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Genetic Explanation in Psychology

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Attempts to explain behavior genetically face two major problems: the application of the concept of genetic coding and the theoretical possibility of decomposing behavior. This paper argues that using the notion of genetic coding is appropriate in explanations of protein synthesis but inadequate and even misleading in the context of explanations of behavior. Genes should be regarded as disparate *components of mechanisms* that account for behavior rather than as *codes* for behavioral phenotypes. Such mechanistic explanations, however, presuppose the possibility of decomposing behavioral phenotypes, which is strongly disputed by researchers holding an interactionist view of behavior. It is argued that these researchers fail to distinguish etiological from constitutive decomposition, and that their objections apply to the former but not to the latter kind. Constitutive decomposition might identify genes as disparate components and open up the possibility of explaining behavior mechanistically by isolating causal paths from genes to behavior. Finally, research on the single gene disorder phenylketonuria is introduced to illustrate and test these views. With respect to this disorder it is demonstrated that applying the concept of genetic coding would be inappropriate and misguiding, while nonetheless the phenotype is decomposable and can be explained mechanistically by singling out a genetic causal path.

How "genetic" is the science of psychology? Might behavior be understood by methods and tools that were originally designed to investigate biological phenomena? Or are these methods of little use for psychologists? These are questions about the relation between two scientific disciplines and their foundations. More specifically, these questions concern the applicability of a particular biological theory to a psychological domain.

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In the last decades new ideas and techniques from biological science have advanced our knowledge of the activity of genes. After Watson and Crick discovered the structure of DNA in 1953, the causal path from DNA to the construction of proteins was largely uncovered. Nowadays, genetics is employed in a much wider domain to explain a large variety of characteristics of organisms, including human behavior (Plomin and Crabbe, 2000). Some examples of human behavior that are claimed to be explainable by genetics are intelligence, cognitive disabilities, attention-deficit hyperactivity disorder, personality, and schizophrenia (Plomin, DeFries, McClearn, and McGuffin, 2000). Some behavioral characteristics, like intelligence, have been exclusively psychological issues. A genetically based theory now brings them into the realm of biological science.[1]

The incorporation of genetics into psychology, however, has not gone uncontested. This paper is about two problems associated with efforts to "genotize" the study of behavior. The first problem concerns the concept of genetic coding. It is generally acknowledged that genes contain a code for proteins, but it is not clear what these coding properties exactly are and whether the concept of genetic coding can be applied to behavior (Godfrey–Smith, 1999). If there is a meaningful definition of coding that sets genetic causes apart from non-genetic causes, genes can be assigned an a priori privileged role for behavioral explanations. It has been claimed, however, that any such definition will be equally applicable to non-genetic factors and consequently fails to provide genes this privileged status (Griffiths, 2001).

The second problem concerns the possibility to decompose phenotypic behavior into disparate genetic and non-genetic causal components (Ariew, 1999; Wahlsten and Gottlieb, 1997). A rejection of decomposability of phenotypes raises problems for the project to find mechanistic explanations for behavioral phenotypes that aims at isolating causal paths from genes to behavior (Gottlieb, 1998). A related problem is that chance events may be a

[1]It is presumed here that genes do influence behavior, an assumption that is also accepted by many of the critics of behavior genetics discussed in this paper (e.g., Gottlieb, 1998; Johnston and Edwards, 2002). Initial evidence comes from heritability analyses based on classical twin and adoption studies. Although severely limited for many reasons, these studies do suggest genetic influences on many behavioral traits (Plomin et al., 2000; for critical discussions, see e.g., Mandler, 2001; Sarkar, 1998, Chapter 4). Conclusive evidence of genetic influence on behavior, however, comes from molecular analyses which reveal *causal relations* between genes and phenotypic traits. The case study of Phenylketonuria presented in this paper is an example of such genetic influences. The focus of this paper is on molecular aspects of genetics, not on classical adoption and twin studies. A difference between the two is that classical genetics examines individual differences by using statistical methods like analysis of variance, while molecular studies aim at full-blown causal explanations. By emphasizing the causality between genes and behavior, molecular genetics extends beyond the merely statistical question of individual differences. It addresses the background of behavior more generally as well.

significant factor in development as well, resulting in the impossibility to anticipate or predict phenotypes from even a complete specification of genes and environment (Lewontin, 2000).[2]

In this paper, these two problems will be analyzed theoretically. After having drawn some conclusions on the appropriateness of genetic coding and phenotypic decomposition for the study of behavior, these conclusions will be weighed against the empirical evidence of phenylketonuria (PKU) research. The disease of PKU has been called the "poster child" for behavioral genetics as it provides us with important characteristics of genetic influences on behavioral phenomena (Carey, 2002).[3] Phenylketonuria is caused by a single mutant gene with a wide range of phenotypic effects, many of which are cognitive in nature and have been investigated by (neuro)psychologists. As a consequence, the relation between the genetic locus of PKU and its psychological sequelae is quite well known. This provides the opportunity to investigate carefully the relation between DNA and behavior in the context of a real life human case.

The Genetic "Code"

Explanations of even so-called "genetic" traits of organisms need reference to genetic as well as non-genetic variables. This is because not only genes but also the right environmental circumstances are required for a proper functioning of the organism. But although both genes and environment are necessary, it often seems that there is no "democracy" among genetic and non-genetic causes as components of such explanations. On the contrary, it seems that genes are often attributed a prominent theoretical role (Godfrey–Smith, 1999; Griffiths and Gray, 1994; Schaffner, 1998). The prominence attributed to genes is reflected by the use of locutions like "gene for" or "genetic code."[4] These locutions indicate an asymmetry in assigning a *representational* or *intentional* role to genetic factors while withholding such a role

[2]The two problems presented here are not unrelated. Decomposability into genetic and non-genetic elements is essential for notions like genetic coding and for genes as privileged explainers (Morgan, 2001).

[3]Some of these characteristics not discussed in this paper are pleiotropy (one gene having effects on more than one phenotype) and the fact that even a 100% heritable disorder can be prevented by an environmental therapy (hence genetic determinism in its most simple form is false).

[4]The issue of whether genes have some special status in the explanations of phenotypes does not depend on whether genes might be regarded as codes. An alternative is that genes are more important than other components because genes explain more variance than, for example, the environment (Sober, 1988). Such an analysis of variance is an empirical matter, while genetic coding would provide a priori reasons to single out genes as privileged explainers.

to environmental factors. For example, scientists do acknowledge the existence of genes that code for obesity, but it seems absurd to consider an environmental factor like having excessively large meals as a code for fatness. Such environmental causes are usually understood merely as co-determining factors. Although the assumed prominence of genes is reflected by the use of these locutions, the problem is whether genes indeed are, and environmental factors are not, representations or codes for behavior. This problem is caused by the fact that an exact and technical definition of the notion of genetic coding is absent, even within the genetic discipline itself (Griffiths, 2001). Moreover, it is not clear whether locutions like genetic coding can be meaningfully applied to very *complex and distal behavioral* phenotypes (Godfrey–Smith, 1999).

According to Godfrey–Smith (2000b) the use of concepts like genetic coding and genetic representation are fruitful only within the theoretical context in which these concepts were originally introduced, which is the specific problem of *protein synthesis* (Crick, 1958). The original question was how genes could determine the exact order of the various amino acids of which proteins are constituted. The answer is that genes contain *the code for the order of amino acids*.[5] This way, genetic coding successfully explains how in a living cell proteins are produced. Although it may be appealing to apply this successful concept of genetic coding to an empirical project to find genetic explanations outside this specific context, such an application needs a separate argument. At present, it is not clear whether this argument exists. Indeed, it is not clear whether the introduction of the concept of genetic coding has any positive theoretical role to play in explanations of complex traits (such as behavior) that involve a mass of causal interactions (Godfrey–Smith, 2000a).

Some Criteria for Genetic Coding

So the problem is to offer an account of genetic coding that marks off genes as genuine codes from other causal factors and also provides the legitimization to apply the concept of genetic coding to explanations of behavioral phenotypes. A number of criteria to place genuine codes apart from mere co-determining causes has been suggested by Maynard Smith (2000) and Wheeler and Clark (1999): the criteria are natural selection, arbitrariness and consumption.

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[5]More precisely, genes are composed of a series of linearly ordered triplets. Each triplet consists of three nucleotides. Because four different nucleotides exist the total number of possible triplets is 64. Most of these triplets correspond to a specific amino acid. So a series of linearly ordered triplets corresponds to series of amino acids. Genetic coding, then, refers to the idea that the constitution of genes corresponds to the amino acid sequence of proteins.

If genetic coding is to denote something more than just a statistical correlation, "gene for" should be best interpreted in terms of its natural function and in terms of *natural selection* (Kaplan and Pigliucci, 2001). Genes are a common bridge between successive generations (Schaffner, 1998). Accordingly, genes have been subject to natural selection and because of the process of natural selection, genetic material is designed to make a phenotypic difference which enhances reproductive fitness (Clark, 1998). It is because of this *natural function* of genes to make phenotypic differences that genes are alleged to code for their phenotypic outcomes: they possess the function of bringing about a particular phenotypic effect. So, according to this view, genes contain encoded information about their phenotypic effects, making genes "special" over environmental causes that have not been likewise selected (Maynard Smith, 2000). Genes do not just correlate with phenotypes, but they "represent" those phenotypes because they are supposed to bring those phenotypes about. In this way, an appeal to natural selection makes the concept of genetic code extend beyond mere covariance.

Natural selection alone is probably too inclusive and cannot separate the "truly representational wheat from the contentless chaff" (Wheeler and Clark, 1999, p. 122). Organisms inherit much more than just DNA (e.g., cytoplasm of the egg cell). These other inherited elements are also effective causes of phenotypes and may be also under the control of natural selection. Therefore, these extra-genetic components also satisfy the criterion of function derived from natural selection (Griffiths, 2001).[6]

Another criterion is *arbitrariness*, which refers to the idea that there is *no necessary connection* between what is represented and *how* it is coded for (Maynard Smith, 2000; Wheeler and Clark, 1999). The mapping between genes and proteins is arbitrary in the sense that there is no chemical reason why a certain gene could not have corresponded with another order of amino acids.

The third criterion is *consumption*: encoded information can only be causally effective if it is recognized and used. In other words, the information must be *decoded* (Wheeler and Clark, 1999). In the case of genes, the genetic code is connected to mechanisms known as transcription and translation. These mechanisms "read" the genetic information and "translate" that information into proteins. In this sense, the information contained by the genes is

[6]Biological mechanisms, other than DNA, that are responsible for the resemblance between parents and offspring are called "epigenetic inheritance systems" (Griffiths, 2001). An example of such a system is DNA methylation (e.g., Kass and Wolffe, 1998). This mechanism involves chemical groups that attach to parts of DNA and consequently regulate the expression of the part it is attached to. Together with DNA, the chemical groups are passed on to successive generations.

decoded by the mechanisms of transcription and translation which therefore serve as consumption mechanisms.

Given these criteria for genetic coding, two issues arise. First, might genes be regarded as codes for *behavior*? Second, is an appeal to genetic coding *helpful* for genetic explanations of behavior? The problem with answering the first question is that there seems to be no empirical warrant for the claim that genes involved in behavior that satisfy the criteria exist. There is, firstly, a lack of empirical evidence that reading mechanisms (like transcription and translation) exist for the relation between genes and behavior, and hence whether the criterion of consumption is satisfied (Sterelny, 2000). Secondly, the criterion of arbitrariness does not seem to be of much help. It can be argued that arbitrariness does not discriminate between codes and other causes: a lack of necessary connection between the form of a causal factor and its effect might be applied to any causal process, because any cause can have many different effects (Godfrey–Smith, 2000b). It is hence unclear whether the relation between proteins and behavior is arbitrary in the same sense as the relation between genes and proteins. So, the existence of genes that code for behavior seems to be merely a theoretical possibility, which is empirically not well supported.

But even if it would be granted that there are genes that code for behavior, it remains unclear whether the theoretical construct of genetic coding is *helpful* for explaining behavior. A potential caveat here is hyper-selectionism (cf. Sarkar, 2000): not every part of DNA that is important for explanations of behavior has been subject to natural selection. Even more problematic would be the case when a gene has been selected for one trait, but also influences another, more interesting trait. A well-known example of such a necessary by-product are the spandrels in the St. Marks Cathedral in Venice (Gould and Lewontin, 1984). Spandrels — the triangular spaces between two rounded arches, covered with a mosaic design — are a necessary architectural by-product, and should not be considered as an adaptation selected *in order to* hold the mosaic. Geneticists are interested in the relation between genes and phenotypes, irrespective of the involvement of natural selection. If the phenotypic behavior of interest is a not-selected by-product, an empirical project to explain behavior by finding a genetic code would *miss* these genes. Genetic coding, then, would actually be misleading and a hindrance for discovering genetic explanations of behavior. This caveat is probably realistic because in general the proximate consequences of genes concern proteins that are typically involved in many different metabolic and biochemical processes. These biochemical consequences typically have a large number of behavioral effects and it is unlikely that all of these effects have been naturally selected for.

So, the upshot is this: given the criteria for genetic coding, it is not clear whether the concept of genetic coding can be meaningfully applied to very complex phenotypes like behavior and it is unclear whether it will be helpful in explaining behavior. If this analysis is correct it might be better to regard genes as just another causal factor for behavior. In that case, to explain behavior would consist of demonstrating (the interactions of) its underlying mechanisms, including genetic causes and genetic interactions (cf. Craver, 2001).

Decomposing Phenotypes?

A number of *interactionist* theorists do not only argue against the use of locutions like genetic coding, they also reject the project to find mechanistic explanations that attempt to isolate genetic causal chains from non-genetic ones.[7] These researchers underscore the interaction between genes and environment and argue that dichotomous views that separate genetic and environmental effects are indefensible (Gottlieb, Wahlsten, and Lickliter, 1998). Distinctions like nature–nurture or innate–learned, consequently, would have no warrant (Griffiths and Gray, 1994; Oyama, 2000) and the phenotype should be understood as a *seamless unification*, an amalgam (see Schaffner, 1998, p. 233).

Based on the idea of the amalgam-like phenotype, Gottlieb (1998, 2000) has criticized the trend in biology and psychology to separate the effects of genes and environment, a trend which he attributed to the *central dogma* of molecular biology. The central dogma holds a *one-directional* causal flow from genes to the structure of the proteins those genes bring about. The protein, moreover, can be seen as "the most delicate expression possible of the phenotype of an organism" (Crick, 1958, p. 142; cited in Schaffner, 1974, p. 124). Thus, according to the central dogma, genetic effects on behavior can be characterized as a series of successive influences: genes determine the structure of proteins, which in turn influence neurological and consequently brain organization, which at last affect behavior. Such a view has been called the *domino model* as it passes on instructions from genes to behavior in a domino style (Bidell and Fisher, 1997). It presumes that genes act in isolation from higher level environmental influences. But evidence suggests that environmental and behavioral signals often influence genetic activity as well: genes

[7]The term "interactionist" is used here to refer to a form of criticism of behavior genetics that emphasizes the interaction between genes and environment. Other terms used for this form of criticisms are "constructionism," "developmentalism," "holism," or "systems approach" (see Schaffner, 1998).

and environment are interacting and mutually dependant. Consequently, the unidirectional central dogma must be replaced, according to Gottlieb, by a *probabilistic-epigenetic framework*, which stresses the *bi-directional* influences between genes and environment. Because of this interaction, the genetic and environmental causal chains cannot be distinguished within the phenotype and as a result, it is not meaningful to separate genetic and non-genetic factors. The proper unit of analysis would be the entire system, including these interactions (Gilbert and Sarkar, 2000; Gottlieb, 1998, 2001).

Ariew (1999) has also argued against the method of isolating genetic causal paths from non-genetic ones. He claims that the interactions between genes and environment are such that the contributions of both factors are not commensurable, which means that phenotypes are not the arithmetic sum of activities of genes and environment. Instead, both kinds of causes have their own tasks in realizing the trait. Richard Lewontin has expressed this idea as follows:

> For example, if two men lay bricks to build a wall, we may quite fairly measure their contributions by counting the number laid by each; but if one mixes the mortar and the other lays the bricks, it would be absurd to measure their relative quantitative contributions by measuring the volumes of bricks and of mortar. It is obviously even more absurd to say what proportion of a plant's height is owed to the fertilizer it received and what proportion to the water, or to ascribe so many inches of a mans height to his genes and so many to his environment. But this obvious absurdity appears to frustrate the universally acknowledged program of Cartesian science to analyze the complex world of appearances into an articulation of causal mechanisms. (1974, p. 402)

Mechanistic Explanations and Emergence

As Lewontin's remark shows, the rejection of decomposability of phenotypes results in a failure to provide *mechanisms* as explanations for behavior. Mechanisms can be defined as "entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions" (Machamer, Darden, and Craver, 2000, p. 3). They are *concrete* systems and the processes occurring in them bring about certain features. Explanations referring to a mechanism that generates the explanandum are *mechanistic explanations*. By reference to concrete systems, mechanistic explanations differ from other kinds of explanation, like the covering law model or the hermeneutic "interpretive" account (Bunge, 1997). Mechanistic explanations also differ from functional or teleological explanations in the sense that a teleological explanation only refers to the proper function of a feature, while a mechanism explains *how* this feature brings about the desired goal.

A common strategy to furnish mechanistic explanations is the *decomposition* of the system into the entities and activities that constitute the mecha-

nism that brings about the behavior (Bechtel and Richardson, 1993). For example, the transmission of a signal from one neuron to another across the synaptic cleft can be explained by a decomposition of the synapse into the terminal buttons of one neuron releasing neurotransmitter molecules that diffuse towards the post-synaptic membrane. The entities of a mechanism identified by a decomposition of a system may often be further decomposed into still smaller component parts (e.g., the post-synaptic membrane consists of ionotropic receptors, which are themselves composed of a receptor and an ion channel.) These ongoing decompositions lead to nested part–whole hierarchies of mechanisms, which bottom out in the components that are accepted as relatively fundamental (Machamer, Darden, and Craver, 2000). Genetic explanations of behavior thus consist of a decomposition of the system into lower level component parts all the way down to the level that is accepted as fundamental, i.e., the level of genes as components of DNA molecules.

Phenomena that constantly resist attempts at decomposition are *emergent* (Bechtel and Richardson, 1993) and it is in this sense that interactionists claim that phenotypes are emergent (Griffiths and Knight, 1998). In their view, the complex interactions between genes and environment result in seamless phenotypes so that a decomposition is not possible. Nor could phenotypes be anticipated by focusing on just genetic or non-genetic activities in isolation. Moreover, critics also claim that even in the hypothetical case that all relevant genetic and environmental factors would be known, the phenotype would still be *unpredictable* as a result of "developmental noise," i.e., chance events at the molecular level that may change the course of development dramatically (Gottlieb, Wahlsten, and Lickliter, 1998; Lewontin, 2000). So, developmental noise would make the outcome of development indeterminate or at best probabilistically predetermined (Gottlieb, 1998, 2000).[8]

To sum up, interactionists argue that the approach to find mechanistic explanations by means of identifying genetic causal chains as distinct elements will not be fruitful because of two reasons. Firstly, from the perspective of the phenotype, genetic causal chains cannot be isolated from non-genetic ones because of relevant interaction. Secondly, chance events during development make phenotypes in principle unpredictable even if all relevant factors, both genetic and non-genetic ones, would be known.

[8]An alternative interpretation of the indeterminate outcome of development is to consider noise as caused by factors that have not been measured.

Constitutive and Etiological Decomposition

A distinction that is often overlooked in debates over the emergent nature of behavior is that between *etiological* and *constitutive* aspects of mechanistic explanation. According to Salmon (1984, pp. 267–276) the entities and activities of a mechanism together form a causal nexus, which is understood as a complex four-dimensional network in space-time. An explanation of an event is a demonstration of how the event is situated with respect to that nexus. Regarding the way an event is situated in the nexus, etiological and constitutive aspects will vary. The etiological aspect, on the one hand, shows how the explanandum event fits *at the end* of a causal nexus. This aspect refers to an *external* network consisting of the *antecedent* processes by which the event occurred. Accordingly, etiological causal explanations are *backward looking* — filling in the history of that event with causally relevant processes and interactions (Craver, 2001). Corresponding to this aspect, an explanation may involve an *etiological decomposition*: within the causal history of the event distinct causal entities and activities that have led to the event are distinguished and treated separately. An example would be the explanation of a heart disease. This explanation might refer to the etiology of the disease distinguishing between distinct components like prior smoking, an unbalanced diet, or a lack of physical exercise.

The constitutive aspect, on the other hand, does not refer to causal antecedents but to mechanisms that *underlie* the explanandum. This aspect shows the relevant causal processes *within* the space-time volume of the event to be explained. Thus, constitutive explanations are not backward but *downward looking*, identifying the lower level mechanisms that directly form part of the explanandum. In order to furnish a constitutive explanation it is necessary to decompose the system into its underlying components, which is a *constitutive decomposition*. In this case, it is not the etiology that is decomposed, but it is the system itself that is — sometimes literally — cut into the distinct pieces that together form the mechanism sought. The explanation of synaptic transmission serves as an example of the constitutive aspect of explanation: the components all fall within the space-time volume of the transmission.

Interactionist criticisms center around the etiological aspect of mechanistic explanations. The criticisms do not of course deny the possibility of an etiological explanation of phenotypic behavior, but they do insist that this explanation *cannot* be furnished by means of a decomposition of the etiology into genetic and non-genetic factors. As we have seen, it is the interaction between genes and environment that is responsible for the construction of the phenotypic behavior. The emphasis on the etiological aspects is reflected by the prominence of *developmental* issues in criticisms of genetics (e.g., Gottlieb, 2001; Johnston and Edwards, 2002; Oyama, 2000), because devel-

opmental explanations are etiological. In the bricklayer example of the explanation of why the wall is there, it is the *etiology* of the wall that is claimed to be indivisible: it is the joint activity of *both bricklayers* that provides the explanation.

However, the claimed impossibility of etiological decomposition leaves open the possibility that behavior allows for constitutive decomposition. Even if phenotypic behavior is emergent in the etiological sense, it may still be possible to decompose that behavior meaningfully into *underlying* genetic and non-genetic elements. William Bechtel (1998, 2001) has argued that emergence is *compatible* with a mechanistic approach involving constitutive decomposition. Mechanistic explanations are compatible with complexity, because "All a mechanist requires is that we can get a first approximation account of what the parts contribute by examining them individually, and then take into account the interactions" (Bechtel, 2001, p. 485). If that is true, *underlying* genetic influences on behavior can be meaningfully isolated, even if only as an *approximation* to be complemented with the relevant interaction. Along these constitutive lines, it might still be possible to apply the central dogma and investigate how genetic components contribute to the overall behavior, at least as a first approximation. Thus, mechanistic research might be useful despite the importance of the interaction between component parts. Behavior genetics as a mechanistic strategy to find molecular genetic explanations for behavior, then, need not be as untenable as its critics claim, because isolated genetic components can still be part of (constitutive aspects of) explanations of behavior.

Phenylketonuria: From Locus to Cognition

The overall picture of the preceding paragraphs is as follows. The concept of genetic coding might not be applicable or fruitful to explanations of behavior, but it may be possible to single out underlying genetic components, at least as an approximation. Below is described an example of how these ideas link up with empirical results of a real life case of human genetics: phenylketonuria (PKU).

Phenylketonuria is a metabolic disorder.[9] Untreated patients show a vast array of symptoms, including severe mental retardation, delayed psychomotor development and a small head size. Phenylketonuria is caused by a genetic mutation in a gene called *PAH*, located on chromosome 12, which is responsible for the production of the enzyme *phenylalanine hydroxilase*, or PAH

[9]General information about PKU can be found at OMIM: Online Mendelian Inheritance in Man, number 261600; http://www.ncbi.nlm.nih.gov/Omim (updated daily).

(Lidskey, Robson, Thirumalachary, Barker, Ruddle, and Woo, 1984).[10] More than 400 different mutations for the *PAH* gene are known.[11] Some of these mutations result in an enzyme that is completely inactive while others result in a PAH enzyme that shows a reduced activity but is not completely inactive. This reduced activity is the result of the instability of the mutant enzyme, although alternative mechanisms involving the binding properties of the enzyme have also been suggested (Gjetting, Peterson, Guldberg, and Güttler, 2001). Only *homozygous* individuals with two copies of a mutant gene have PKU.[12] *Heterozygous* individuals with only one mutant gene are not affected because the other, "normal" gene provides sufficient amounts of active PAH to prevent abnormal development (although these individuals are carriers of the disease).

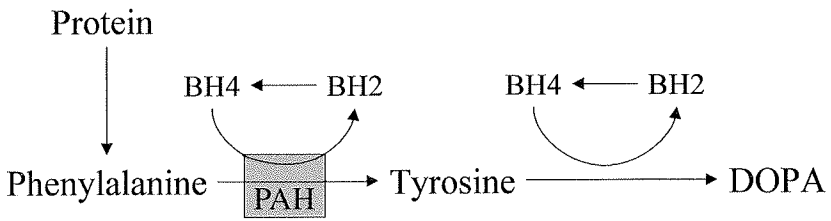

Figure 1: Penylalanine metabolism. PAH (phenylalanine hydroxilase) is an enzyme necessary for the conversion of phenylalanine into tyrosine. The cofactor BH4 is also a necessary component in the conversion. Most cases of phenylketonuria are caused by a deficiency in PAH, some cases are the result of a deficit with the cofactor.

The enzyme PAH operates within the phenylalanine metabolism (see Figure 1. For an extensive review of the molecular and metabolic aspects of PKU and related disorders, see Scriver, Kaufman, Eisensmith, and Woo, 1995). Phenylalanine hydroxilase is necessary for the conversion of the amino acid phenylalanine (phe) into tyrosine (tyr) which in turn is a precursor for the important neurotransmitter dopamine. Because of the deficiency of PAH, this conversion does not take place with PKU patients. Consequently, the level of phe in the blood builds up and the level of tyr drops, which results in a lack of its metabolites. Severe mental retardation is caused by the high

[10]Following standard practice, the terms for genetic loci are indicated with italics while the terms designating the gene products are not italicized. So *PAH* refers to the gene, while PAH refers to the protein produced by *PAH*.

[11]See the *PAH*db electronic database at http://www.pahdb.mcgill.ca

[12]That is, PKU is a recessive disorder.

levels of phe that interfere with the myelination of neurons in the developing brain, which is one of the structural damages found among untreated PKU patients (Huttenlocher, 2000; Surtees and Blau, 2000).

Since the 1960's, all newborn children in most western countries are screened for abnormal phe levels (using the Guthrie test on blood samples obtained by the heel prick). If abnormally high levels are found, patients are put on a phe-restricted diet that effectively prevents brain damage and mental retardation. However, treated patients still encounter moderate cognitive and behavioral problems (Griffiths, Demellweek, Fay, Robinson, and Davidson, 2000; Smith and Knowles, 2000; Sullivan and Chang, 1999; Weglage et al., 2000). Among the causes of these problems are the somewhat elevated levels of phe in the blood that can be found when the patients do not completely adhere to the diet. Because these phe levels are an important factor for cognitive and behavioral problems, research has concentrated on the impact of dietary control on functioning. Thanks to these studies, the knowledge of the relations between genes, metabolic phenotypes, and psychological outcome has advanced significantly. Because of this knowledge, PKU presents itself as a good model to interpret the relationship between genes and behavior.

Coding Properties of the PKU Gene

As Clark states, "PKU disease is classified as a *paradigmatic* case of a genetic problem" (1998, pp. 92–93, original italics), even though both genetic and environmental causes are involved. But exactly what does it mean that PKU is "genetic" and what is the role that the concept of genetic coding might play in explanations of PKU?

The *PAH* mutation that causes PKU has been subject to natural selection. The relatively high frequency of PKU, especially in some geographic regions like Ireland and West Scotland, suggests that heterozygosity for PKU may be of some reproductive advantage. This advantage is also reflected in the fact that mothers of PKU patients (who are necessarily heterozygous) have fewer spontaneous abortions than controls. Woolf (1986) believes this is so because fetuses of heterozygous pregnant women are better protected against a specific mycotoxin: ochratoxin A. Ochratoxin A is produced by molds that preferably grow in mild, wet climates. Moreover, countries like Ireland and West Scotland have repeatedly suffered serious famines and it is likely that products made from moldy grains that would otherwise have been avoided are consumed in times of famine.

So, the *PAH* mutation has been selected because of the consequent protection against a toxin. In that sense, the *PAH* allele can be regarded as coding for this protection. But, among the *psychologically* relevant phenotypes of

PKU are attention deficits, intelligence and social and behavioral problems. Because the *PAH* mutation has not been selected for these traits, an appeal to natural selection does *not* justify talk about the *PAH* gene as a code for behavior. The only way the mutation is related to psychologically relevant phenotypes is by a causal connection. A research project focusing on genes as codes would only grasp the relation between the *PAH* locus and ochratoxin A protection. It would completely overlook the much more relevant relation between *PAH* and its psychological phenotypes.

Disease versus Normal Behavior

It might be argued in opposition that PKU is not representative for behavior genetics because it is a disease and natural selection typically does not favor genes because of dysfunctional byproducts. It could thus be contended that for normal behavior the genetic code locution is meaningful. Such a view, however, faces at least three difficulties. First, it requires a definition of "normal behavior" as distinct from disease. By itself it is already hard enough to come up with such a definition. But if the purpose is to denote genes as selected representations for behavior this definition becomes virtually impossible. In that case the definition of normal behavior is not allowed to refer to natural function for which the behavior has been selected on the pain of circularity.

Second, even if such a definition could be given, it would not be of much help, because it would exclude some paradigmatic cases of genetic coding where a gene is claimed to be for a disease. Behavior geneticists are highly interested in disorders like Alzheimer's disease, schizophrenia, attention deficits, eating problems, and addictions like smoking or alcoholism (Plomin et al., 2000). So, in that case genetic coding would be saved as a fruitful theoretical construct at the cost of loosing such paradigms.

But, finally, even if it would be accepted that such exemplars as schizophrenia are barred, genes do not always code for the normal behavior that needs to be explained. Phenylketonuria itself presents a case: carriers of one mutant gene (who are themselves not affected) demonstrate a somewhat lower IQ (Bessman, Williamson, and Koch, 1978; Plomin et al., 2000, p. 179). This indicates that variation in the *PAH* gene is a factor for variation of intelligence *in the normal range* as well. Because even normal behavior is influenced by genes that have not been selected for that behavior (like the *PAH* mutation) an empirical project to discover genes coding for normal behavior would miss important genetic causal factors.

"Genetic" and "Under Genetic Control"

The best interpretation of the empirical evidence of recent PKU research seems to be Godfrey–Smith's (2000a) analysis that the special coding properties of genes disappear *after* the protein has been formed. The *PAH* locus thus codes for the PAH enzyme. Via this PAH the genetic locus plays a distal role in metabolic causal processes and its effects extend to metabolites of phe. But the *PAH* gene cannot be called a representation of these effects. In a similar vein, although behavior associated with PKU is causally related to a genetic mutation, it is not present in the gene in any *symbolic* way.

A definition introduced by Sarkar (1998, p. 182) might be useful here. Sarkar gives a systematic definition of what it is for a trait to be genetic as distinct from "merely" being under genetic control. Genetic traits are those traits that are under genetic control and satisfy the additional criterion that the immediate product of the genetic locus (or several loci) forms a part of the biochemical characterization of the trait. The immediate product of the *PAH* locus is the PAH enzyme which is part of phe metabolism. Thus according to this definition, Phe metabolism can be said to be genetic. However, the PAH enzyme is not part of the behavioral phenotypes associated with PKU. So this behavior is not genetic, although it is under genetic control.

In sum, in the context of PKU there exists an important connection between a specific gene and a resultant behavior. Nevertheless, this relation cannot be properly cast in terms of genetic coding. So, it turns out that whether genes can be regarded as codes is an empirical question: it cannot just be assumed that genes are for a particular behavioral trait (Kaplan and Pigliucci, 2001). An empirical project to find genetic explanations of behavior based on a notion of coding would misguide research because important genetic components of such explanations would be overlooked, like the *PAH* locus affecting intelligence. The project to discover genes affecting behavior should regard genes rather as "merely" causal components of complex mechanisms that underlie behavior, trying to understand as much as possible of these mechanisms.

Mechanistic Explanation in PKU research

Is it possible to decompose meaningfully the mechanisms involved in PKU and single out genetic causal chains from the *PAH* allele to behavior? Phenylketonuria researchers recognize that phenotypes are the result of both etiological and constitutive processes. One such behavioral phenotype is *sustained attention*. Patients with PKU, even when treated, demonstrate increased reaction times (RTs) on neuro-psychological tasks measuring sustained attention, which indicate an impaired sustained attention. Asso-

ciations have been found between sustained attention and both *lifetime* and *concurrent* plasma phe levels (Huijbregts, de Sonneville, Licht, von Spronsen, Verkerk, and Sergeant, 2002; Schmidt, Burgard, and Rupp, 1996; Schmidt, Rupp, Burgard, Pietz, Weglage, and de Sonneville, 1994; Weglage, Pietz, Fünders, Koch, and Ullrich, 1996). These irreversible lifetime and reversible concurrent effects of phe levels correspond respectively to the etiological and constitutive aspects of mechanistic explanation.

Evidence for *long-term* effects of phe levels is provided by Huijbregts et al. (2002). This study examined 7–14 year old children with PKU and found that, besides age, lifetime phe concentration was a good predictor for the performance on attention tasks. *Concurrent* effects of plasma phe levels were demonstrated by Schmidt et al. (1994). They experimentally varied plasma phe levels of early-treated adult PKU patients who were off diet in a high–low–high design, and a test for sustained attention was conducted at these three points in time. During the first test, patients performed worse than controls. After a reduction of the plasma phe level, however, performance considerably improved. During the third test, when phe levels were increased again, task performance worsened significantly as compared to the second test time.

Mechanisms of PKU

The lifetime effects of the phe level call for an etiological explanation. One proposed explanation concerns the *interaction* of the elevated phe level with the development of functions like strategic planning behavior, and systematic problem solving (Huijbregts et al., 2002). A normal development of these functions may be required for attentional control later in life. High phe levels during the developmentally important stages of these functions may interfere with a normal development and thus affect attentional performance later in life. If that is correct, an isolated causal path from gene to sustained attention cannot be singled out from the etiological background as explanation for the increased RTs.

What about constitutive decomposition? Empirical research has demonstrated that it *is* possible to isolate underlying components from the genetic locus to a behavioral phenotype for the concurrent effects of plasma phe levels. As schematically illustrated in Figure 2, the effect of concurrent phe levels on attention is explained by a *prefrontal cortex dysfunction* (Diamond, Prevor, Callender, and Druin, 1997). The idea is that elevated levels of phe in the *blood*, caused by decreased activity of the PAH enzyme, result in a lack of tyr *in the brain*. The reason is that phe and tyr share the same limited supply of transporter molecules to pass the blood brain barrier. Phe, however, has a greater affinity with these transporter molecules than tyr does, placing

tyr at a competitive disadvantage in finding transport into the brain. As a consequence, elevated levels of phe may result in a serious decrease of tyr levels in the brain. Tyr is a precursor of dopamine (tyr is hydroxylated to DOPA from which dopamine is produced). Because neurons that project to the prefrontal cortex are more sensitive for a lack of dopamine than other brain regions, it might be expected that especially those functions that are dependent on the prefrontal cortex will be impaired. These functions are executive functions, one of which is sustained attention.

The criticisms against decomposition of phenotypic behavior may be justified with respect to prior causal paths (etiological decomposition). The task to decompose phenotypes in underlying component parts, however, need not be in vain (constitutive decomposition): PKU presents a case where *concurrent* effects are explained by isolated underlying genetic components. This explanation is remarkably similar to the "domino model" which was the target of interactionist criticisms.

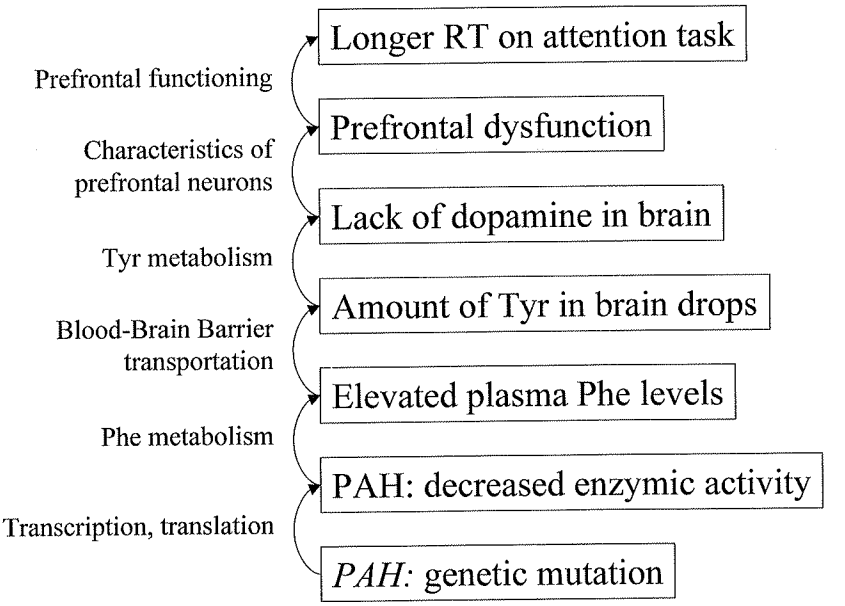

Figure 2: The path from gene to behavior in (early treated) PKU. This domino schema of genetics forms a constitutive explanation for the longer reaction times (RT) on sustained attention tasks found among PKU patients. Such schema is usually targeted by critics who stress the interactive nature of genes and environments.

Genetically Based Predictions

An outright holistic interpretation of PKU is not only undermined by the possibility to furnish mechanistic explanations, it is also weakened by the possibility to make reliable *predictions*. Although modest, it is possible to predict aspects of phenotypic properties of PKU on the basis of genetic and environmental information. Some studies have suggested a simple correlation between *PAH* genotype and metabolic phenotype (Guldberg et al., 1998; Kayaalp, Treacy, Waters, Byck, Nowacki, and Scriver, 1997; see also Güttler and Guldberg, 2000), which can be used to predict the severity of PKU on the basis of the genotype alone and subsequently anticipate dietary requirements. This indicates that existing interactions do not make the phenotype unpredictable.

More interesting in this respect is the prediction of cognitive phenotypes, like the genotype-based prediction of *intellectual performance* (Greeves et al., 2000; Güttler et al., 1999). Many patients who discontinue dietary therapy around the age of eight demonstrate a drop in IQ points later in life but others do not loose points, or even gain in IQ.[13] Whether discontinuing the dietary treatment results in intellectual decrease or increase depends on the residual activity of the mutant PAH enzyme. Because the *residual activity* of the mutant enzyme is dependent on the genotype, the genotype of PKU patients can be used to predict IQ change after diet discontinuation. Greeves et al. (2000) demonstrated that if the mutant gene codes for a mutant enzyme with a residual activity of 25% or less, the patient will probably loose IQ points after diet relaxation at eight years, while the patient may gain IQ points if the residual activity is above 25%. In other words, based on the information about the genetic and environmental factors (the *PAH* genotype and the restriction on dietary uptake of phe respectively), predictions about a phenotypic property as complex as the IQ can be made.

Limitations of Mechanistic Explanations

It is important not to overestimate the status of the mechanistic explanations presented in this section. Firstly, mechanistic explanations do not tell a complete story: they are at best *partial* accounts since the etiological aspect is not paid attention to. In most real life cases, both lifetime and concurrent plasma Phe levels will affect phenotypes, such as an impaired sustained attention. These phenomena need an account that involves *both* the constitution and the etiology.

[13]A gain is possible because of positive social and psychological effects of discontinuing the burdensome treatment, e.g., more opportunities to participate in relationships with peers.

Secondly, constitutive explanations are *context sensitive* (Looren de Jong, 2000; Schouten and Looren de Jong, 2001), which adds a *pragmatic* dimension to genetic explanation (Gannett, 1999). Charles Scriver and Paula Waters (1999) reviewed much of the PKU research on complexities at different phenotypic levels and concluded that even a monogenic trait like PKU is multi-factorial at all of these levels. The cognitive phenotype, for example, is modulated by individual differences between non-genetic characteristics of the blood–brain barrier (Möller, Ullrich, and Weglage, 2000). The metabolic phenotype (the phe homeostasis in the blood) turns out to be a complex process too, involving, next to PAH activity, intestinal absorption of phe and phe uptake by the liver. Thus, even though genes play a role in mechanistic explanations, these explanations are just approximations. A complete story would include the integration of these different subsystems as part of the description of the underlying mechanisms that account for the overall behavior.

Thirdly, the predictions that are based in genetic information do not support an outright genetic determinism, because they are at best probabilistic. Despite broad and significant correlations, inconsistencies appear in both examples. Discordance between *predicted* metabolic phenotype on the basis of the genotype and the *observed* phenotype occurs for a significant number of subjects. Kayaalp et al. (1997) explicitly state that the hyperphenylalaninemia phenotype cannot be deduced from even complete knowledge of the component properties such as residual enzyme activity. Such failure of prediction supports the claim that significant stochasticity exists in the relation between genes and phenotypes. Therefore, "it will always be better to observe and monitor the phenotype in the particular individual than to assume that it can always be predicted with confidence" (Kayaalp et al., 1997, p. 1314).

Conclusions

It has been demonstrated that the conceptions of genes as coding for phenotypes cannot be easily applied to behavior and, more seriously, that these conceptions misguide empirical endeavors striving for genetic explanations of behavior. Genes speak "biochemistry" (Scriver and Waters, 1999, p. 271): they code only for the amino acid sequence of proteins. With regard to behavior this means that research aimed at finding genetic explanations had better consider genes as "merely" *causal components* of mechanisms that account for that behavior, rather than to adhere to the misleading notion of genes as representing the behavior to be explained.

The assumption that genes code for behavior in a similar manner as genes code for proteins places too much confidence in the theoretical universality

of genetics (cf. Cartwright, 1999).[14] Interpretation of genetic explanation calls for an explanatory pluralism, which rejects the idea that explanations are to be sought at only one particular level (McCauley, 1996; McCauley and Bechtel, 2001). Research should focus on explanatory components at different levels of analysis and try to understand how these can be integrated into the causal background responsible for the behavior to be explained (Craver, 2001). Such an approach assumes that behavior can be meaningfully decomposed. It is important to recognize two kinds of decomposition: etiological and constitutive. Even if an etiological decomposition of behavior is not possible, a constitutive decomposition may yield genuinely mechanistic explanations which can even initiate interventions and thus be of practical use for clinicians. The rejection of research that aims at an understanding of the way genes in isolation affect behavior is unnecessary. Although psychology is different from biology and thus should not focus too much on biological methods, psychology can nevertheless benefit from biological tools like genetic accounts of behavior.

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[14]Interestingly, Cartwright provides PKU as a counterexample to her own thesis because PKU would be a case where a genetic analysis has been successfully implemented into a treatment preventing behavioral problems:

> Now that we understand that the serious mental handicaps of phenylketonuria (PKU) are due to a single point mutation that leads [to] too much accumulation of one amino acid and not enough of another with a resulting failure of neurological development, we can adjust the diet of the children affected till the relevant period of development is over. (1999, p. 17)

Historically, however, Cartwright is mistaken on this point. The development of the dietary therapy *preceded* the discovery of the genetic origin and was based on the findings about Phe levels and enzymatic activity, not on an analysis of DNA. It is perhaps even impossible to give an example of a disease of which an effective therapy has been developed completely or partly on the basis of a DNA sequence.

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Human Consciouness: A Systems Approach to the Mind/Brain Interaction

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This paper focuses on a logical systems flow-down of a set of consciousness requirements, which together with biological quantification of human brain anatomy sets limits on the neurological network in the cerebrum in order to produce the mind. It employs data (where available) to validate inferences, or when data do not exist, proposes methods for acquiring valid evidence. Many of these systems requirements will be imposed after some fundamental assumptions are made. These assumptions are not new to theories on consciousness. However, their application as fundamentals may actually represent a new approach. Concurrent with these fundamentals, explicit periods of awareness while conscious are employed. Justification for their use is found in a theoretical process described as cerebral fusion. Additionally, storage of memory elements is postulated within local glia sites, proximal to synaptic nodes, and conductive transport through the astrocytes responsible for recall of data. The model permits variations in neural–glial interface physics and allows forecasts of mind/brain dysfunctions to be inferred. One key result from the model is hypothesized and expanded upon, and may have impact in certain types of dementia, such as Alzheimer's disease.

Advances in imaging technologies, along with a focus on the importance of cerebral processing in medicine and computer development during the last two decades, have provided the framework for many new approaches in both the theory and experimental data pertaining to the mind/brain interaction (Baars, 1997; Damasio, 1994; Dennett, 1991; Newman, 1977). During this period, newly formed departments of conscious awareness and cognitive science have appeared at university centers worldwide. Together with institutional research and development projects, scientists and philosophers from many disciplines have joined this quest: How indeed does the human mind perceive reality, form thought and reason, and experience qualitative emo-

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