availability for the study of large samples. To date, the major method of investigating brain function that meets these criteria is through event-related brain potentials (ERP) derived from the EEG.

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) or internal (e.g., the subject's movement). Because 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. In genetic designs, these many trials are quite advantageous, because they can be used to model measurement error and optimize estimates of genetic and (true) environmental variance (van Baal *et al.*, 1998). ERPs are often classified into two broad categories of exogenous and endogenous components (Fabiani *et al.*, 2000). Early exogenous components (auditory, visual, somatosensory EPs, N100, P200) are used, among others, to study the projection pathways to primary sensory cortices, selective attention (Mangun *et al.*, 1998), early object recognition (Sergent *et al.*, 1992), and processing perceptual mismatch (Näätänen and Alho, 1995). Later endogenous components are used to tackle many higher order cognitive operations like working memory (Donchin and Coles, 1988; Polich and Kok, 1995), uttering semantically and syntactically correct language (Hagoort and Brown, 2000; Kutas and Iragui, 1998), memory rehearsal (Geffen *et al.*, 1997; Ruchkin *et al.*, 1995), error processing (Scheffers *et al.*, 1996), inhibitory executive control (Kopp *et al.*, 1996), or preparing for action (Van Boxtel and Brunia, 1994). Examples in this special issue are the P300, by far the most researched ERP, that arises in response to non-frequent task relevant trials mixed with frequent task irrelevant trials; and the SW, a slow negative potential that can discriminate working memory engagement from simple sensory perception.

The various electrophysiological and behavioral measures reported on in this special issue represent only a very small part of the endophenotypes available, with new additions flowing from the booming field of neuroscience on a regular basis. Which criteria do we have to select the optimal endophenotypes from this abundance? To hold promise in the hunt for genes affecting cognitive ability, we propose that endophenotypes must meet the following criteria:

1. Endophenotypes must be reliable and stable traits (reliability and stability).
2. Endophenotypes must show evidence of genetic influences (heritability).
3. Endophenotypes 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 criterion also applies:

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

The first two criteria are necessary because all genetic approaches are based on interindividual variance, that must be stable and genetic in origin. The latter three criteria of validity simply aim to select an endophenotype that is—or indexes—a functional or structural trait truly intermediate between genes and cognition such that genes cause variance in the endophenotype and the endophenotype causes variance in the cognitive operation of interest. The theoretical sensibility of the fifth criterion is most difficult to establish with certainty. Although it is quite reasonable to suggest that appropriate attention or high working memory capacity cause good performance during intelligence testing, such good performance may itself improve attention or allow 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 understanding of brain and behavior can be used to guide "genetic neuroscience" here.

The obvious way to explore potential endophenotypes with respect to the above criteria is through examination of their genetic architecture in twin family studies. The bulk of papers in this special issue has aimed to do just that. First, the substantial genetic contribution to P300 amplitude was confirmed in large groups of Dutch and Australian adolescent twin pairs (Van Beijsterveldt *et al.*, this issue; Wright *et al.*, this

issue). Heritability of the P300 had been established previously, and it is one of the first endophenotypes to be used in actual genomic searches (Almasy *et al.*, 2001; Begleiter *et al.*, 1998; Noble *et al.*, 1994; Williams *et al.*, 1999), usually in the context of disturbed cognition as part of a genetic susceptibility for alcohol dependence. Results presented in this issue show, however, that the genetic architecture of the P300 amplitude is more complex than currently appreciated. First, results of van Beijsterveldt *et al.* (this issue) suggest that during adolescence genetic influences on P300 may be limited to males. Second, in the same sample, Anokhin *et al.* (this issue) show a strong dependence of P300 amplitude on background EEG power. Perhaps counterintuitively, both findings should be considered good news for gene finding attempts with this endophenotype. Use of P300 amplitude in males only, and appropriately adjusted for EEG power, could well improve the chances of finding linkage with genes influencing cognition.

Five papers in this special issue focus on endophenotypes from the related domains of speed of information processing and working memory capacity. Reaction time (RT) has been the most studied behavioral correlate of intelligence (Jensen, 1998) and plays a crucial role in the "neural speed and efficiency" hypotheses of intelligence (Vernon, 1989, 1993). Luciano *et al.* (this issue) show significant genetic correlation for reaction times during tasks of increasing complexity, confirming the usefulness of this endophenotype in the search for genes of cognitive ability. Reaction time itself encompasses a number of serial and parallel cognitive processes that lead up to the final motor response. These separate processes can be indexed by lower level endophenotypes, and an example is inspection time (IT), 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 (Deary and Stough, 1996), and Posthuma *et al.* (this issue) show this IQ-IT relation to be entirely mediated by common genes. A compelling case is made for selecting genes related to central nervous system (CNS) axonal conduction velocity as candidate genes for intelligence.

The latency of the P300 provides a second alternative to using full reaction time as the measure of information processing speed. P300 latency is thought to reflect the onset of the engagement of attention and working memory processes, which clearly could constitute a meaningful cognitive trait (Polich and Kok, 1995; Polich and Herbst, 2000). Previous studies, most using an odd-ball paradigm, have not consistently shown a genetic contribution to individual variation in P300 latency which would declassify it as a useful endophenotype (Katsanis *et al.*, 1997; O'Connor *et al.*, 1994; Van Beijsterveldt *et al.*, 1998). Wright *et al.* (this issue), however, found genetic sources to explain up to half of the variance in the latency of the P300 elicited by the onset of the target in a strenuous working memory task. They remind us that tasks used to evoke the P300 may have to be sufficiently cognitively demanding to drag up the relevant individual differences in the brain's biology.

A final index of processing speed is the peak frequency of the dominant brain rhythm, the alpha peak frequency. Although Posthuma *et al.* (this issue) find it to be highly heritable, it did not appear to be useful as an endophenotype for any of the four main dimensions of the WAIS: verbal comprehension, working memory, perceptual organization, and processing speed. Both phenotypic and genetic correlations of alpha peak frequency with these dimensions were zero, with the exception of alpha peak frequency and working memory in the elderly sample. Possibly the association of alpha peak frequency with individual differences in memory performance is limited to the very specific process of long term memory storage (Klimesch, 1996, 1999). Even more so than the encouraging findings in the other papers, this demonstrates the need to explore the bivariate genetic architecture of an endophenotype and its target phenotype before doing anything else.

Working memory refers to the limited capacity system that integrates incoming information, storing it temporarily for decision-making, judgement and response, and allowing us to attend to events, maintain them, integrate them with past experience and monitor our actions. Working memory capacity partially depends on processing speed, but can also include qualitative elements like inhibitory control of the "central executive" in the frontal lobe (Baddeley, 1986; Kramer *et al.*, 1994), and the extent of corticocortical connectivity of frontal regions to the inferior temporal cortices (object processing) or to the parietal cortices (spatiovisual processing). Recent evidence (Duncan *et al.*, 2000) suggests that the frontal executive may partly overlap with *g*. In this issue, various behavioral and electrophysiological indices of working memory are explored as potential endophenotypes for future genomic searches. Hansell *et al.* (this issue) measured slow wave-evoked brain potentials elicited over the different regions involved in spatiovisual working memory. They found different genes to influence the two

main regions active in this task. At the prefrontal site genes accounted for an estimated 35% to 37% of the reliable variance. At the parietal site, a largely independent set of genes accounted for 51% to 52% of the reliable variance. Surprisingly, general task-related and attentional processes (keeping task instruction on-line, inhibition of responses, and maintenance of fixation task) but not memory rehearsal *per se,* appeared to be the source of genetic variation.

Behavioral indices of working memory performance are known to show significant phenotypic correlation to psychometric IQ scores, particularly on tests of fluid intelligence (Daneman and Merikle, 1996). Two papers in this issue (Luciano *et al.,* Ando *et al.*) now extend this finding by showing significant genetic correlation to psychometric IQ for the performance in spatial and verbal working memory tasks. However, in addition to a common genetic factor, modality specific genetic factors influencing only working memory but not verbal or performance IQ were also found and, conversely, specific genetic factors were found to affect IQ but not working memory. Clearly, endophenotypes do not *only* track genes for general cognitive ability, and certainly a single endophenotype, by definition, will not track *all* genes for general cognitive ability.

In an extension of one of the most successful genomic search efforts so far—the linkage of reading disorder to a QTL on chromosome 6—Davis *et al.* (this issue) provide a clear demonstration of the combined use of endophenotype and the target cognitive phenotypes in a genomic search. Children with reading disability tend to name visually presented items, including numbers, colors, objects, and letters, more slowly than normally-achieving readers. This speed of processing measure, commonly referred to as rapid naming (RN), could be associated with abnormal processing in a subsystem specialized for rapid visual information processing. Bivariate DeFries and Fulker (DF) linkage analyses for selected twin pairs (at least one member with evidence of reading difficulties) were conducted to test the hypothesis that the QTL for reading difficulties (phonological decoding and orthographic) on chromosome 6p21.3 (Cardon *et al.,* 1994; Fisher *et al.,* 1999; Gayán *et al.,* 1999) is pleiotropic for the endophenotype of slower performance on rapid naming tasks. Results obtained from these analyses provided only suggestive evidence for bivariate linkage, but the authors caution us that larger samples are required to test this hypothesis more rigorously. Yet another caution is provided in the final paper by van Baal and colleagues. Particularly in children, contribution of a gene to cognition need not be fixed across the life span. In young childhood, the relative impact of genetic factors on cognitive ability gradually increases, but it remained undecided whether this is due to gene amplification (i.e., the same genes have larger impact with age) or whether new genes come into play with ageing (Boomsma and van Baal, 1998; Cherny and Cardon, 1994). Using EEG coherence as an index of intrahemispheric neuronal connectivity, van Baal *et al.* now clearly show that, in the course of brain maturation, new genes do appear to be expressed. The window of opportunity to detect such genes in genomic searches may be quite small. To define an individual's maturational brain state, electrophysiological endophenotypes may again be of help.

Purpose of this Special Issue

As yet an unfortunate gap exists between behavior genetics and cognitive neuroscience. Behavior genetics, through its sophisticated statistical modelling in twin and family studies, focuses mainly on individual differences in cognitive ability. Cognitive neuroscience tends to focus on species universals in specific cognitive operations, isolated by clever experimental design, and located in the time and (brain)space by modern imaging techniques. Both parties could gain from a complementary approach. As explained earlier, 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 will, in turn, profit greatly from successfully identified genes, that can provide insight in the "black box" between molecular events and cognition. Knowledge of anatomical distribution of the brain proteins affected by the gene (e.g., Tokuyama *et al.,* 2000) and the development of both knockout and transgenic animals (Bibb *et al.,* 2001; Ivic *et al.,* 2000; Rampon *et al.,* 2000; Silva *et al.,* 1992; Tang *et al.,* 1999; Tsien, 2000) has already greatly advanced the neuroscientist's understanding of neuronal function and its signalling to other neurons. In human studies, identified genes offer many opportunities to lay bare genotype by environment (task demand and task structure) interactions, or genotype by genotype interactions if more than one gene influences the same (endo)phenotype. Finally, understanding the genetics of individual differences in cognitive processes can be used to tackle psychopathology. Many psychopathologies show parallel impairments in cognition (Carlson *et al.,* 1999; Kuperberg and Stephan, 2000;

Pierson *et al.*, 2000) and a genetic grip on cognition may suggest an approach to these disorders, with the additional hope of improved diagnosis and molecular therapeutic strategies.

This special issue originated from a symposium on this topic at the 30th meeting of the BGA in Burlington, Vermont, in July 2000, where a number of the papers were first presented. It was pleasing to see then, as it as now, that the lists of authors and co-authors of the papers in this special issue are a balanced mix of geneticists, cognitive psychologists, and neuroscientists. In view of the mutual benefits of such a collaboration, we hope this special issue will further encourage admixture of the expertise in process-oriented cognitive neuroscience with that of trait-oriented behavior genetics.

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