



## Editorial

# Introducing genetic psychophysiology

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**Abstract**

Genetic psychophysiology examines interindividual variation in psychophysiological traits using behavioral genetic and molecular genetic techniques. It aims to delineate the pathways that lead from genomic variation to individual differences in cognitive abilities, affect regulation, and mental and physical health. This editorial provides an introduction to the twin design and gene finding strategies using psychophysiological endophenotypes. It also gives a brief outline of the papers presented in this special issue on genetic psychophysiology. Its main objective, and the objective of the entire special issue, is to interest psychophysiologicalists in the enormous potential of research in this area and to foster the development of collaborative relationships between psychophysiologicalists and molecular and behavioral geneticists that are necessary to move research in this area forward. © 2002 Published by Elsevier Science B.V.

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**1. Introduction**

This special issue of *Biological Psychology* has been set up as a synergistic mix of behavior genetics and psychophysiology, regarding both the content and the authors of the 11 papers that make up this issue. This mix gives rise to a new field that we have previously labeled genetic psychophysiology (Boomsma et al., 1997), or, when animal genetics is included, genetic neuroscience (de Geus and Boomsma, 2001). A simple operational definition of genetic psychophysiology is ‘the application of molecular and behavioral genetic techniques to psychophysiological traits’. A first aim of this special issue is to present the most recent data on the heritability of some

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key measures in biological psychology. Two reviews in this issue give a thorough overview of twin studies in electrophysiology (van Beijsterveldt and van Baal) and cardiovascular psychophysiology (Snieder, Harshfield, Barbeau, Pollock, Pollock and Treiber). Four ensuing papers present heritability estimates of structural MRI volumes (Carmelli, Swan, DeCarli and Reed), P3 amplitude and latency (Wright, Luciano, Hansell, Geffen, Geffen and Martin; Carlson, Iacono and McGue) and the Lateralized Readiness Potential (Posthuma, Mulder, Boomsma and de Geus). Two papers illustrate the main gene finding techniques of allelic association (Busjahn, Freier, Faulhaber et al.) and linkage analysis (Porjesz, Begleiter, Wang et al.).

In all papers a genetically informative design is used, most often the twin design. The twin study is often called ‘the work horse of behavior genetics’, and it is a very elegant and powerful research design. In general, if two siblings are more alike for a given trait than a random pairing of subjects across families, this points to familial influences on the trait. Twins are special, because they allow a further decomposition of these familial influences into influences reflecting the sharing of environmental factors (any habits, values, practices or neighborhood shared by the siblings, often linked to the parental SES) or the sharing of parental genes. Monozygotic twins share all their genes, whereas dizygotic twins share on average half of their genes. Shared family environment, however, has been shown to contribute equally to pair similarities in both types of twin pairs (Martin et al., 1997). So if monozygotic twins are much more alike on a trait than dizygotic twins this must be due to the fact that monozygotic twins have all genes in common against an average of 50% in the overlap of genes in dizygotic twins. By using the principles of path analysis, a set of equations can be derived in which the contributions of genetic shared and unique environmental influences to the observed traits are the unknown parameters. Using the known difference in the sharing of genes, 50% in the dizygotic and 100% in the monozygotic twins, these parameters can be estimated in a maximum likelihood procedure that fits the observed covariance to different possible combinations of values for these parameters. Based on solid biometrical principles outlined much earlier by Sir Ronald Fisher (1918), the twin method works for single gene Mendelian traits as well as for complex traits that are influenced by many interacting genes and environmental influences. To make this special issue fully accessible to an audience not already familiar with twin studies, a tutorial paper by Evans, Gillespie and Martin lays out the biometrical basis of the twin study in detail. The elegance of the twin study comes at a price, since adequate statistical power is obtained only if large groups of monozygotic and dizygotic twin pairs are used. It is pleasing to see, therefore, that this issue features contributions from some of the largest twin samples with psychophysiological data around the world (Georgia Twin Study, German Twin Registry, Netherlands Twin Registry, NHLBI Twin Study, Minnesota Twin Family Study). The twin data presented in this issue effectively makes obsolete any further nature-nurture debate for most of the psychophysiological traits studied. Table 1 presents a quick overview of the heritability estimates cited in the papers of this issue (including meta-heritabilities cited or computed in the reviews). Most psychophysiological traits showed significant heritability with estimates varying from 26% for a stimulus-response incongruency (the flanker effect) on

LRP onset to 81% for the EEG alpha peak frequency, with unique environment usually explaining the remaining individual variation. These percentages, and there is much misunderstanding about this, are population statistics and deal with effects on variance, not means. A heritability of 100% for IQ, for example, does not mean that parental care, education, food availability or composition do not influence IQ. It simply means that the variation among individuals in the current population is completely due to genetic variation. In the case of IQ, such a result might occur because living conditions and the educational system are optimal and, therefore, maximize each individual's intellectual potential. Put formally, interindividual variance in an outbred population in an extremely homogenous environment will be due mainly to genetic variation, but variance in the same trait may be completely environmental in an inbred strain in an extremely heterogenous environment.

Although it is an important first step, twin studies and other family designs merely establish the presence of genetic influences on psychophysiological traits. Genetic factors in path models are indicated as latent factors, little circles with a 'G' in the middle: the actual genes and the mechanisms of their influence remain anonymous. In fact, work of the founding fathers of behavior genetics like Galton and Fisher predates the discovery of the double helix by Watson and Crick by more than half a century. This anonymity of the actual genes seems to contrast sharply with the huge

Table 1  
Heritability estimates for psychophysiological traits found in this issue

Trait	$h^2$ (%)	Source
Flanker effect on LRP onset (young cohort)	26	Posthuma et al.
Flanker effect on accuracy	27	Posthuma et al.
Flanker effect on decision time	28	Posthuma et al.
Plasma NO metabolite levels	30	Snieder et al.
Frontal slow wave	35	van Beijsterveldt and van Baal
LRP onset (young cohort)	43	Posthuma et al.
Natrium-excretion (24 h)	43	Snieder et al.
LRP peak latency (older cohort)	46	Posthuma et al.
P3 latency (working memory)	46	Wright et al.
Ambulatory blood pressure	50	Snieder et al.
P3 latency (odd ball)	51	van Beijsterveldt and van Baal
Left frontal brain volume	53	Carmelli et al.
P3 amplitude (odd ball)	60	van Beijsterveldt and van Baal
Stress reactivity of blood pressure	63	Snieder et al.
P3 amplitude (working memory)	69	Wright et al.
Left lateral ventricle volume	70	Carmelli et al.
Right frontal brain volume	75	Carmelli et al.
Right lateral ventricle volume	78	Carmelli et al.
EEG alpha power	79	van Beijsterveldt and van Baal
EEG peak alpha frequency	81	van Beijsterveldt and van Baal

increase in our understanding of the ‘Book of Life’, as the collection of human genes is called in reports from the Human Genome Project. The (nearly completed) base pair coding of all human genes influencing behavioral variation is now available through public domain databases. Clearly, under these conditions it becomes feasible to identify the actual genes underlying complex traits. Nonetheless, current successes in gene hunting are, by and large, limited to single gene mutations with rather severe effects on physiological, cognitive or affective functioning (McKusick, 1998). In spite of the overwhelming evidence for significant genetic contribution to variation in virtually all of the more complex aspects of human behavior (Bouchard and McGue, 1981; Kendler et al., 1987; Plomin and Crabbe, 2000), the identification of the actual functional genomic variation, often abbreviated as ‘the genes for’, has only just started.

To identify human genes, two broad molecular genetic strategies can be employed: (1) whole genome scans through linkage analyses, or (2) allelic association or ‘candidate gene’ studies. The major strength of whole genome scans through linkage is that all relevant genes can be detected, including unknown genes (Kruglyak, 1999). However, very large samples of genetically related subjects (> 10 000) are required to identify genes of small or medium effect size through this method. In contrast, allelic association studies have the statistical power to detect much smaller gene effects (e.g. 1% of variance) in much smaller samples (100–1000 subjects) (Risch and Merikangas, 1996). Allelic association is often used to investigate associations with known functional candidate genes, i.e. 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 (Plomin and Crabbe, 2000). Unfortunately, spurious association between any candidate gene and the trait may arise as a consequence of population stratification. This means that many genes may yield false positive results that hamper progress by focusing research attention on the wrong molecular pathways. Many failed replication studies are then needed to return to the right path (Hamer and Sirota, 2000). It is also a real possibility, though less discussed, that a population stratification can act to oppose that of the candidate allele effect, and thus prevent detection of a true allelic association (Witte et al., 1999; Posthuma et al., 2002).

Correct application of both association and linkage techniques requires solid understanding of both their molecular genetic and statistical basis. In the burgeoning number of genetic association studies appearing in medicine, biology and psychology, such solid understanding is not always apparent. In this special issue, Slagboom and Meulenbelt provide a tutorial overview of the organization of the human genome, and the molecular geneticist’s toolkit to identify genetic variation relevant to human traits. Vink and Boomsma then review the strengths and weaknesses of the current gene finding strategies. It is hoped that the readership of *Biological Psychology* will find these tutorials, together with the paper of Evans and colleagues on the twin method, a useful source of reference in judging future genetic psychophysiology.

## 2. Endophenotypes

Ultimately, future success of gene hunting, particularly that of whole genome scans, depends crucially on the amount of variance that the gene explains in the observed trait. Geneticists, therefore, increasingly rely on intermediate traits, referred to as endophenotypes, that could be provided to the field by psychophysiologicalists. The basic idea is illustrated in Fig. 1. It is easier to identify the effect of a gene on a more elementary neurobiological trait than to identify its effect on a complex behavior (Almasy and Blangero, 2001; Boomsma et al., 1997; de Geus and Boomsma, 2001; Lander, 1988; Leboyer et al., 1998).

The various electrophysiological and behavioral measures described in this special issue represent only a very small portion of viable endophenotypes. To hold promise in the hunt for genes affecting complex behavioral traits, we have proposed that endophenotypes must meet the following criteria (de Geus and Boomsma, 2001):

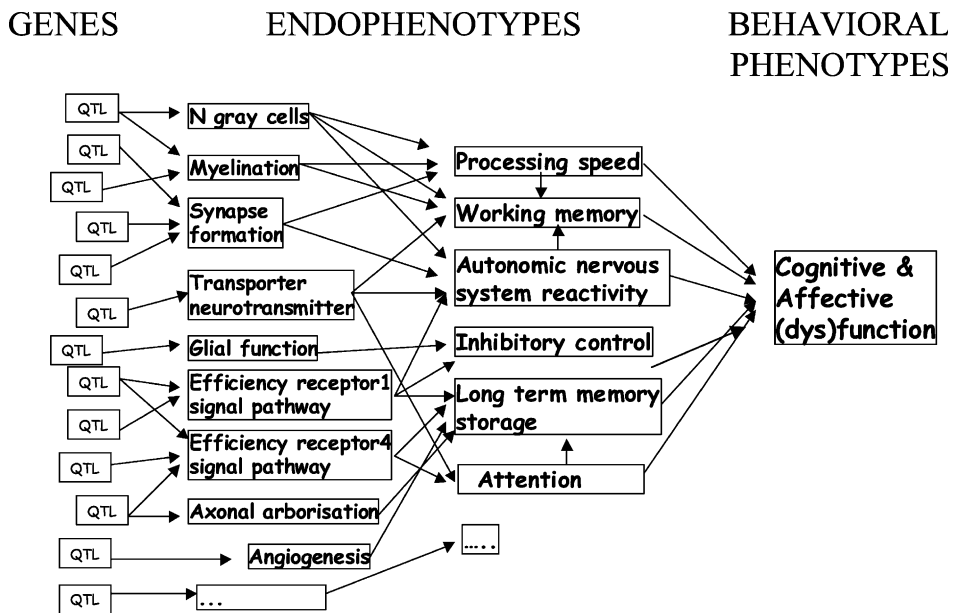


Fig. 1. Using endophenotypes in gene finding. A continuously distributed trait is likely to be influenced by many genetic loci, each with small effect. Such loci are called quantitative trait loci (QTL). QTLs, although explaining only a small part of the variance in behavioral traits, may explain a larger part of the variance in anatomical, neurophysiological, psychophysiological and neuropsychological endophenotypes. For instance, genes for complex 'downstream' traits like IQ, depression or cardiovascular disease should be more easier to detect through their effects on 'upstream' processes like attention, affective response to emotional stimuli, or autonomic nervous system reactivity. The figure illustrates that by reducing phenotypic complexity and moving physiologically 'closer' to the gene products one hopes to boost the statistical power to identify these genes in whole genome searches.

- 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 behavioral trait or disease of interest (phenotypic correlation).
- 4) The association between endophenotype and trait of interest must derive partly from the same genetic source (genetic correlation).
- 5) The association between the endophenotype and the trait of interest 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 the behavioral or disease trait of interest such that genes cause variance in the endophenotype and the endophenotype, in turn, causes variance in trait of interest.

A powerful way to explore the association between endophenotypes and the trait of interest is through the examination of their bivariate genetic architecture in twin and family studies. This allows a direct test of whether their association derives from the same genetic source (criterion 4 above: evidence of a genetic correlation). The basic principle of such a bivariate genetic analysis is best illustrated by the cross-trait cross-twin correlation in monozygotic twins. Suppose that the size of the left ventricular volume is associated with performance on an executive function task like the Stroop word color interference task. If this association were to derive from an underlying genetic factor, we would predict that the ventricular size of a monozygotic twin would not just predict his own Stroop performance, but also that of his co-twin brother (who shares all of their genes). This is in fact exactly what was found by Carmelli and colleagues in this issue. In male World War II veteran twins, aged 69–80 years, they showed that various measures of executive function (including the Stroop color word interference task) were significantly related to the ventricular volumes. Almost 60% of the observed relationship between left ventricular volume and executive function was due to overlapping genes.

Using a similar bivariate twin analysis, Posthuma et al. examined whether performance on another task putatively tapping into executive control, the Eriksen flanker task, was genetically correlated to psychometric IQ measured by the WAIS. In this case, the prediction was that the performance loss due to distraction by incongruent flanker elements predicts IQ, and that again performance loss in a monozygotic twin predicts her own IQ as well as that of her co-twin. It was found that verbal and performance IQ correlated significantly with stimulus-response incongruency effects on performance, and this correlation was entirely mediated by an underlying set of common genes. This strongly suggested that the flanker task yield viable endophenotypes of cognitive ability. But there is a catch. In this example, perhaps more so than for the association between brain volume and executive function, one could question the exact source of the genetic correlation between flanker performance and cognitive ability. To use flanker task performance as an endophenotype in gene finding studies for cognitive ability we would like the

following chain of causality to apply: genes influence flanker task performance by effects on the neural circuitry behind individual differences in selective attention/inhibitory control; such differences in selective attention/inhibitory control, in turn, have a causal influence on general cognitive ability. Two alternative explanations must be considered, however. First, genes may influence general cognitive ability through other routes than selective attention/inhibitory control. If general cognitive ability has a causal influence on flanker task performance, this scheme will also give rise to a genetic correlation, i.e. the genes for IQ will be genes for flanker task performance also. Second, a genetic correlation may derive from some general aspect of the brain that independently influences IQ and flanker task performance, for instance a mild but wide-acting genetic effect on synaptic plasticity through proteins affecting the docking of vesicles to the presynaptic membrane (Verhage et al., 2000). This is usually denoted as genetic pleiotropy.

In this special issue, three ways to resolve this problem of causality are presented. A definite way to prove genetic pleiotropy is to measure the actual genotype, and to establish an independent functional effect of an allelic variant on both of the two genetically correlated traits. Busjahn and colleagues come some way towards this goal. They show that blood pressure and the Emotional Coping style are genetically correlated. At least part of this correlation could reflect a true genetic pleiotropy because allelic variants in the beta-receptor gene were shown to be associated with Emotional Coping. Three markers around this gene also showed evidence of linkage to some of the components of this coping style. Most importantly, in previous analyses (Li et al., 2001) variants in this gene were shown to be associated with blood pressure level. Although this finding needs replication in other samples, and the independent functional effect of variation in the beta-receptor gene on coping and blood pressure still needs to be fully resolved, it is a nice demonstration of the principle of pleiotropy.

Two other ways of resolving the causality underlying a correlation are feasible in twin family based samples. Under optimal conditions it is possible to use cross-sectional data in twins to separate unidirectional causality from genetic pleiotropy. These optimal conditions are stern, but attainable: large sample sizes are needed, the size of the heritabilities for the trait of interest and the endophenotype must be different, and some quantification of measurement error must be available (odd–even retest correlations for ERPs, for instance). A straightforward example of the principles involved can be found in the paper by Evans and colleagues in this issue (see their Figure 4). Another strategy to resolve causality is illustrated by Carlson and colleagues. They examined the hypothesis that P300 amplitude is a biological vulnerability marker for alcoholism in a large sample of twins concordant for (the absence of) alcohol abuse/dependence and twins discordant for alcohol abuse/dependence. Although the sons of alcoholics have been repeatedly found to have reduced P300 amplitude (e.g. Polich et al., 1994), it has been heavily debated whether the reduced P3 amplitude reflects an underlying vulnerability, or is simply the consequence of alcohol abuse. The approach to causality in the discordant twin approach is again best exemplified by the monozygotic twins. If monozygotic twins who are discordant for alcohol abuse would nonetheless resemble each other in P3

amplitude, a causal effect of alcohol use on the P3 becomes unlikely. This is what Carlson et al. found, and the total of their results that also included dizygotic twins and concordant versus discordant pair comparisons, strongly suggested that reduced P300 amplitude indexes the risk for, rather than the expression of an alcohol use disorder. The striking comorbidity of both substance abuse and P3 with externalizing disorders, led the authors to suggest that the P300 amplitude may be a marker of genetic risk for a broad externalizing phenotype including alcoholism.

A prolonged latency of the P3 has repeatedly been proposed to be a genetic marker of impaired information processing. In a multivariate twin study that included the P3 as well as measures of working memory performance and psychometric IQ, Wright and colleagues in this issue confirmed the expected significant genetic correlation between P3 latency and working memory capacity (> 70% of the covariation explained by genes), but did not find evidence of common genes influencing P3 latency and IQ. Such results demonstrate that multivariate genetic modeling of elements from different levels of cognitive processing do not necessarily yield the idealized outcome depicted in Fig. 1. Wright and colleagues recorded the P3 during a working memory task rather than in the more usual odd-ball paradigm. In support of findings by Carlson and colleagues, and the studies reviewed by van Beijsterveldt and van Baal, substantial heritability of the P3 amplitude and latency was found in this task. The repeated finding in behavioral genetic studies that the P3 component is a heritable trait, was directly supported at the molecular genetic level in a final study of Porjesz and colleagues in this issue. They report on the progress of their linkage analyses in the Collaborative Study on the Genetics of Alcoholism (COGA). In the COGA project, linkage analyses are performed in large sample of families with a high density of alcohol dependence for electrophysiological traits (EEG, ERP) that can potentially identify individuals at risk for alcoholism. This project, therefore, is a direct illustration of the use of psychophysiological endophenotypes in actual gene finding. Evidence for genetic loci influencing interindividual variation in P3 amplitude were identified for P3 at chromosome 2, 5, 6 and 17. In addition, several genetic loci were found to influence the N100 and N400 amplitudes, and EEG beta power was found to be associated with genetic markers near the GABA<sub>A</sub> receptor gene.

### **3. Purpose of this special issue**

In summary, this special issue describes recent progress in twin research on the genetic architecture of some key measures in psychophysiology. Although research with twins remains the cornerstone of genetic psychophysiology, it is important to note that access to a twin sample is not essential for one to become involved in research in this area. Collecting psychophysiological data in any set of multiple (biological) family members can be used to estimate familial influences, and depending on the exact family structure, heritability as well. For gene finding through linkage or association, a study design with multiple siblings, and preferably their parents, is one of the most optimal designs, as amply demonstrated by the



COGA project. For most psychophysiological experimentation there is no good reason to use genetically unrelated subjects. Even purely process-oriented psychophysiological questions (as opposed to individual differences oriented questions) could be dealt with in a sample of multiple members of a family as good as it could in the usual sample of unrelated subjects. So why not think ahead? In the same vein, the simple collection of DNA from blood (or even buccal swabs) in subjects that come in for psychophysiological experimentation could prove a valuable resource. Although genomics has been equated with a bottom-up approach that begins with genes and proteins in cells, the psychophysiological level of analysis may pay off more quickly in terms of diagnosing, treating and preventing disorders, once genes have been identified.

This editorial started with an operational definition of genetic psychophysiology: the application of existing behavioral and molecular genetic techniques to psychophysiological traits. However, genetic psychophysiology as a field of research, and as a collaborative effort between psychophysiologicalists and molecular and behavioral geneticists, should grow beyond this mere operational definition. In this era of rapid progress in knowledge of the human genome, genetic psychophysiology could play a key role in understanding the molecular and biological pathways that underlie individual differences in affective and cognitive function and ultimately physical and mental disease risk.

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