

**Nature via Nurture: What to do with Cases of Gene-
Environment Covariance**

by

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Abstract

Heritability studies have traditionally sought to partition phenotypic variation into genetic and environmental sources. In simple cases, a high heritability estimate (H^2) is meant to correspond to phenotypic differences which have been, in some sense, genetically caused. Gene-environment (G-E) covariance, which occurs when different genotypes assort non-randomly among different environments, can lead to a H^2 that does not accord with common-sense ascriptions of genetic causation. Some have argued that this phenomenon undermines the effectiveness of H^2 as a means for causal inquiry. Others believe that the resulting variance can be ascribed to existing variables in the heritability model, however, which variables is subject to further debate.

The aims of this thesis are twofold. The first is to draw attention to G-E covariance in both human and animal research, as an underrepresented source of phenotypic variance, and potential contributor to ‘missing heritability’. The second is to examine the controversy surrounding the interpretation of G-E covariance. Although G-E covariance does not necessitate a causal relation, it is often interpreted causally, and causal motivations appear to shape different interpretations. I use concepts from the interventionist account of causation to demonstrate: That 1) heritability represents a (limited and specific) causal relationship and 2) different types of G-E covariance vary in their underlying causal structures. While identifying causal differences between cases provides *some* clues regarding interpretation differences, I show that these structures are not sufficient to explain the discord between common-sense ascriptions of genetic causation and the results of some G-E covariant heritability results. Other considerations including the environmental variables specified, the role that agency and blame play in causal attributions, and the concepts embedded in the phenotype under study, are also built into the interpretation of these cases. Taken together these factors account for the dispute regarding interpretation, and shed light on how identified cases of G-E covariance should be treated.

Statement of Candidate

I certify that the work in this thesis entitled “Nature via nurture: What to do with Cases of Gene-Environment Covariance” has not previously been submitted for a degree nor has it been submitted as part of the requirements for a degree at any other institution. I declare that this thesis is an original piece of research and contains no material written by any other person. Any assistance that I have received in my work has been appropriately acknowledged.

.....

Kathleen E. Lynch (41913604)

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List of Symbols and Abbreviations

μ	Mean
σ^2	Variance
2Cov_{GE}	Gene-Environment covariance variable
cG	Childs genotype
Cn	Causal variable (n denotes number differentiating variables)
c_n	Causal value (n denotes number differentiating values)
cV_G	Children's genetic variance
DC	Dichorionic
DZ	Dizygotic
En	Effect variable (n denotes number differentiating variables)
e_n	Effect value (n denotes number differentiating values)
F0, F1, F2...	Sequential ordering of generations. F1 is the offspring of F0. F2 the offspring of F1 etc.
G-E Covariance	Gene-Environment covariance
H^2	Broad Heritability
h^2	Narrow Heritability
MC	Monochorionic
MZ	Monozygotic
MZA	Monozygotic twins reared apart
MZT	Monozygotic twins reared together
pG	Parents genotype
pV_G	Parents genetic variation
R	Response to Selection
S	Selection Differential
V_A	Additive Genetic Variance
V_D	Dominance Genetic Variance
V_E	Environmental Variance
V_{Ep}	Epigenetic Variance
V_G	Genetic Variance
V_{GxE}	Gene-Environment Interaction
V_I	Epistatic Genetic Variance
V_P	Phenotypic Variance
\bar{X}	Grand Mean

List of Equations Used

$$V_P = V_G + V_E \quad (1)$$

$$\sigma^2 = \frac{\sum(x-\mu)^2}{n} \quad (2)$$

$$H^2 = \frac{V_G}{V_P} \quad (3)$$

$$V_P = V_A + V_I + V_D + V_E \quad (4)$$

$$h^2 = \frac{V_A}{V_P} \quad (5)$$

$$H^2 = 2(r_{MZ} - r_{DZ}) \quad (6)$$

$$V_P = V_G + V_E + V_{G \times E} \quad (7)$$

$$V_P = V_G + V_E + 2\text{Cov}_{GE} \quad (8)$$

$$V_P = V_G + V_E + V_{G \times E} + 2\text{Cov}_{GE} \quad (9)$$

$$R = h^2 \times S \quad (10)$$

Chapter 1 Introduction

It is undisputed that both genes and the environment are causally essential for the development of phenotypes. Acknowledging their inescapable interaction during development has been termed the interactionist ‘credo’ (Kitcher 2001) or ‘consensus’ (Sterelny & Griffiths 1999). This widely accepted platitude has often been used as an argument for the dissolution of the nature-nurture debate (Kitcher 2001). However, the false dichotomy between genes and environment represents a straw man for a substantial part of the discussion concerning nature and nurture. This is because a large amount of the debate is in reference to heritability, an estimation of the causes of phenotypic differences. Under a heritability framework it makes sense to ask whether nature or nurture contribute more, for despite the interaction of the two for the development of a phenotype, it is an empirical matter as to how much each contributes to *phenotypic variation*.

In simple cases, a high heritability estimate is meant to correspond to some notion of genetic cause or genetic determination – where a large amount of phenotypic variation is accounted for by genetic differences among individuals in a population. However, examples involving more complicated causal stories, such as a covariance of genes and environment¹, can yield a heritability estimate that does not accord with common sense attributions or intuitions of ‘genetic causation’. This problem has led to debate amongst philosophers, psychologists, and geneticists, concerning the validity of heritability estimates and the way in which gene-environment covariance (henceforth G-E covariance) should be treated. Some believe that the estimates should be maintained, others that the estimates should be rejected, and some that an additional variable should be added to the heritability model. Those that suggest the estimate be rejected or amended appear to be

¹ There are other conceptual and methodological reasons to question the validity of heritability estimates. These shall be discussed in more detail in chapter 2.

motivated by a belief that when heritability estimates do not accord with intuitions about genetic causation, the fault is with the heritability estimates, rather than the causal intuition(s).

This thesis does not attempt to determine whether to favour the intuition or the estimate when causal intuitions and heritability claims conflict. Instead I aim to shed light on the salient factors at the root of the G-E covariance debate. That is, to make clear the implicit determining factors that underlie current disagreements and contribute to the intuition conflict that occurs with some heritability estimates. By understanding the role of causal structures, variable specification, notions of agency, and phenotype specific concepts, those engaged with the debate can reach an understanding of the factors that are driving their causal intuitions. Thus I hope that by considering these underlying factors, more informed decisions can be made about how to interpret G-E covariance cases in heritability studies.

While discussion of G-E covariance gained prominence in the 1970s and 1980s, debate appears to have reached an impasse, with some prominent quantitative geneticists dismissing the phenomenon altogether. In contrast, its more popular cousin gene-environment interaction (discussed in chapters 2, 3 and 7) is gaining increasing attention as empirical and philosophical evidence affirms its importance. In addition to providing tools for its interpretation, this thesis shall argue for the importance and relevance of G-E covariance in both animal and human research.

In order to place this discussion in context, a brief overview is given to situate the nature-nurture debate in the contemporary battle-ground of the study of heritability.

1.1 Nature versus Nurture: A Historical Overview of the Debate

The ‘nature versus nurture’ debate has had an enduring history, with origins tracing back to Hellenic debates. In Plato’s Republic, Socrates recounts a fable to Glaucon in which he justifies² the ranking of individuals and their assignment to different roles in society. This justification is based on innate and heritable distinctions between individuals (Republic III, 414e – 414d). While the genotype is not recognised as a determinant in this story, the sentiment that inherited factors are paramount to explaining individual differences parallels the ‘nature’ position in more current debates.³ Additionally, the story alludes to an early statement of eugenics: ‘...there is nothing which should so anxiously guard, or of which they are to be such good guardians, as of the purity of the race’ (415c).

Similar ideas were later re-emphasised in a biological setting in the 1870’s, the beginning of what Matthew Ridley (2003) calls the ‘hereditarian heyday’, which lasted until the 1920’s. A key factor in this movement was the publication of Sir Francis Galton’s ‘Hereditary Genius’ (1869) which examined the heritability of intelligence by comparing the relatives of successful men. Later in 1874 Galton published ‘English Men of Science: Their Nature and Nurture’ in which he concluded that the men he had studied owed their success mostly to inherited innate factors.^{4,5} It is this text in which the terms ‘nature’ and ‘nurture’ are first introduced.

² It is worth mentioning that this tale is told as a fable which both Socrates and Glaucon consider to be untrue. As Socrates tells the story he first admits that it is ‘a royal lie’ and an ‘audacious fiction’ of which Glaucon agrees.

³ A related historical parallel is the debate between the rationalist and empiricist movements of the 17th and 18th centuries. This debate primarily concerned the origins of knowledge, rather than the kinds of behavioural and physiological phenotypes studied in today’s nature-nurture debate, and as such shall not be included in this thesis.

⁴ Although he did maintain that a ‘suitable’ environment also needed to be provided.

⁵ Although Galton was a eugenicist and strong adherent of hereditarianism, he recognised that both nature and nurture must contribute in some way. For instance, though a serious proponent of the heritability of cognitive abilities, he recognised some of the methodological issues in ascertaining this information, like the environmental confound of parental encouragement (see Sesardic 2005, p. 16).

The hereditarian hey-day also saw a shift in the focus of phenotypes under study, with an emphasis emerging on cognitive abilities, particularly intelligence. This was partially facilitated by the work of psychologist Cyril Burt, who published studies similar to Galton. His results⁶ showed that children with academic parents had higher IQ scores than ordinary children (Burt 1909 as cited in Hearnshaw 1979). Burt used this information to conclude that intelligence is a heritable trait and also believed, like Galton, that each child had a limited capacity for learning and intelligence.

In opposition to the ideas of Galton and Burt was the psychologist Alfred Binet. Binet was the first to develop a standardised test for intelligence – measured by the intelligence quotient (IQ). His quantification of intelligence was intended to aid educational interventions for children with below average scores. Binet believed that the environment, or ones ‘nurture’ could influence their intelligence (as measured by IQ). However, despite Binet’s motivations it was the Galtonian concept of capacities and limits that prevailed for the most part of the 19th Century, and which underlies many assumptions about IQ made today.

Presently, the nature and nurture of intelligence is the most widely studied phenotype in behavioural genetic research (Plomin & Spinath 2004). Recent controversy in this area has concerned attempts to use heritability studies of intelligence to explain racial differences (Herrnstein & Murray 1994; Jensen 1968; 1969; Wade 2014), and to promote (Heckman 1995; Turkheimer et al. 2003) or oppose (Herrnstein & Murray 1994; Jensen 1969) interventionist educational programs. The significance of the focus on intelligence in heritability studies is explored in chapter 8.

⁶ Since the publication of Burt’s studies his results have been shown to be fraudulent. For details of this scandal see Gould (1996, Chapters 4 and 5); Hearnshaw (1979) and Lewtonin, Rose and Kamin (1984).

1.2 Does Nature versus Nurture equal Genes versus Environment?

It is worth noting that the hereditarians, like the earlier philosophers, were unaware of the mechanisms of inheritance. Galton was inspired by his cousin Charles Darwin's, *The Origin of Species* (1859), which introduced the first widely accepted biological theory of evolution. However, at that time the mechanisms underlying phenotypic variation and inheritance were still unknown. These days, nature-nurture type discussions centre on heritability studies, which is the domain of quantitative and behavioural genetics.⁷ In this debate, 'gene' is synonymous with 'nature', while any non-genetic causes are usually labelled as the 'environment' and correspond with 'nurture'.

1.2.1 The Nature of Genes and the Environment

Heritability is a statistical parameter where phenotypic variance (V_P) is partitioned as the additive effects of variation in genes and environment (equation 1).

$$(1) \quad V_P = V_G + V_E$$

As one of the variables factored into this parameter is genetic variance (V_G) it is important to distinguish what is meant by 'gene', 'genotype' and 'genetic', throughout this thesis.

The gene concept has many faces, and some of these different meanings have been thought to contribute to misunderstandings in related philosophical debates (Fogle 2000; Griffiths & Stotz 2007; 2013; Moss 2004). These complications have led some philosophers to conclude that there is no precise definition of a gene (Burian 1985; Fogle 1990; 2000; Morange 2000). For instance Fogle (2000) believes that the gene concept is a large abstract

⁷ In this thesis I make reference to both the fields of quantitative and behavioural genetics. Quantitative genetics arose from the fusion of the biometric tradition with the tenets of Mendelian inheritance, which has led to the model of heritability referred to throughout this thesis (this integration is described in more detail in chapter 2). Although quantitative genetics could be used as an umbrella term for all the fields that utilise heritability estimates, it is commonplace to refer to behavioural genetics when heritability models are applied to behaviour, generally in humans, and to delegate the term quantitative genetics to studies that investigate the heritability of physiological traits, usually within animal and plant populations.

amalgamation of different features, with ‘flexibly applied parameters’. Similarly, Carlson (1991), Portin (1993), and Griffiths and Stotz (2006; 2007; 2013) believe that the gene concept is pluralistic, with a large reference potential, and that the exact usage of the term can be deduced by context. Keller (2000, as cited in Neumann-Held 2001) has argued that this disarray provides conceptual value; however, many others have pointed out that this treatment of the ‘gene’ can lead to confusion. When multiple concepts are encompassed under one term, it allows for the possibility for theorists to ‘talk past each other’, stalling or derailing fruitful debate (Griffiths & Neumann-Held 1999; Griffiths & Stotz 2013; Moss 2001). While this conflation has not generally been problematic for experimental biologists, it has impacted theoretical and philosophical discussions, including debate regarding the validity of heritability estimates (Griffiths & Stotz 2013, chapter 7).

Some have reacted to this problem by calling for a rejection of the term ‘gene’ altogether. For example, Kitcher (1982) has suggested that the term ‘gene complexes’ should be used as a replacement concept. Others have attempted to pluralise the gene concept by addressing the multiple meanings that occupy the reference class of ‘gene’ (Griffiths & Stotz 2007; 2013).

Another response has been to dichotomise this plurality by defining two distinct gene concepts (Griffiths & Neumann-Held 1999; Moss 2001). Although the details of these dichotomies vary, they can be amalgamated to roughly divide the gene concept into two camps⁸: The Molecular gene and the Mendelian gene. These two gene concepts have been shown to play different explanatory roles, and to be suited to different scientific contexts (Griffiths & Stotz 2006; 2007).

⁸ Some of the concepts presented here as being congruent actually differ subtly, however, for the purpose of this thesis it is not necessary to canvass these differences.

The molecular gene is a sequence of DNA that plays a functional role in producing an RNA template, which then leads to the production of a polypeptide (Neumann-Held 2001). This concept roughly corresponds to Moss's (2001) 'gene-D' (D for developmental resource), and what Dawkins (1976) terms a cistron – a term originally due to the molecular biologist Seymour Benzer. One feature of the molecular gene is that it has informational specificity, meaning that its nucleic acid sequence specifies the sequence of a gene product, either a RNA sequence or polypeptide chain (Griffiths & Stotz 2013). These sequences sometimes appear clearly as a section in the genome, as the beginning and end of the genes are marked by start and stop codons, which are identifiable nucleotide sequences used by enzymes, RNA polymerase, and ribosomes to commence and cease the transcription and translation process respectively.

Such a clear delineation, however, is not always the case, as often the specification of the linear sequence of a particular protein derives from more than one gene, which can be spread throughout the genome. Additionally, the regulated synthesis of a polypeptide needs more than a coding region alone (Neumann-Held 2001). Stotz (2006) has argued that the specificity required for a particular polypeptide is distributed throughout the genome, gene-products, and cellular environment. The complexity of interactions within the genome and with other molecules can be problematic for conceptualising the Molecular gene. However, these are not issues that are dealt with in this thesis. This is because this thesis utilizes a different conception of the 'gene', namely, the Mendelian gene.

The Mendelian gene does not refer to a particular molecular sequence in the genome, but instead serves as a statistically valid predictor of phenotypes. Thus Mendelian genes are identified in reference to their phenotypic effects, rather than their physical basis (Sterelny & Griffiths 1999). This concept stems from the 'factors' concept used by Gregor Mendel to predict the outcome of breeding experiments (Griffiths & Stotz 2013), which for a long

time remained unobserved theoretical entities. The Mendelian gene is synonymous to the classical gene of transmission genetics, and is closely related to what Moss (2001) has termed ‘gene-P’ (P for phenotype, prediction or preformation). As the Mendelian gene concerns the statistical association of genotypes and phenotypes in a population, it is this concept which is used in quantitative and behavioural genetics (Griffiths & Stotz 2013), and thus the concept which shall be used in this thesis.⁹

The concept of ‘environment’ also has a variety of contested meanings. For some, the environment refers to only factors outside of the organism, such as temperature, latitude, food abundance, and social structures. This is the way the environment is most commonly measured in heritability studies. For others, the environment encompasses features internal to the organism, like cells and extra-cellular structures, including cellular factors that can impact on DNA expression. These include proteins and RNAs, as well as other sections of DNA sequence (Brakefield 2006; Gilbert 2000; Haig 2012; Riegler 2008; Schmalhausen 1949; Sterelny & Kitcher 1988; Waddington 1942; Williams 1966).

In heritability studies, the environmental parameter, V_E , is estimated by subtracting the variance inferred by V_G , as measured by family resemblances. V_G is quantified by the ratio of genetic similarity between family members. For instance, monozygotic twins are known to have identical DNA sequences ($V_G = 0$), parents share 50% of their DNA with their offspring, and dizygotic twins as well as siblings share, on average, half of their DNA. Thus when used in this thesis, the term genotype, gene, and genetic variance (V_G) refer only to some section or sections of DNA, however, *which* sections are usually not specified or relevant.

⁹ While the Molecular gene refers specifically to DNA in its conceptual content, the Mendelian gene is not principally restricted to any particular material basis. On this basis some have argued that the Mendelian gene should encompass heritable factors other than DNA (Bourrat & Lu, unpub.). For simplicity in this thesis I shall not be extending the definition in this way. This decision is partially based on the common usage of the terms in behavioural and quantitative genetics, and partially based on the methods used, and assumptions made that are factored into heritability models.

Thus for heritability, the environment is interpreted to mean anything that is not genetic (Falconer & MacKay 1996). V_G represents variation in *genotypes*, which encompasses all the nuclear DNA within an organism.¹⁰ Under this definition of genes, genetic and genotype, the environment referred to in this thesis refers to the aggregate of what Williams (1966) called the ‘somatic’ and ‘ecological’ environments. As it is variation across whole genomes that are studied in quantitative genetics (V_G), the genetic background is not counted in this definition of the environment.

1.2.2 Additional Heritable Factors

An additional problem with the ‘nature equals genes’ assumption is the presence of non-genetic heritable factors. Firstly, organisms inherit a maternal-internal environment. Placental mammals inherit the maternal environment of their mother’s womb, and all organisms inherit environmental conditions within their mother’s egg cell, and, depending on the organisms, the place where the fertilised egg is laid. In humans the first 9 months of development has been shown to be a significant factor for later health (Gluckman & Hanson 2004; Gluckman, Hanson & Pinal 2005). This has also been demonstrated in animal models. For instance, stress in rats has been shown to affect the function of the kidney, cardiovascular system, and pancreas (Gluckman et al. 2008), and it has been established that foetal under-nutrition affects leptin and insulin action, causing higher blood pressure, increases in appetite, and obesity (Vickers et al. 2000). Foetal under-nutrition has also been demonstrated to produce pups with a higher degree of sedentary behaviour, independent of postnatal nutrition (Vickers et al. 2003). A similar result in humans has been observed, by examining the consequences of the Dutch famine.

¹⁰ Another issue with defining genes, genetic, and genotype is the presence of mitochondrial DNA (mtDNA), which is inherited only through the maternal line. As such, if included in V_G , the standard ratios of genetic similarity between siblings, parents and offspring do not apply. Because of this, MtDNA shall also be absent from the discussion of genes, genotypes and genetic in this thesis. This is not to deny their phenotypic importance, but simply to show consistency with quantitative genetic methods, to avoid complications, and to limit the scope of this discussion.

Individuals who experienced the famine while in-utero were more likely to have coronary heart disease, altered blood clotting, and higher rates of obesity and diabetes (Painter, Roseboom & Bleker 2005). Devlin et al. (1997) have suggested that maternal effects contribute to phenotypic variance for complex cognitive traits like IQ, and argue for their consideration in heritability estimates. This is described in more detail in section 2.7.

Secondly, animals that experience parental care also inherit an environment in which they are reared. This can span from the physical environment, like the particular cave, nest, burrow, or house that one grows up in, to behaviours from parents such as feeding, grooming, and the vertical transmission of skills and knowledge.¹¹ Thirdly, non-genetic cellular materials are inherited through the maternal line, such as methyl groups and histone modifying compounds which attach to DNA sequences and regulate gene expression. This type of inheritance is called epigenetics.

In quantitative genetics inherited environmental conditions are traditionally partitioned under V_E (Sesardic 2005, p.104). Their correlation with inherited genotypes exemplifies passive G-E covariance, which is discussed in chapter 4. Prenatal conditions in the maternal environment are principally also part of the environment as defined in the previous section, and so variations in exposure to these conditions should also be subsumed under V_E according to traditional quantitative genetic models (Plomin et al. 2008, pp.306-307). However, in practice this is often not undertaken¹², and the limitation is largely ignored. So while practically these first two factors may not be separated according to principle, there is consensus as to how we *should* treat the first two heritable sources of phenotypic variation.

¹¹ Others (for example Avital & Jablonka 2000; Jablonka & Lamb 2005) have focussed on the evolutionary implications of these different kinds of inheritance systems, however, these are not the focus of this thesis.

¹² Although some animal studies do take care to control for these kinds of influences. See for example Barber and Arnott (2000), Francis et al. (2003), Rice et al. (2009) and Dias and Ressler (2013).

The treatment of inherited epigenetic variation (V_{Ep}) is much more complex. Epigenetics is ‘...the study of the mechanisms that lead to persistent developmental changes in gene activities and effects, but do not involve altered DNA base sequences’ (Jablonka & Lamm 2012, p.7) and epigenetic inheritance ‘...occurs when phenotypic variations that do not stem from variations in DNA base sequences are transmitted to subsequent generations of cells or organisms.’ (Jablonka & Raz 2009, p.132). In essence, it encompasses heritable factors which impact upon phenotypic variation, that do not appear to fit a traditional picture of genes or environment.

Some commonly discussed epigenetic mechanisms include DNA methylation and histone modification (see Figure 1.1). Both of these processes work by altering the ease of transcription of DNA sequences. Methyl groups attach to regions of the genome (cytosine bases) and can interfere with transcription factors and enzymes needed to bind DNA to transcribe those DNA sequences. Methyl groups can also recruit enzymes that modify histones, another type of epigenetic modification. Histones are proteins used to package DNA into chromosomes, and have dangling N-terminal tails that can be covalently modified. Epigenetic modifications of histones can affect the expression of the DNA packaged in the histones (nucleosomes), by making it easier or more difficult for transcription factors and RNA polymerase to access and transcribe the sequences.

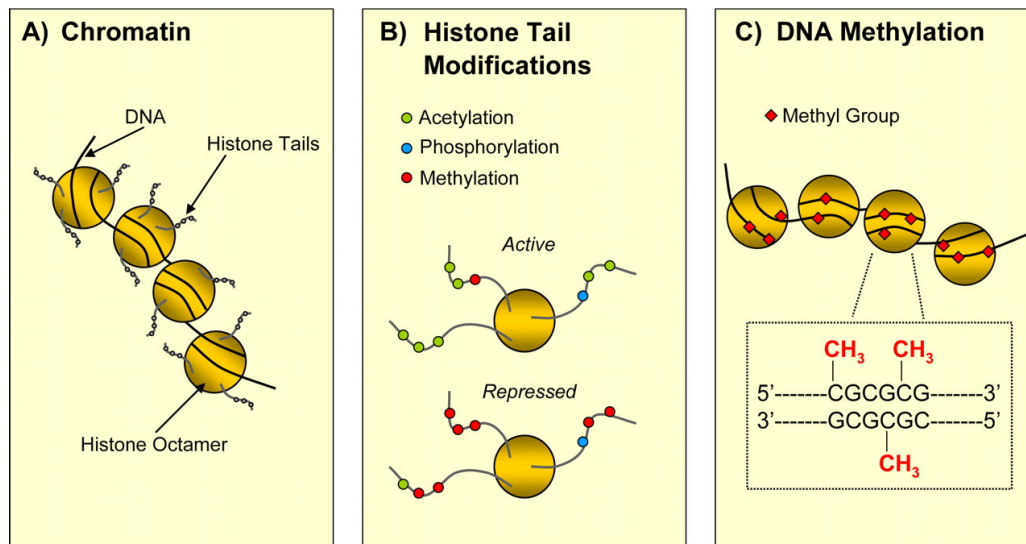


Figure 1.1 A Schematic of Epigenetic Marking In A) DNA is condensed and packaged with histones. B) shows the N-terminal tail of a histone which contains multiple sites for epigenetic marking via acetylation (green circles), methylation (red circles), and phosphorylation (blue circles). C) displays another method of epigenetic marking, DNA Methylation, where methyl groups (red diamonds) attach to cytosine bases in genomic regions in and around gene promoters that are rich in cytosine-guanine nucleotides (CpG islands). The addition of methyl groups at gene promoters is generally linked to transcriptional repression (Image from Jiang et al. 2008, p.11754).

While epigenetics is gaining increasing attention in biological research, limited work has been done in relation to heritability estimates. Those who have explored this area (Bonduriansky 2012; Bonduriansky & Day 2008; Jablonka & Lamb 1995; 2005; Jablonka & Lamm 2012; Jablonka & Raz 2009; Johannes, Colot & Jansen 2008; Johannes et al. 2009; Johannes & Colome-Tatche 2011; Mameli 2004; Nelson, Petterson & Carlborg 2013; Pigliucci & Muller 2010; Richards, Bossdorf & Pigliucci 2010; Slatkin 2009) have largely concentrated on evolutionary implications and technical experimental design considerations. As such, epigenetic causes of phenotypic variance are yet to be formalised into quantitative genetic models or reconciled with heritability estimates.

A likely reason for this is the complexity and unpredictability of epigenetic inheritance mechanisms and systems, and the difficulty of distinguishing epigenetic from genetic

inheritance. For instance, some epigenetic variations have been shown to stably persist for multiple generations, paralleling genetic inheritance (Cubas, Vincent & Coen 1999; Johannes et al. 2009; Manning et al. 2006). In contrast, other epigenetic variations appear to decay over time, with the related phenotype and underlying epigenetic mechanisms decreasing in proportion over subsequent generations (see for example Boucher, Ewen & Stowers 1994).¹³

Another complexity is that epigenetic modifications can be both acquired (environmentally induced) and inherited. For example the toadflax (*Linaria vulgaris*) displays natural variation in its floral symmetry, with two morphological variants: wild-type and peloric (Figure 1.2). These variants were first described more than 250 years ago by taxonomist Carl Linneaus, and have since been thought to be due to the segregation and inheritance of Mendelian alleles (Gustafsson 1979). However, Cubas, Vincent and Coen (1999) discovered that this variation was actually due to the presence of epi-alleles, where the *Lcyc* gene is transcriptionally silent in mutants because of epigenetic modifications.

We do not know where and how the first epi-allele in the toadflax originated. This can be contrasted by recent work by Dias and Ressler (2013), in which epigenetic variation was induced by environmental variation, causing phenotypic variation that was subsequently inherited through the germ line. In this study one generation (F0) of male mice were conditioned to fear the smell of acetophenone, by subjecting them to a conditioning treatment involving electric shocks.

¹³ See Jablonka and Raz (2009) for a comprehensive list of epigenetically inherited traits and their transmission stability.



Figure 1.2 Wild Type (left) and Peloric epimutant (right) morphologies of *Linaria vulgaris* (Image adapted from Bird 2007, p.397).

It was found that the male offspring of these mice (F1) and their grandsons (F2) were more sensitive to the smell of acetophenone, and produced a more pronounced fear response in its presence. Furthermore, the F1 and F2 generations had a larger acetophenone responding glomeruli in their olfactory bulb than control mice (Figure 1.3). This inheritance of behavioural and neurological phenotypes was maintained even when mice were cross-fostered and when in-vitro-fertilisation was used to control for maternal effects. To demonstrate that this acquired inheritance was due to epigenetic mechanisms, the sperm of the mice was studied and was found to be hypomethylated at the *Olf151* gene – which codes for odourant receptors activated by acetophenone.

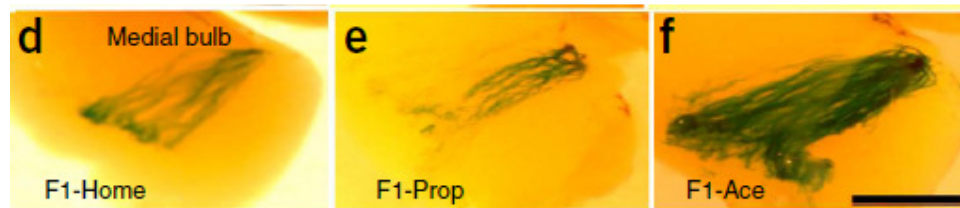


Figure 1.3 β -galactosidase staining of The M71 glomueril in medial bulb of F1 mice d) shows the offspring of a mouse that had not been conditioned to fear any smells; e) shows the offspring of a mouse that had been conditioned to fear a different smell, propanal; and f) is from the offspring of a mouse conditioned to fear acetophenone. Scale bar represents 1mm (Image adapted from Dias & Ressler 2013, p.3).

Another example of acquired epigenetic inheritance is the epigenetic programming of fear response and maternal behaviours in rats. Meany (2001), Weaver et al. (2004) and Champagne and Curley (2009) demonstrated in cross-fostering experiments that the amount that pups have been licked and groomed by their mothers (including foster mothers) induced differential epigenetic modifications at gene promoters in their hippocampus. These modifications persisted into adulthood resulting in the same maternal behaviours towards their own pups, and caused the same epigenetic modifications in subsequent generations. The experiments showed that stressed mothers produced lower levels of licking which down-regulated gene expression, causing their offspring to produce a higher stress response throughout their lifetimes. When the offspring grew up into mothers, they displayed the same stressed behaviour of sparsely licking their own pups. Relaxed mothers licked and groomed their pups more generously, producing relaxed and frequently licking mothers in the next generation. As Meany (2001) points out, producing stressed offspring may not be a bad thing, since being stressed prepares pups for the environmental conditions they are born in to. This form of epigenetic inheritance facilitates phenotypic plasticity that allows for adaptation to the environment over small timescales.

The transmission of epigenetic markings in these studies differs from the Dias & Ressler experiment, as the modifications were not inherited through the germ line, but acquired anew each generation, and transmitted via behavioural inheritance (Stotz & Griffiths 2013).

As well as being affected by environmental influences, some epigenetic variation can be induced by genetic mutations. For example *Arabidopsis thaliana* (rockcress) strains with mutations in the *ddm1* gene displayed methylcytosine reduction which produced phenotypic effects such as developmental abnormalities. When bred to outcross the mutation, the methylation (epigenetic) profiles and developmental abnormalities of these mutants continued to be stably transmitted (Kakutani et al. 1999).

Thus the relationship between V_{Ep} , V_G and V_E is still subject to much investigation, and as such the partitioning of a separate V_{Ep} variable in heritability estimates is questionable. Given this, factoring V_{Ep} into a model predicting outcomes over multiple future generations would be very difficult, as epigenetic variation, whilst conceptually different to both V_G , and V_E , could be intimately and complexly intertwined with genetic or environmental variation (which may or may not coincide with the variation that figures in the model). Epigenetics is briefly discussed again in chapter 5, where epigenetic covariance is mentioned as a possible alternative to explanations in terms of G-E covariance. Aside from this brief mention, epigenetic considerations are left out of this thesis. To sufficiently cover the complex issues related to epigenetics and heritability would require an additional thesis. Instead a discussion of the non-additivity of epigenetics is something I hope to address in future work.

1.3 Nature via Nurture: an Introduction to Gene-Environment Covariance

G-E covariance refers to cases where different genotypes assort non-randomly among different environments. That is, there is a covariation (sometimes just termed correlation) between the genotype of an individual and its environment. These cases are important because they challenge intuitions about what is and what is not genetically determined. G-E covariance cases can present a highly heritable trait that may not coincide with intuitions of ‘genetic causation’. In contrast, they may lower a heritability estimate for a trait which may intuitively be thought of as genetically determined (see chapter 4). This happens when particular genotypes are correlated with particular environments because of an apparent causal link. One way that this can happen is when genotypes cause individuals to develop within specific environments, leading to indirect genetic causation.

Although in heritability estimates covariance is a functional relationship, G-E covariance is typically presented causally. For example, suppose you have a population of children, where some possess genes which engender a love for the musty smell of books, while others do not. In this population there is variation in genotype (V_G) – at least at the book-smell-preference locus (*BSP*). Because of this genetic variation some children are compelled to seek out and surround themselves with books, developing in a different, more book-filled environment than the others who do not possess this gene variant.

Because of the constant surrounding of books, these children are more likely to pick one up and start to read. This means that the children with the *BSP* genes spend, on average, a larger amount of time reading and learning from books than the others. In other words, there is a variation in environments (V_E) between the *BSP* and non-*BSP* children.

This extra reading and learning through books aids the *BSP* children in the skills needed to perform in IQ tests (vocabulary, comprehension skills, etc.) and as a result they are

measured as being more intelligent than those who do not possess the *BSP* genotype. This means that children with different genotypes (*BSP* versus non-*BSP*) have different phenotypic measures in terms of IQ. As such, variation in genotype (V_G) correlates with variation in phenotype (IQ). As I shall show in chapter 6, under an interventionist account of causation, variation in genotype is also said to cause variation in IQ in this kind of situation. For this reason, heritability of this trait would be estimated as high (under an additive heritability model, introduced in section 1.3.1).

However, given common-sense attributions of causation, differences in genotypes with respect to smells do not appear to (at least fully) account for variation in IQ. Variation in educational environment also appears to play an important role. It is these kinds of cases that have sparked the most debate surrounding G-E covariance. Some maintain that the high heritability estimate, and thus attribution of V_P to V_G , should be upheld, and others argue otherwise. Thus the phenomenon of G-E covariance presents a problem for how to partition the relative contributions of variation in genes (V_G) and variation in the environment (V_E) to phenotypic differences.

Situations of this kind gave rise to the title of this thesis - ‘nature via nurture’. The phrase ‘nature via nurture’ has been made famous by popular science writer Matthew Ridley (2003), although the meaning behind this it is not the same as the phrase referred to here. Ridley’s phrase refers to development, much like Kitcher’s (2001) interactionist credo, where genes require an environment to be expressed.¹⁴ However, under a heritability framework, ‘nature’ corresponds to genetic differences (V_G), and ‘nurture’ to differences in the environment (V_E). As such in this thesis the term ‘nature-via-nurture’ refers to cases of

¹⁴ Other writers, such as Keenan, Wallig and Haschek (2010) and Wermter et al. (2010) also use the term in this way.

G-E covariance^{15,16}, which expresses V_G via V_E . These situations embody cases where V_G acts via some environmental selection, impacting V_E , which in turn impacts on phenotypic differences (V_P).

G-E covariance is conventionally separated into active, reactive, and passive forms (Plomin, DeFries & Loehlin 1977). The *BSP* locus example is an active case, as an individual's genotype caused its carrier to actively seek out and modify their own environment. In reactive cases, the covariance between genotype and environment is due to a reaction towards particular individuals with particular genotypes, based on some phenotypic manifestation of their genotype. For example if a society prevents some children from accessing books based on a manifestation of genetic differences, indicated by hair colour, then their educational environment will be correlated with the genotype related to hair colour. Lastly, passive G-E covariance occurs when an individual's phenotype is the result of both their own genotype and the environment they inherited from their parents. Thus because one inherits both an environment and a genotype from their parents, the two covary. This was illustrated briefly in section 1.2.2, and is explained more fully in section 4.1.3. Detailed examples of each kind of G-E covariance are given in chapter 4.

1.3.1 A Purely Academic Problem?

G-E covariance is an example of a non-additive phenomena in heritability estimates. Traditionally, heritability studies partitioned phenotypic variance (V_P) as simply the addition of variation in genes and environment (equation 1). However, when there is a relationship between V_G and V_E , the additivity of this model breaks down.

¹⁵ More specifically, active and reactive cases of G-E covariance.

¹⁶ The term has also been used in such a way by Lykken et al. (1990).

Alongside G-E covariance, Gene-Environment Interaction ($V_{G \times E}$) is a non-additive factor which can skew the results of heritability estimates, and lead to an H^2 that conflicts with common sense attributions of genetic and environmental causes. $V_{G \times E}$ occurs when the effect of a change in value of one variable (such as V_G) varies depending on the values of the second variable (such as V_E). In humans, for example, environmental exposure to benzene is significantly associated with shorter gestation periods in pregnant women possessing the *CYP1A1* gene, whereas no such association exists in non-carriers (Wang et al. 2000). Thus the way that the environment affects a phenotype is dependent upon the genetic background of the individual, and vice-versa.

$V_{G \times E}$ is routinely factored into heritability estimates using techniques such as an analysis of variance (ANOVA) (Falconer & MacKay 1996), and is fairly well recognised and accepted as a limitation by quantitative and behavioural geneticists (Bazzett 2008; Falconer & MacKay 1996; Lynch & Walsh 1998; Plomin et al. 2008). $V_{G \times E}$ has been relatively well studied (Griffiths & Tabery 2008; Tabery 2008; 2014; Tabery & Griffiths 2010), and has known importance to evolutionary contexts such as mate-quality signalling (Kokko & Johnstone 2002). However, this was not always the case. As Tabery (2014) has documented, in the early days of discussing heritability analysis, R.A. Fisher, who invented the ANOVA and was one of the founders of quantitative genetics, dismissed $V_{G \times E}$ as ‘a purely academic problem’ (Fisher as cited in Tabery 2014, p.33). It was not until Lancelot Hogben demonstrated empirical support for the problem that $V_{G \times E}$ was taken seriously as a limitation for heritability (Tabery 2008; 2014). This debate was further developed as more empirical support for the problem came to light, and conceptual and philosophical discussion¹⁷ further contributed to its interpretation (Griffiths & Tabery 2008;

¹⁷ Such as the conflation of two different understandings of the $V_{G \times E}$ term (statistical versus developmental). See Griffiths and Stotz (2013), Griffiths and Tabery (2010), Tabery (2008; 2014), and Tabery and Griffiths (2008).

Tabery 2014; Tabery & Griffiths 2010). Today the debate surrounding $V_{G \times E}$ has shifted somewhat, and now concerns how pervasive the problem is, and what kind of statistical power is needed to detect it (Griffiths & Stotz 2013).

The early history of the $V_{G \times E}$ discussion seems to parallel contemporary attitudes towards G-E covariance. A prominent and oft-quoted textbook still refers to G-E covariance as ‘seldom an important complication, and can usually be neglected in experimental populations, where randomization of environments is one of the chief objects of experimental design’ (Falconer & McKay 1996, p.131). One of the reasons for this current attitude is that unlike $V_{G \times E}$, few studies have been able to estimate and quantify the presence of G-E covariance. This is partially because of the methodological differences in designing an experiment to test for G-E covariance, rather than $V_{G \times E}$. These issues shall be discussed in chapters 3 and 4. Another reason for the difference in attitude may be the conceptual issues surrounding G-E covariance, which have in part been shaped by the history of the discussion. These issues shall be discussed in chapters 5 to 8.

1.4 Thesis Outline

Chapters 2 and 3 frame the argument by introducing concepts from the philosophical literature on causation, and the statistical concept of heritability. Chapter 2 introduces the concept of heritability, and demonstrates how it is estimated. Chapter 3 presents the interventionist account of causation, which I shall use as the foundation for talking about causation throughout this thesis. This chapter also describes causal dimensions that have been used to privilege or select some causes above others within a given system. I show how the statistical concept of heritability relates to this causal account, and how

dimensions of causation such as invariance can be used to inform debate surrounding interpretations of heritability estimates (section 3.5).

Chapter 4 introduces the problem of G-E covariance, and illustrates the three different types: active, passive and reactive. Here I introduce the conflicting opinions on how to interpret G-E covariance cases, and how these appear to arise through an appeal to causal intuitions and ‘common sense’. Although G-E covariance is often overlooked in heritability analyses, especially in non-human studies, I illustrate just how significant its effects are, and how likely the phenomena is to occur in chapter 5.

The latter half of the thesis addresses the reasons for these conflicting opinions, and provides tools for how G-E covariance could be interpreted. In chapters 6 and 7 I use concepts from the causation literature to demonstrate differences and similarities in the underlying causal structures between different types of G-E covariance. In chapter 6 I show how passive G-E covariance differs from the active and reactive types. In chapter 7 I demonstrate the relationship between G-E covariance, and another limitation to heritability, gene-environment interaction. This chapter also describes the role that agency, blame and norms play in shaping causal intuitions. I argue that the only difference between active and reactive cases of G-E covariance is that the intermediate variable is a conscious agent in reactive cases, and not in active ones.

Lastly, chapter 8 addresses a problem particular to active G-E covariance, which has experienced the greatest controversy in interpretation. In active G-E covariance cases there is disagreement as to whether the phenotypic effects generated should be considered as genetic variance, or as a separate source of variation. I show that, depending on the phenotype under study, active G-E covariance cases will differ in how well they accord to common sense accounts of genetic causation. This, I argue, is because the process of active G-E covariance, whereby one modifies their own environment, is related to the motivation

of the individual. This means that when active G-E covariance occurs for phenotypes with some motivational component as part of their concept, they are more likely to appear to be a ‘natural manifestation’ of the genotype (Sesardic 2005, p.94). In contrast, active G-E covariances for phenotypes that do not appear to be related to motivation seem problematic.

This is especially important as the debate in which the problem of G-E covariance is situated revolves around the study of intelligence and IQ. These are phenotypes which have vague and contested conceptual contents, and the motivational aspects of the phenotype are not clear. By considering different kinds of phenotypes and their divergence or convergence on common sense attributions of genetic causes, one can see how the IQ focus of the G-E covariance debate has skewed its interpretation. This shifts the debate from a general dichotomous disagreement about what to do with active G-E covariance in all cases, to one where G-E covariance is assessed on a case-by-case and phenotype specific basis.

On the basis of these considerations, I make several conclusions about G-E covariance. Firstly, G-E covariance is an important factor to be considered in heritability estimates, yet is often overlooked. I argue that it may account for a proportion of the problem of ‘missing heritability’, and is likely to occur in experimental settings where it is currently dismissed. Secondly, interpretation of G-E covariance can be aided by considering the implicit factors which shape conflicting causal intuitions. I show that these are: the underlying causal structure of the system, the variables factored into the system, the presence of other blame-worthy agents in the causal system, and phenotype-specific motivational considerations. I propose that an application of these features can benefit the ongoing debate as to how to reconcile G-E covariance cases with heritability estimates.

Chapter 2 Heritability

Heritability is a statistical parameter that is used to measure the causal contribution of variation in genes (V_G) and environment (V_E) to variation in a given phenotype (V_P). In simple cases, a high heritability estimate is meant to correspond to some notion of a genetic cause or genetic determination. This chapter introduces the statistical notions of broad and narrow heritability, and details some of the ways that they can be estimated. This thesis focuses on broad heritability, as it is the most widely used heritability concept in the social sciences, and relates best to the examples used in the remainder of this thesis. In chapter 3 I give a more thorough account of the causal relationship involved in broad heritability claims.

This chapter starts by introducing the kinds of questions that heritability estimates apply to (sections 2.1 and 2.2), and then explains the statistical notions of heritability (section 2.3). I show how these are used in practise to attain an estimate in section 2.4, using a hypothetical example to detail the ANOVA technique. This example is drawn upon in subsequent chapters (3, 4, 6, 7 and 8) to demonstrate different types of G-E covariance. Section 2.4 also describes other ways that heritability can be estimated - using twin studies. Sections 2.3 and 2.4 assume an additive model of heritability, where variation in genes and environment contribute to variation in phenotype independently from one another, but this is not always the case. Section 2.6 looks at one way that genes and environment can contribute non-additively, via gene-environment interaction ($V_{G \times E}$). This is one of two non-additive limitations to heritability, the second being G-E covariance. While the focus of this thesis is G-E covariance, the relevance of $V_{G \times E}$ to the causal attributions involved with heritability is drawn upon in chapter 3, and the relationship between G-E covariance and $V_{G \times E}$ is explored in chapter 7. Finally section 2.7 introduces the problem of ‘missing

heritability', where high heritability estimates do not accord with the phenotypic variation that can be accounted for in molecular genetic studies. While a myriad of factors have been suggested to explain this, G-E covariance is a potential factor that appears to have been overlooked.

2.1 Individuals, Populations, and a Question that Makes Sense

Heritability has been used within the biological and social sciences to make claims about the relative contribution of genes and environment to particular phenotypes. For instance, in both popular media and within the academic press it is common to hear that a particular trait is 'genetic'. Bipolar disorder (McGuffin 2003), schizophrenia (Greenwood 2007), and autism (Sasson 2013) have all been given recent attention, with popular focus tending to rest on behavioural and personality traits. Conversely, others, usually life history traits like longevity and fecundity, are deemed 'environmental' (Price & Schluter 1991). It is assumed that the terms 'genetic' and 'environmental' imply some form of causation; yet the causal concept invoked is underspecified, so the exact meaning of such claims is not immediately clear. Usually assertions of this type are derived from heritability estimates, which use statistical methods to capture the causal contribution of genes and environment to variation in a given trait or phenotype.

The prevalence and degree of 'genetic' versus 'environmental' phenotypes is central to the nature-nurture debate. But this issue does not always concern heritability. As Evelyn Fox Keller (2010) and others (see Stotz 2012) have made clear, a large part of the controversy surrounding the causal importance of genes and the environment has arisen from a conflation of ideas, or meaning slippage (Keller 2010).

One sense of a trait being ‘genetic’ concerns developmental causal pathways, where genes and environment interact to produce phenotypes. As mentioned in chapter 1, the interactionist consensus is a truism for developmental causes. While one could give an account of how my blonde hair or ten fingers are genetically (and environmentally) caused in this sense, this account would not provide any insights regarding a quantified or comparative contribution of the two. Both genes and an environment are required for the production of phenotypes in individual development, so it makes little sense to privilege one above another, or to assign values of relative responsibility. As Hans Kummer has remarked:

Trying to determine how much of a trait is produced by nature and how much by nurture, or how much by genes and how much by environment, is as useless as asking whether the drumming that we hear in the distance is made by the percussionist or his instrument. (Kummer as cited in Keller 2010, p.7)

Another helpful analogy from Keller (2010) regards the filling of a bucket of water.¹⁸ Imagine two individuals, Billy and Suzy. Suzy is holds a hose to the bucket, while Billy turns on the tap (Figure 2.1). Once the bucket is full, one could ask: ‘How much of the water is due to Billy’s contributions, and how much to Suzy’s?’ The example is meant to illustrate that this question does not make sense, as partitioning causes in this kind of way is not possible. Both the hose-holding and the turning of the tap are required to fill the bucket, and it is not possible to assess ‘how much’ each caused the bucket to fill, relative to the other. The same can be said of genes and environment contributing to individual phenotypes. Because of the necessary interaction of genotype and environment, distinguishing which is more important in an individual developmental case is argued as incoherent (Eisenberg 1995; 2001; Jensen 1972; Keller 2010; Lewontin 1974; Lykken 1998; Pearson 2007; Ryle 1974; Sarkar 1998; c.f. Sober 1988; 1994; Waters 2007).

¹⁸ Lewontin (1974, pp. 181-182) offers an analogous example concerning the laying of bricks and mortar to build a wall.

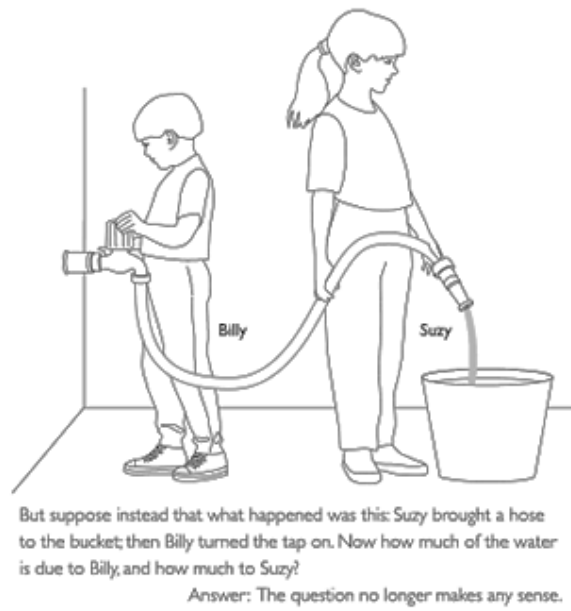


Figure 2.1 The Bucket Model (Adapted from Keller 2010, p.9)

Heritability involves a different type of causal claim, where a discrimination of relative causal importance is possible. Namely, it concerns the causes of *variation* in a phenotype, within a given population. As the causal claim regards phenotypic variation, it is possible to assign a numerical value quantifying how much is caused by differences in genes or the environment.

For example, if the heights of people in a population were measured there is likely to be some variation – some will be short, some tall, and some in-between. Heritability tells us whether this variation occurs because people have different genes or because they live in different environments, or both. If most of the variation in height is due to genetic differences between individuals in the population, then the trait is highly heritable. If most of the variation is due to environmental differences between them, then it has low heritability. The total amount of phenotypic variation can be broken down into the

percentage that can be accounted for by genetic variation, and the percentage that is accounted for by environmental variation. For example if height has a heritability of 0.8, then 80% of the variation in height can be attributed to genetic differences within that population. It is important to note that claims made using heritability estimates can only pertain to the causes of variance in a population, and not individuals in isolation. It does not make sense to say that my particular height (165cm) is 80% genetically caused, so that 132cm is genetically caused growth and 33cm environmental. Fisher, when he first described the methods for this kind of partitioning was careful to note this:

...we may now ascribe to the constituent causes fractions or percentages of the total variance, which they together produce.'

It is desirable... that loose phrases about the 'percentage of causation' which obscure the essential distinction between the individual and the population should be carefully avoided. (Fisher 1918, pp.399-400)

One *prima facie* surprising consequence of the heritability method is that seemingly 'genetic' traits can have low heritabilities. For instance, 'walking on two legs' is a human trait which does not vary much. When it does vary this is usually due to environmental variations, such as accidents where people lose the function of one or both legs. As a consequence, 'walking on two legs' has a heritability close to 0 (example taken from Herrnstein as cited in Block & Dworkin 1976; Bateson 2001; Sesardic 2005). This does not mean that genes are not necessary for the phenotype. At a developmental level of explanation walking on two legs is genetically caused. However, *variation* in walking on two legs is not largely caused by *variation* in genetics. A low heritability estimate shows that variation in this trait is caused primarily by non-genetic factors.

As heritability is a population-dependent estimate, another strange consequence is that the estimate can change depending on the population examined. For example, the heritability of hair colour in a Japanese population would be quite low, yet in Australia quite high.

This is because in Japan there is very little ‘natural’ (or genetically based) variation in hair colour (quantitatively measured by pigment concentration) – that is, variation that is genetically caused. As such, any large variations are usually due to environmental factors, such as artificial dyes.

To return to the height example, imagine a population of clones, all with identical DNA. As there is no genetic variation present to account for phenotypic differences, any and all phenotypic variation must be caused by differences in the environment. In this case, therefore, height (and all other phenotypes that vary) would have a heritability of 0. A population of clones is far-fetched, but the point can be applied to more realistic populations in which individuals have more similar genotypes, for example communities that are more closely related, or have a high inbreeding rate.

Accounting for environmental differences is also tricky.¹⁹ Imagine that every individual in a population is exposed to an identical developmental environment. In this case all the height differences observed would be due to differences in genotypes within the population. As a result, this population would have a heritability of height that is close to 1. This is again unrealistic as individual development always varies to some degree, but the point can be extended to groups that experience more similar environments than others.

So for a single phenotype, like height, the heritability estimate can differ depending on the genetic architecture of the population under study, as well as the environments in which they develop. This shows that while heritability does measure the causal impact of genes and environment, it does so in a very specific and limited way. More about the causal claims that heritability estimates relate to are discussed in chapter 3.

¹⁹ An additional difficulty is that environments and environmental differences are extremely difficult to assess and measure in human populations.

2.2 Quantification and Quantitative Traits

The most common way to describe trait differences in behavioural genetics is by measuring phenotypes as quantitative variables. Phenotypes like height, aggression, and intelligence are quantitative traits as they exhibit a multitude of values existing along a continuum. Other phenotypes like diabetes, handedness, and blood type are qualitative traits as their values fall into distinct categories. For instance, the handedness phenotype has two values: left and right (or three values if ambidexterity is included). The variable blood type (when referring to the ABO system) has four values: A, B, O and AB. For each of these phenotypes the values that can be taken are distinct, with no intermediaries. These kinds of traits are *not* usually assessed in heritability estimates, however, the two are related. In the case of quantitative traits, the underlying supposition is a high number of quantitative traits with small additive effects. This is explained further below.

The English polymath and founder of eugenics Sir Francis Galton pioneered an interest in quantitative phenotypes and their relative causes. He was one of the first people to introduce the quantification of trait differences, or variation, and famously attempted to quantify all manner of traits, including the weather (1863), height (1889), finger print patterns (1888; 1892; 1893), beauty (1909), boredom (1909), criminal characteristics (1885), and the effectiveness of prayers (1872). This obsession led S. J. Gould to term him ‘the apostle of quantification’ (Gould 1996, p.107). It was popular in Galton’s time to concentrate on the population means of trait, however, for Galton the differences between individuals, not the mean of a population, was of most interest:

It is difficult to understand why statisticians commonly limit their enquiries to averages and do not reveal more comprehensive views. Their souls seem as dull to the charm of variety as that of the native of one of our flat English counties, whose retrospect of Switzerland was that, if its mountains could be thrown into its lakes, two nuisances would be got rid of at once. (Galton 1889, p. 62)

Galton was part of the biometric tradition of the late 19th Century, which concerned itself with the inheritance of phenotypes between parents and their offspring. This was done by statistically analysing population level data, and looking for phenotypic associations between relatives. When Galton began to study the inheritance of human characteristics, he concentrated on the *variation* found within populations of particular phenotypes. For example the inheritance of differences in height, intelligence and sensory discrimination, which had varied with continuous values (Galton 1883). In order to do this Galton devised the correlation coefficient in 1888, where two variables are plotted against each other in order to assess the relationship between them. He also invented the regression line in 1885 – where a modelled line is fit to the data, representing the overall trend between the two variables (for example parents and offspring).²⁰

However, conceptualizing phenotypes quantitatively was, at the time, at odds with Mendelian genetic theory – which described a pattern of inheritance for phenotypes which displayed discrete values. These values were subject to reliable probabilistic patterns of inheritance, given sufficiently large populations. Under Mendel's laws, separate heritable factors exist for separate traits, and are passed on to offspring independently from one another (the law of independent assortment). Each individual inherits two copies (now known as alleles) of a particular factor (now known as a gene locus), and these two alleles separate during gametogenesis, so that one of the two is inherited randomly from each parent (the law of segregation).

Under Mendelian rules, phenotypes can be divided into discrete categories, corresponding to what is now termed a qualitative trait. In his now famous experiments Mendel observed that a pea flower was either purple or white, and the pea itself was either wrinkled or

²⁰ This is an estimation of a type of heritability different to the one I will be using in this thesis. But the general aim was the same: to quantify the contribution made to phenotypic variance by genetic and environmental differences. For more on the Galtonian heritability concept see Jacquard (1983).

smooth. Intermediate phenotypes of white-ish purple colour, or somewhat-wrinkled skin did not exist for these traits.²¹

In many cases of Mendelian genetics, one allele is dominant over the other, so that offspring inheriting two different types of alleles only display the phenotype for one. Say a flower has a single locus that determines colour and this locus has two alleles, P (purple) and p (white). A genotype (a representation of the locus in one individual which has two alleles) PP would yield a purple flower, as both alleles produce purple. A genotype pp would yield a white flower, as again, both code for white (both called a homozygote). Since P is dominant over the recessive p (as indicated by capitalised form), a genotype Pp, which combines two different alleles (called a heterozygote), would produce a purple flower. This example involves dominant and recessive alleles, but other inheritance patterns exist, including co-dominance, incomplete dominance, and sex linkage.²²

While Mendelian inheritance patterns are recognised for some human phenotypes such as blood type, albinism, and Huntington's disease, we now understand that many phenotypes with a genetic basis require multiple genes, or alleles at multiple loci for their expression. These are called polygenic or complex phenotypes, and their inheritance patterns cannot be directly predicted by Mendel's laws at a phenotypic level. This has led geneticists to distinguish between Mendelian and quantitative traits. Mendelian traits have a discrete number of values, and are inherited following the predictable patterns described above.

²¹ Mendel intentionally selected his study plants to look at qualitative characters. He recognised phenotypes that did not have these characteristics, and as such advised that plants selected for 'experiments of this kind must be made with all possible care if it be desired to avoid from the outset every risk of questionable results' (Mendel 1865 as cited in Edelson 1999, p. 41).

²² Codominance occurs when both alleles combine to produce a 'blended' phenotype, for instance if Pp produced a light purple flower (a blend of purple and white). Incomplete dominance occurs when both alleles are expressed at once – for instance if the flower petals contained purple and white patches. When the locus is inherited on either the X or Y chromosome, sex-linked inheritance can occur, where inheritance patterns differ depending on if the individual is female (possessing XX sex chromosomes in humans and most mammals), or male (XY). As these types of inheritance patterns are not important for this thesis, they are not discussed any further.

Quantitative traits require the expression of multiple genes, often from distant areas of the genome, and their phenotypic values are varied. These include morphological traits like height and weight; physiological traits like enzyme activity or cardiovascular performance; behavioural traits like aggression, dominance, sociability or intelligence; and life history traits such as lifespan, age at maturity, and developmental rates. Each of these phenotypes can be quantified along a scale – termed continuous variation.

Continuous variation in phenotype is related to the fact that the phenotype is sensitive to multiple genes that typically vary in a population, and is often significantly affected by environmental influences. The more genes that have an effect on a phenotype, the greater the number of allelic combinations possible, and so a greater number of phenotypic values are possible. This explains the increased number of values for quantitative traits, and also accounts for the way that the trait values are often distributed. A large number of quantitative traits display a normal distribution (sometimes called bell curve) of trait variance, where the distribution of trait values varies around the mean value, which is identical to the median. Most individuals have values close to the mean, as the combinations of alleles contributing to these phenotypes have a higher probability of occurring than those further from the mean.

Heritability estimates provide a way of predicting the phenotypes of offspring from their relatives (the biometric approach) that is compatible with Mendelian principles of inheritance. It also preserves the interests of Galton and the other biometricians concerning the partitioning of causes for trait differences. The first attempts at integrating biometrics with Mendelian inheritance were made by Yule in 1902 and 1906 (Roff 1997; Tabery 2004), but gained the most attention in R.A. Fisher's 1918 publication 'The Correlation Between Relatives on the Supposition of Mendelian Inheritance'. This paper showed that correlations between relatives were predictable from a Mendelian framework, which

integrated the biometric approach of comparing resemblances between relatives with Mendelian theory. Wright (1921) and Haldane (1932) also contributed to the synthesis of these two theories by providing additional quantitative genetic methods of estimation²³, and later developments were made by Cockerham (1954) and Kempthorne (1954).

It is worth noting that until the mid-20th century, the material nature of the unit of inheritance, and the mechanism by which they were inherited and exerted their effects, was unknown. The effect is double edged: On the one hand this is an advantage of heritability analyses, since the methods and statistics used (explained in sections 2.3 and 2.4) require no knowledge of the physical underpinnings responsible. On the other hand, the consequence of the technique is an obscured picture of the causal relationships involved, which can encompass problems such as G-E covariance (and $V_{G \times E}$). This will be further explored in chapters 4 to 8.

2.3 Heritability as a Statistical Parameter

As mentioned in section 2.1, quantitative geneticists are interested in variation or differences in phenotypes, within a population. For heritability these differences are parameterised as variance (σ^2), and are calculated by squaring the sum of the differences of each individuals' score (x), from the mean of the phenotypic measures within a population (μ). This is then divided by the number of individual measures taken (n).

$$\sigma^2 = \frac{\sum(x-\mu)^2}{n} \quad (2)$$

²³ See Sarkar 1998 (p. 105-116 and footnote 9) for a dispute of this historical account.

There are two senses of heritability²⁴; narrow and broad. Broad heritability estimates (H^2) partition the causes of variance in phenotype (V_P) into variance in genotype (V_G) and variance in environment (V_E). When the effects of V_G and V_E are assumed to work additively to contribute to V_P , the model for broad heritability is²⁵:

$$V_P = V_G + V_E \quad (1)$$

To estimate the genetic influence on V_P , heritability (H^2) represents the proportion of the genetic variance over phenotypic variance, with a value $0 \leq H^2 \leq 1$:

$$H^2 = \frac{V_G}{V_P} \quad (3)$$

Genetic variance (V_G) can be further subdivided into three main components.²⁶ These are additive genetic variance (V_A), variance due to dominance (V_D), and variance due to epistasis (V_I).

When these are recognised the heritability model is expanded to:

$$V_P = V_A + V_I + V_D + V_E \quad (4)$$

Dominance variance (V_D) concerns phenotypic variance that arises from the interactions of different alleles at the same locus. As described in section 2.2, when one allele is dominant over another the effects of the dominant allele are expressed in the phenotype, while the other (recessive) allele is inhibited. Epistasis variance (V_I) occurs when the expression of

²⁴ Jacquard (1983) suggests a third heritability concept, concerning the resemblance of parents and offspring more broadly – which stems from Galton’s regression measure. This resemblance may be due to both genetic and environmental factors (some of which are covered in sections 1.2.2, 4.2.2 and 5.3.1). This thesis focuses on the two senses of heritability studied in quantitative and behavioural genetics –broad and narrow.

²⁵ This is assuming no gene-environment interaction or gene-environment covariance, which shall be introduced in later sections (2.6 and chapter 4)

²⁶ V_G can be further compounded by parental effects, which are inherited by offspring from their parents (most often their mother), but are included in the V_G term due to the limitations of detecting these in heritability studies. Some of these were mentioned in section 1.2.2. While it is recognised that these factors can significantly impact phenotypic variance, there is not scope in this thesis to consider them in detail. Some forms of parental effects are discussed in chapters 4 and 5, as they relate to a type of G-E covariance.

one gene at a particular locus is affected by the expression of a gene at a different locus. That is, there are modifier genes, or genetic interactions within the genome. These interactions can act analogously to dominance effects – where one allele is dominant over another - but at a different loci. They can also occur in a quantitative way, affecting the rate or level of expression at a different locus.

For example, imagine that two alleles at a hair colour locus display a dominant expression pattern where red hair (R) is dominant over blonde hair (r).²⁷ RR and Rr genotypes have red hair, while rr express as blondes. Variance in hair colour in a population would partially be accounted for by V_D in this case, as R dominates over r. If at a different locus there are two other alleles: B for bald (dominant), and b for having a hair (recessive), then an individual with the genotypes: BB Rr, Bb Rr, BB RR or Bb RR will be bald, despite having the red hair alleles. In this case the genes at the baldness locus inhibit or override the effects of the genes at the hair colour locus, meaning that some of the differences in hair colour in this population can also be accounted for by V_I .

The remaining genetic variance – that which contributes to phenotypic variance without affecting other loci or alleles – is termed additive genetic variance (V_A). V_A is separated from V_D and V_I because it is the only type of genetic variance that responds to artificial and natural selection. This is because V_D and V_I are context dependant – their expression arises as a result of a particular combinations of alleles and loci in an individual, and so depends on particular genotypic backgrounds. During mitosis and recombination the dominance and epistasis interactions are ‘jumbled’ across generations, so these sources of variation are not reliably heritable, and cannot contribute to cumulative evolutionary change. The effects of V_A on the other hand are always visible to selective pressures, and

²⁷ It is likely that hair colour is determined by multiple loci, but just one is considered here for ease of example.

can therefore be acted on directly. Only additive genetic effects can reliably predict breeding outcomes and evolutionary consequences, so in order to forecast the heritable effects that will respond to artificial and natural selection, narrow (h^2) heritability is used, which represents the proportion of phenotypic variance that can be accounted for by additive genetic variance:

$$h^2 = \frac{V_A}{V_P} \quad (5)$$

Generally, narrow heritability is used by evolutionary and population geneticists who study animal and plant populations. They may be interested in forecasting and/or selecting breeding outcomes for an agricultural species, or determining how able a species is to adapt to a changing environment (see section 5.1.2 for details). Broad heritability is more often used within the social sciences, as researchers are interested in the total genetic contributions that influence variation in a trait. The utility of broad and narrow sense heritability is discussed further in section 5.1. Unless otherwise indicated, reference to heritability in this thesis concerns broad heritability (H^2), as most of the work introduced relates to human populations and causal claims in behavioural genetics.

2.4 Methods of Estimation

In agricultural science and behavioural ecology heritability estimates can be attained using carefully controlled experiments. Most often this is done using an ANOVA, where a range of environments and genotypes are measured.²⁸ In human behavioural genetic studies these kinds of experimental controls are not possible, and so heritability is inferred by looking at phenotypic resemblances between related individuals – often using twins. This shall be

²⁸ This technique also allows for the detection of gene-environment interaction, discussed in section 2.6.

discussed in subsection 2.4.1. Although this thesis focuses heavily on human behavioural genetics, I will spend most of the remainder of this section detailing the ANOVA technique, which I will use as an example of a broad heritability estimate, and shall refer to in later chapters. By referencing the hypothetical study based on an ANOVA design detailed in this section, I will be able to discuss the issues related to G-E covariance throughout this thesis without being detracted by the problems that can arise due to limitations in human behavioural genetic methods.

2.4.1 Analysis of Variance

ANOVA can be used to illustrate heritability by comparing the effects of multiple genotypes, environments, and their combinations. In the example I am about to introduce individuals in each genotype group are genetically identical, and the environments studied are uniform and discrete. This is not always the case in heritability estimates, genotypes can be classed instead according to family, species, or haplotype,²⁹ but these additional complications are avoided here.

Consider the following scenario: Three genotype groups, G1, G2 and G3, are cloned in a laboratory, with 100 individuals in each. These individuals are adopted out to 300 different homes as young children. The homes can be divided in to four groups (E1, E2, E3, E4) of seventy-five homes, each group corresponding to sufficiently similar environments, controlling for social class, climate, educational resources, cultural differences etc.³⁰ This means that there are 25 children in each treatment group, where a treatment group corresponds to a particular combination of genotype and environment (see Table 2.1).

²⁹ This term is a contraction for haploid-genotype, and refers to a collection of alleles that are likely to be inherited together and are therefore statistically associated.

³⁰ As mentioned in text, this example is intentionally far-fetched so as to set aside additional issues related to heritability estimation. This includes concerns about the similarities of environments, and confounds between groups, which are valid concerns for many experimental studies, but are not present in this thought experiment.

	E1 ($n_e=75$)	E2 ($n_e=75$)	E3 ($n_e=75$)	E4 ($n_e=75$)
G1 ($n_g=100$)	n= 25	n= 25	n= 25	n= 25
G2 ($n_g=100$)	n= 25	n= 25	n= 25	n= 25
G3 ($n_g=100$)	n= 25	n= 25	n= 25	n= 25

Table 2.1 ANOVA Experimental Design n indicates the number of individuals in each treatment group, n_g the number of individuals in a genotype group, and n_e the number of individuals in an environment group

After 10 years each child takes the same IQ test in the same conditions. Children with a G1 genotype score significantly better on the test than those with G2, who in turn have significantly higher scores than those with G3. In addition to the statistically significant variation between genotypic groups, the variance within genotypic groups is minimal – G1 children have similar scores to each other in each environment, as do G2 and G3 children (see Table 2.2 and Figure 2.4).

	E1 ($n_e=75$)	E2 ($n_e=75$)	E3 ($n_e=75$)	E4 ($n_e=75$)	N=300
G1 ($n_g=100$)	$\mu= 120$	$\mu= 118$	$\mu= 119$	$\mu= 123$	$\mu_{G1} = 120$
G2 ($n_g=100$)	$\mu= 100$	$\mu= 101$	$\mu= 98$	$\mu= 101$	$\mu_{G2} = 100$
G3 ($n_g=100$)	$\mu= 80$	$\mu= 81$	$\mu= 78$	$\mu= 81$	$\mu_{G2} = 80$
N=300	$\mu_{E1} = 100$	$\mu_{E2} = 100$	$\mu_{E3} = 98.33$	$\mu_{E4} = 101.67$	$\bar{X} = 100$

Table 2.2 ANOVA Experiment Results μ indicates treatment means, μ_{Xn} group means, and \bar{X} the grand mean

Equation 2 in section 2.3 gave the definition of variance (σ^2), which can be used to calculate the variance in IQ scores in each treatment group. For instance, the variance within the first treatment group, G1 x E1, is determined by calculating the difference between each individual score from the mean score of that group (120). So if the individual scores for the children in this treatment group have the values {121,117,118,120,120...}, then the variance would be computed in the following way:

$$\delta^2 = \frac{(121-120)^2 + (117-120)^2 + (118-120)^2 + (120-120)^2 + (120-120)^2 + \dots}{25}$$

In this example let us say the variance is 1. A large variance means that individual scores are spread out at a distance around the mean. This indicates a high amount of variation within that group. Low variance means that individual scores cluster around the mean, so they are similar, and there is low variation within the group. An alternative way to measure variation is the standard deviation (δ), which is the square root of variance, also 1 in this example. A δ of 1 represents a 1 point difference on the IQ test, meaning that on average each participant in treatment group G1xE1 scored just one point away from the mean of that group.

A graphical representation³¹ of these scores is shown in Figure 2.2, where individual scores are closely clustered around the mean. Within-group variance indicates how much error, or ‘noise’ is in the measurement. For example, if under a fixed environment the mean IQ scores varied between groups G1, G2 and G3 by twenty points (as in this example), but also varied within each group by 50 points, then it would seem that there are other sources of variation significantly contributing to the observed variation in IQ scores. This other variation may point to an environmental variable that had not been accounted for, or may

³¹ While the norm of reaction graphs (Figures 2.4-2.7) and tables 2.1 and 2.2 have been generated from actual simulated data, Figures 2.2 and 2.3 are simplified schematic representations of within- and between-group variance, as showing the variance from the actual data in this case would not have provided an illustration as clear as is shown in these figures (due to the increased number of data points).

be due to parental effects or epigenetic differences. A high within-group variance makes claims about the genetic and environmental causes of variation problematic, as it points to a potential confound. A low within-group variance allows researchers to focus on the differences measured between groups – in this case, between different genotypes and different environments.

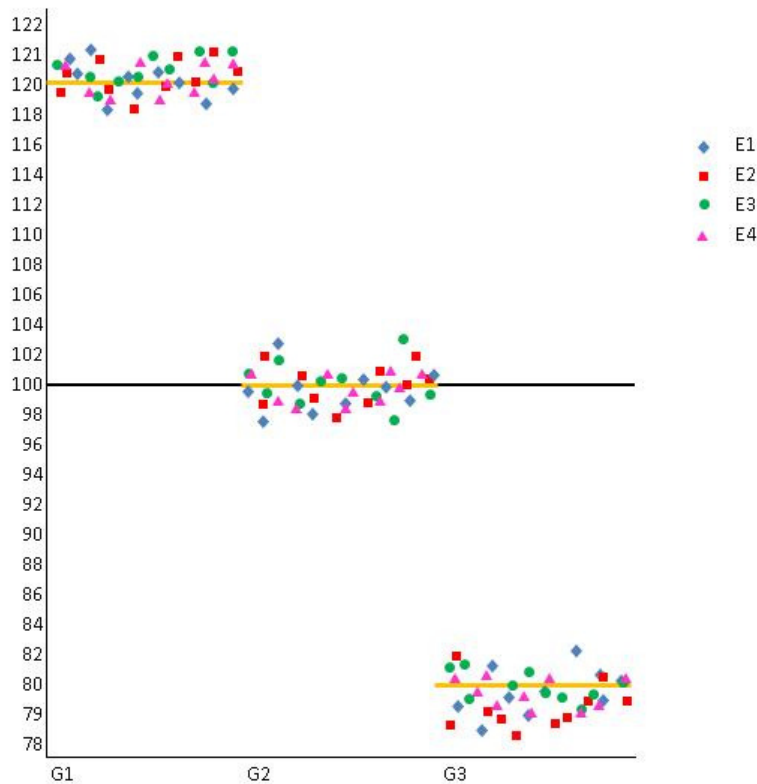


Figure 2.2 Within-Group Variance and Between-Group Variance for Genotypes

Between-group variance can be visualised by comparing the distances of the genotype means (yellow lines) from the grand mean (solid black line). Coloured dots represent individual data points. Within-group variance is indicated by the distance from the data points to the group means. The treatment group for each data point is indicated by the genotype on the x-axis, and the environment as shown in the key.

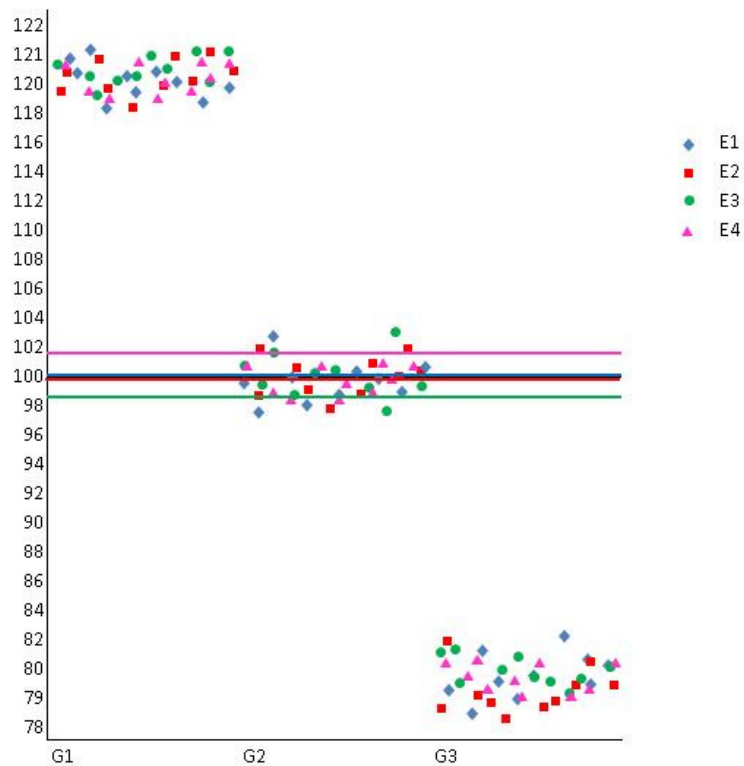


Figure 2.3 Within-Group Variance Between-Group Variance for Environments

Between group variance is shown by representing the distance of the environmental means (pink, red, blue and green lines) from the grand mean (solid black line)

So long as the within-group variance is sufficiently low, an ANOVA can provide information about the degree that V_P is influenced by V_E and V_G . These are the variances *between* groups. The variances between genotype groups are represented in Figure 2.2. Here you can see that the three genotype means (represented by the yellow bars) are spread apart along the y-axis. This indicates a high degree of between-genotype variance. In Figure 2.3 the environmental means (represented by the pink, red, green and blue bars) are clustered closely together, indicating low variance between these groups.

Between-group variances are calculated by seeing how much the group means, or marginal averages (μ 's) vary from the grand mean (\bar{X}). Marginal averages are the overall averages for a given genotype, or for a given environment – but not for a combination of genotypes

and environments (the treatment group means). The grand mean is the average of all scores across all treatment groups.

For the calculation of genotypic variance (V_G), the group means for each genotype are subtracted from the grand mean and squared, the total then divided over the number of genotype groups. Below is an example from the dataset in Table 2.2.

$$V_G = \frac{(\mu_{G1} - \bar{X})^2 + (\mu_{G2} - \bar{X})^2 + (\mu_{G3} - \bar{X})^2}{n_G}$$

$$V_G = \frac{(120 - 100)^2 + (100 - 100)^2 + (80 - 100)^2}{3}$$

$$V_G = 266.67$$

Similarly, for environmental variance (V_E), the group means for each environment are subtracted from the grand mean and squared, the total then divided over the number of environment groups.

$$V_E = \frac{(\mu_{E1} - \bar{X})^2 + (\mu_{E2} - \bar{X})^2 + (\mu_{E3} - \bar{X})^2 + (\mu_{E4} - \bar{X})^2}{n_E}$$

$$V_E = \frac{(100 - 100)^2 + (100 - 100)^2 + (98.33 - 100)^2 + (101.67 - 100)^2}{4}$$

$$V_E = 1.38$$

The total phenotypic variance (V_P) is calculated by adding V_E and V_G .³²

$$V_P = V_G + V_E$$

$$V_P = 268.05$$

³² For the sake of this example I am assuming that genotypic and environmental variation are additive –that is, the ratios of V_E/V_P and V_G/V_P should both add to 1. This is not always the case, as I shall show in section 2.6 and chapter 4.

Once these variances have been computed heritability measures are given by a ratio of the genotypic variance to the phenotypic variance: $H^2 = V_G / V_P$ (equation 3).

The ratios of V_G / V_P and V_E / V_P can be compared to see which counts for the most phenotypic variance. In this example the ratio for V_G / V_P ($266.67 / 268.05 = 0.9948$) is much higher than that of V_E / V_P ($1.38 / 268.05 = 0.0052$), showing that almost all of the variance in phenotype is accounted for by variance in genotype ($H^2 = 0.9948$). Very little (less than 1%) is accounted for by variance in the environment. This is an incredibly unlikely result for a heritability study. Heritability estimates rarely approach 1, as both genetic and environmental variations usually make a substantial contribution to phenotypic variation. I have used an extreme example with such a high estimate intentionally, so that I can focus on the issues of G-E covariance in an abstracted context without accounting for other possible confounds that should normally be considered. I will return to this example in chapter 4, where I introduce G-E covariance.

2.4.2 Twin Studies

Studies like the one described above are not practically possible in human behavioural genetics. We are not able to carefully control participants' developmental environments, and we do not have access to large numbers of genetically identical individuals. So in order to estimate heritability in human populations, alternative methods are required.

One approach is to study twins. Monozygotic (MZ) twins are genetically identical, as they develop from the same zygote, and so are good representations of a single genotype group. Jinks and Fulker (1970) proposed a design in which the phenotypic similarity of MZ twins reared together (MZT) is compared to the similarity of MZ twins reared apart (MZA).

MZT twins share both their genotypes and developmental environments, while MZA twins

have identical genotypes but experience different environments³³. When the two types of twin groups are compared, researchers are able to ascertain the relative impacts of genetic and environmental variation on phenotypic differences.

To do this the correlation coefficient for a population of MZT twins is measured, which represents a contribution of both V_G and any shared V_E .

$$r_{\text{MZT}} = \frac{V_G}{V_P} + \frac{V_E(\text{shared})}{V_P}$$

This is more commonly written as a contribution of H^2 a shared environment (c^2)

$$r_{\text{MZT}} = H^2 + c^2$$

MZA twins do not share an environment, yet have the same degree of genetic similarity as the MZT twins, so any phenotypic similarity (measured by the correlation coefficient) should be due to genetic variance alone:

$$r_{\text{MZA}} = H^2$$

To determine the relative effects of heritability and shared environment, the correlations between MZT and MZA twins are compared. By subtracting the MZA correlation from the correlation coefficient of MZTs, the phenotypic contribution of a shared environment can be ascertained:

$$r_{\text{MZT}} - r_{\text{MZA}} = H^2 + c^2 - H^2 = c^2$$

The difference between the two correlations gives a measure of shared environment, and the similarities between the two gives a measure of heritability. Studies of this kind have

³³ Although the twins still share the prenatal environment, and possibly other early developmental environments, which, if they affected V_P , would bias the V_E measure downwards as they are subsumed under V_G .

been conducted for IQ, which have yielded broad heritability estimates between 0.64 and 0.78, with a weighted average of 0.75 (McGue & Bouchard 1998).

The sample sizes for adopted twin studies are generally small, making the results obtained questionable. There are also often environmental confounds, as several families involved in early MZA twin studies adopted one twin to a related family member, so the MZA twins remained in contact with their twin sibling, meaning that not all environmental factors were non-shared (Hay 1985). Block and Dworkin (1976) have also pointed out that adoption agencies sometimes try to match adoptive parents to biological parents in social and economic factors.

A more common practise is to study MZ twins reared together (referred to just as MZ twins here), and compare them to dizygotic (DZ) twins, who develop from separately fertilised eggs, and so share only 50% of the same DNA, just like non-twin siblings. If MZ twins are more phenotypically similar than DZ twins, then V_G is likely to play a role in driving phenotypic differences. Heritability calculations are made by comparing a correlation coefficient (r) for MZ twins to the correlation between DZ twins. As mentioned above, the correlation of a trait for MZ twins is thought to be due to H^2 and a shared environment (c^2):

$$r_{MZ} = H^2 + c^2$$

The correlation coefficient for DZ twins is thought to be due to c^2 and some genetic similarities. Because DZ twins have half the genetic similarity of MZ twins, their correlation coefficient is:

$$r_{DZ} = \frac{H^2}{2} + c^2$$

Comparing the differences between these two correlation coefficients gives:

$$r_{MZ} - r_{DZ} = H^2 - \frac{H^2}{2} + c^2 - c^2$$

Which gives:

$$r_{MZ} - r_{DZ} = \frac{H^2}{2}$$

Or:

$$H^2 = 2(r_{MZ} - r_{DZ}) \quad (6)$$

For IQ, this method has estimated H^2 from 0.64 (Wilson 1983) to 0.88 (McGue et al. 1993).

But these studies also have limitations. Although the symbol H^2 has been used in equation 6 above, twin studies do not exactly estimate broad heritability, *nor* do they estimate narrow heritability (Falconer & McKay 1996, p.172). This is because MZ twins share 100% of their DNA, which means that V_A , V_D , and V_I are all shared between MZ twin pairs. DZ twins are expected to share $\frac{1}{2}$ of V_A , but only $\frac{1}{4}$ of V_D and V_I (Heath, Martin & Eaves 1984). This is due to the probability of inheriting alleles at two interacting loci. When parents transmit their genes to DZ twins (or non-twin siblings), for any given locus they can have only one dominant allele each. Assuming that both the mother and father have different alleles at different loci, and are heterozygotic at these loci, the probability that two siblings will inherit the same alleles at two interacting loci is $\frac{1}{2}$ for locus 1, and $\frac{1}{2}$ for locus 2. $\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$. So when MZ and DZ twins are compared, the resulting heritability estimate is somewhere in-between broad and narrow.

Really the equations should look like:

$$r_{MZ} = V_A + V_D + V_I + c^2$$

$$r_{DZ} = \frac{V_A}{2} + \frac{V_D}{4} + \frac{V_I}{4} + c^2$$

And comparing the differences between these two correlation coefficients gives:

$$r_{MZ} - r_{DZ} = V_A + V_D + V_I + c^2 - \frac{V_A}{2} + \frac{V_D}{4} + \frac{V_I}{4} + c^2$$

$$r_{MZ} - r_{DZ} = \frac{V_A}{2} + \frac{3V_D}{4} + \frac{3V_I}{4}$$

Schaffner (2006, p.21) states for this problem: ‘What most behavioural geneticists say is that for this kind of simple model, we are just interested in the narrow heritability, so we can assume that $H^2 = h^2 \dots$ ’. This is in line with how the formula is used by Tenesa and Haley (2013, p.142), Plomin et al. (2008, p.382) and Feldman and Otto (1997, Table 1). However Falconer and MacKay (1996, p.172) say that the result from this method ‘...is nearer to the degree of genetic determination (broad-sense heritability) than it is to the heritability (narrow-sense), which is perhaps what is wanted from human data.’ This is presumably because the estimate includes some of the V_I , and V_D components of V_G , even though they are not accurately estimated. This broad heritability interpretation is also used by Lynch and Walsh (1998, p.584), and McClearn and DeFries (1973, p.206).

Contrary to Schaffner (2006), others have claimed that the primary interest of behavioural geneticists is broad heritability, as: ‘The measure of broad heritability is used in relation to psychological traits, because total genetic contribution to these traits is of interest’ (Oftdal 2005, p.702) (see also: Loehlin, Lindzey & Spuhler 1975, p.81; Jensen 1976, p.88; Sesardic 2005, p.21). In line with this general consensus, it is the broad heritability concept that shall be referred to in this thesis.

Another limitation to twin studies more generally is that there are only two individuals per genotype, meaning that within-group variance is not detectable. Twin studies also limit the application of heritability estimates to a small and unique subset of individuals, so the results may not be representative of the wider population. DZ twins are more likely to be

born to mothers that already have three or more children, and maternal age and birth order also affect twin birth rates (Record, McKeown & Edwards 1970). Twins also usually have smaller birth weights (30% smaller on average than non-twins), are shorter (by 17%), are often born prematurely, and experience a unique developmental environment with a sibling of the same age (Hay 1985). So it is questionable how well twin study results can be extrapolated to non-twin populations.

But that is not all. Another issue with twin studies is the equal environment assumption: that both MZ and DZ twins in a family experience roughly the same level of shared environment (c^2). It is possible that MZ twins are treated more similarly by others than DZ twins, due to their physical appearance and other assumptions about similarity based on shared genetics. If MZ twins are treated more similarly than DZ twins, then heritability will be overestimated using the twin method. Scarr (1968), Scarr and Carter-Saltzman (1979), and Kendler et al. (1993) tested this hypothesis by examining twins which had misperceived their zygosity. If MZ twins who identified as DZ twins were treated less similarly than correctly identified MZ twins, then the reactions of people surrounding the twins may play a role in environmental differences. They found that MZ twins who were thought to be DZ experienced the same kinds of similarity in environments as correctly identified MZs.

Jackson (1960 as cited in Beckwith & Morris 2008) and Feldman, Otto and Christiansen (2000) have argued that MZ twins shared a special bond that DZ twins do not, which may contribute to V_P . This is a separate issue to the way that other people in the environment react to MZ and DZ twins³⁴, as it is related to the environment that twin pairs create for themselves. The studies conducted by Scarr (1968) and Scarr and Carter-Saltzman (1979) recognised that MZ twins still generally experience a more common environment than DZ

³⁴ This is related to reactive G-E covariance, which is introduced in chapter 4.

twins do, but attribute this difference to an active shaping of the environment by the twins themselves – which is similar due to their identical genotypes.³⁵ This active shaping of the environment is a form of G-E covariance which is discussed in section 4.1.2.

Another problem is that there are two different types of MZ twins. Monochorionic (MC) MZ twins result from a single zygote that split in two between the 4th and 8th day after fertilization. These twins share the same chorionic sac and placenta throughout development in-utero. MZ dichorionic (DC) twins result from a zygote that has split by the third day of fertilisation, and as a result they develop their own chorionic sacs and placentas. DC MZ twins therefore share different developmental environments to one another, while MC MZ twins do not. Some studies have shown that MC MZ twins have higher heritability for some phenotypes than DC MZ twins, indicating that differences in the prenatal environment has phenotypic effects, and thus could confound the H^2 estimated from twin studies if MC and DC twins are both being used in the same sample (Robert 2000).

Finally, there is the problem of maternal effects. Even twins that have been reared apart share a maternal environment of some sort – especially MC MZ twins. This means that a comparison of MZA and MZT twins may attribute shared maternal effects to V_G . A meta-analysis by Devlin et al. (1997) fitted existing heritability estimates to a model which accounted for a shared in-utero environment, and found that maternal effects accounted for 20% of the correlation between twins, and 5% between non-twin siblings for IQ. The paper argued that twin studies may over-estimate heritability, as maternal effects are encompassed in the V_G term. Taking this into account, Devlin et al. (1997) estimated that the H^2 of IQ is closer to 0.48.

³⁵ C.f. Rutter 2002.

Because of the potential confounds within twin study methods, I shall be referring to the ANOVA example from section 2.4.1 throughout this thesis. This will allow me to discuss issues related to G-E covariance without needing to account for other likely confounds such as those described above, and in section 1.2.2. This is not intended to detract from the importance of the maternal environment, shared developmental environment, and epigenetic variation in generating phenotypic variation. I recognise these features as generators of V_P , and refer back to them in chapters 4 and 5, but the detail required to properly acknowledge these additional sources of V_P is beyond the scope of this thesis. Instead this thesis focuses on another, less acknowledged contributor to V_P : G-E covariance.

2.5 The Norm of Reaction

In the ANOVA example from the section above (2.4.1) an incredibly high H^2 of 0.9948 was attained. Figure 2.4 shows a graphical representation of these hypothetical results - called the norm of reaction. Reaction norms demonstrate the changes to phenotype (y-axis) across both changes to the environment (x-axis) and changes to genotype (lines).

For reasons discussed in the next chapter, some (Block 1995; Kitcher 1985; Lewontin 1974; Sarkar 1998; Sober 1988) have suggested that this graphical representation should replace numerical heritability estimates altogether. For now it is sufficient to see how a high heritability estimate corresponds with the patterns observable on the norm of reaction graph.

The example from 2.4.1 using three sets of clones produced a straightforward 'additive' reaction norm. Figure 2.4 shows that in these hypothetical results, there are obvious differences in IQ between the different genotypes, but large differences are not observed

by looking at changes in environment. The genotypic effects remain fairly uniform across varying environments: The curve for each genotype remains at a constant value for phenotype (y-axis) across a range of different values for environment (x-axis), illustrating that despite changes in environment each different genotype produces consistently different phenotypic effects. Each genotype gives rise to a fixed phenotype over a range of background conditions. This is regarded as a 'genetically determined' reaction norm (Griffiths 2009).

This is in contrast to an 'environmentally determined' or 'socially determined' reaction norm, where phenotype varies with environment, but not with genotype. This kind of result is represented in Figure 2.5. In this case variation in environment (E1-E4) significantly affects phenotype, whereas variation in genotype does not – evident by the clustering of the three genotype curves. This is a case in which a low heritability estimate (H^2) would be attained, as the primary cause of V_P is V_E .

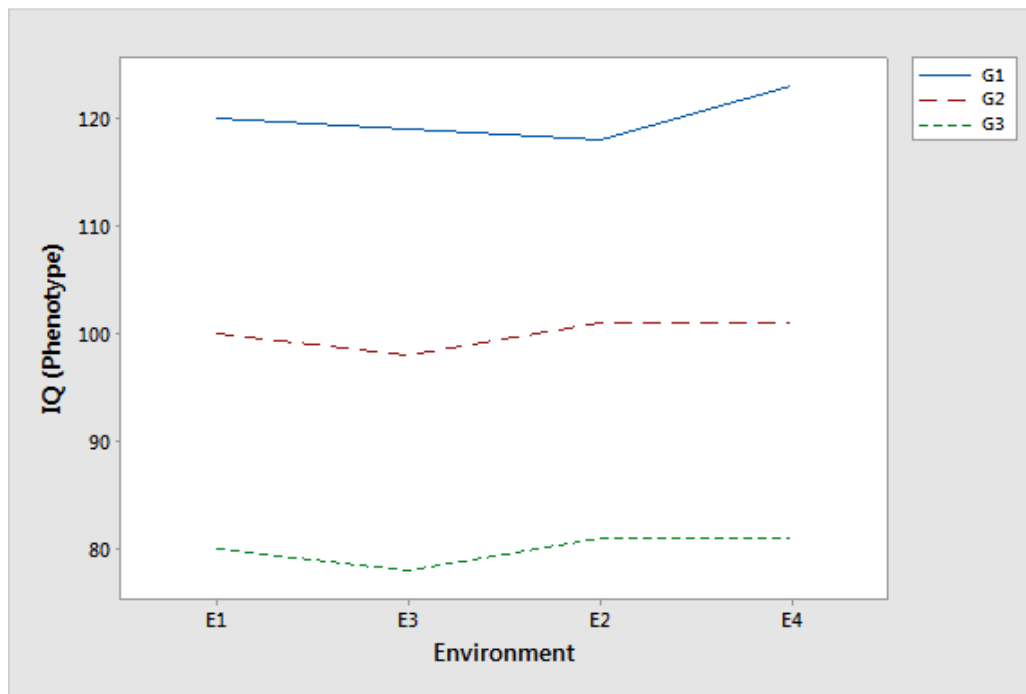


Figure 2.4 A Genetically Determined Norm of Reaction

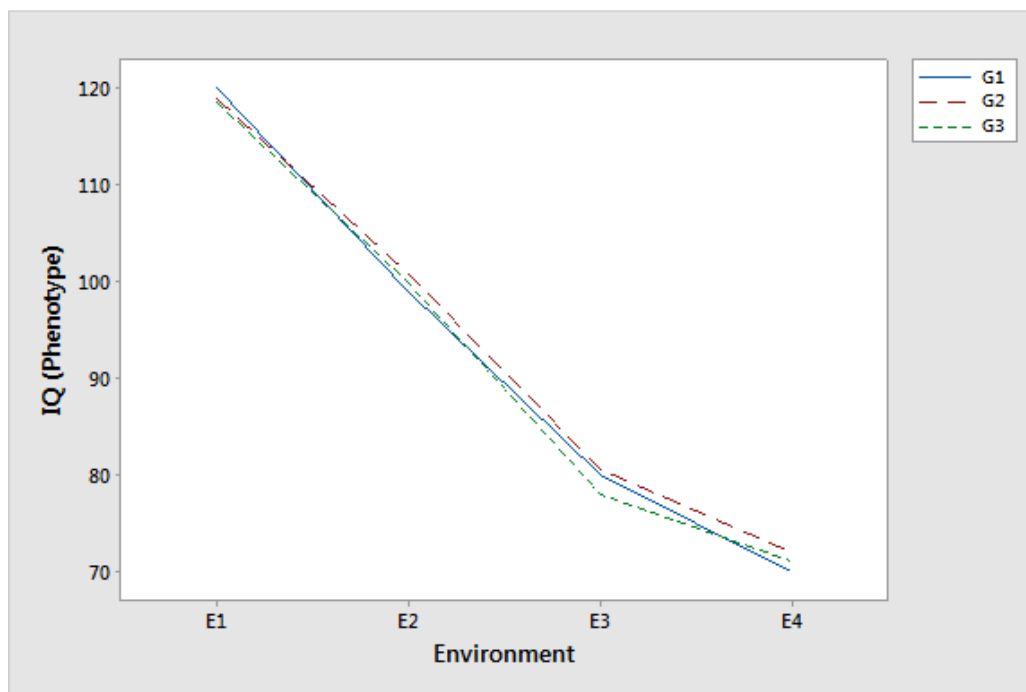


Figure 2.5 An Environmentally Determined Norm of Reaction

It is also possible, and more common, to obtain a norm of reaction that reflects a H^2 where both V_G and V_E contribute to V_P . An example of this is represented in Figure 2.6. Changes in environment (E1-E4), as well as differences in genotype (G1, G2, G3), produce variation in IQ (y-axis). This can be regarded as both environmentally and genetically determined, as the environment makes exactly the same kind of difference for each genotype, and the differences between genotypes are roughly the same at each environment.

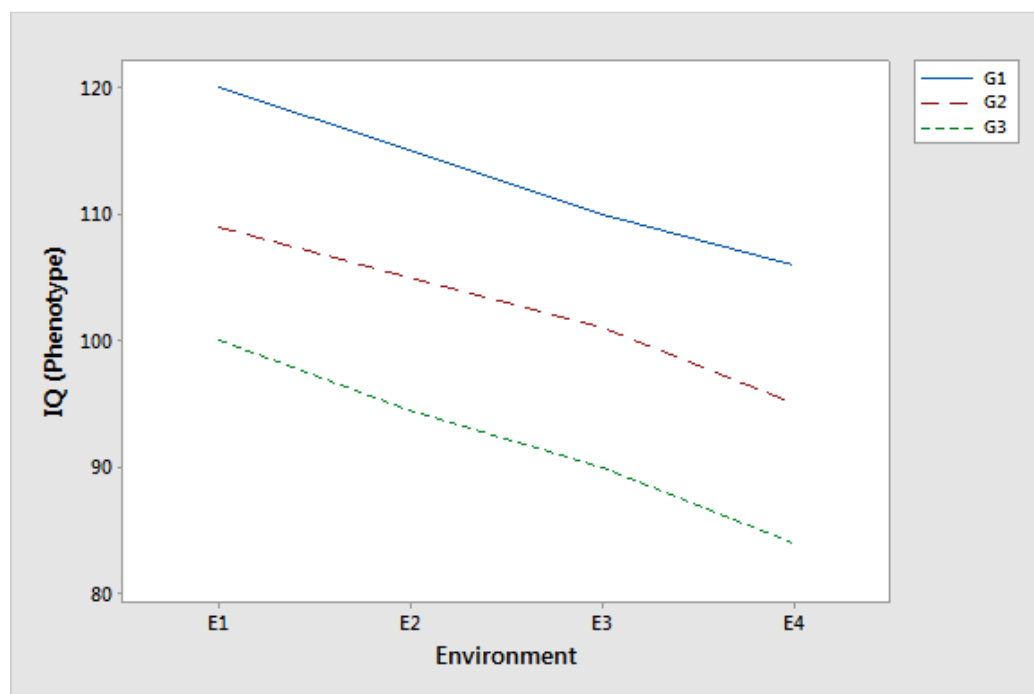


Figure 2.6 Norm of Reaction with both V_G and V_E Effects

2.6 Gene-Environment Interaction

As well as illustrating the relative effects of genetic and environmental differences, the norm of reaction can be used to represent interactions between genotype and environment. Figures 2.4-2.6 all displayed an additive norm of reaction, where the effects of genotype and environments varied consistently. In Figure 2.4 G1 produced the most intelligent

individuals, and did so consistently across the various environments (E1-E4). The phenotypes associated with G2 and G3 were similarly consistent across environments. In Figure 2.5, genotypes G1, G2 and G3 all produced similar phenotypes in a given environment, yet changed over differences in the environment. Figure 2.6 showed how G1 individuals consistently scored higher than G2s, who in turn scored than G3s, even though these scores also varied as the environment changed. Each of these three reaction norms reflects *additivity*. That is, the effects of genes and environments can be analysed additively when calculating V_P .

Recall equation (1): $V_P = V_G + V_E$

Here, V_P is simply the product of genetic and environmental variance which makes it relatively easy to partition the two. It also makes it easy to analyse the data by simply looking at the reaction norm graphs. Figure 2.4 clearly shows a high heritability for IQ; Figure 2.5 illustrates that IQ would have a low heritability; and Figure 2.6 is somewhere in-between. However, it is possible to attain reaction norms where the corresponding H^2 is not so obvious. An example is shown in Figure 2.7.

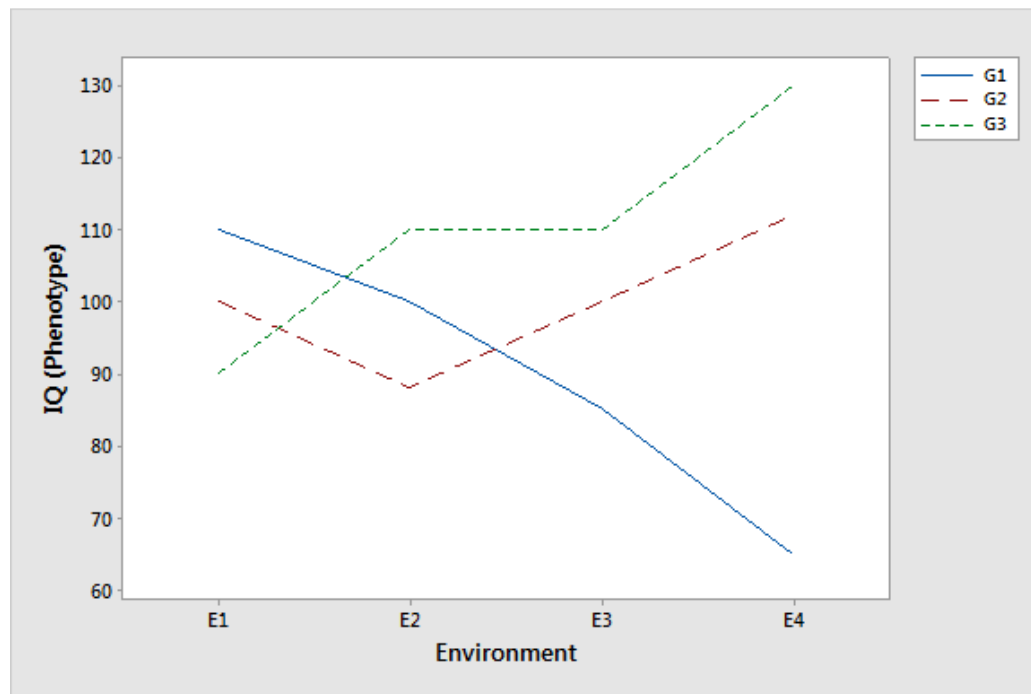


Figure 2.7 An Interactive Reaction Norm

In this reaction norm it is not obvious whether the heritability estimate attained would be high, low or somewhere in the middle. Phenotype, shown on the y-axis, changes as environments change, suggesting a level of environmental determination. However, differences in genotype also correspond to differences in phenotype. This suggests that both V_G and V_E contribute substantially to V_P .

Despite this initial appearance, the numbers used to generate this figure correspond to an incredibly high heritability estimate under the additive model. $H^2 = 0.968$, suggesting that V_G contributes to the large majority of V_P . This is problematic because the norm of reaction seems to indicate that both V_E and V_G have substantial effects on V_P . The data and equations used for this graph are displayed in Table 3.6 and in text.

	E1	E2	E3	E4	Means
G1	$\mu = 110$	$\mu = 100$	$\mu = 85$	$\mu = 65$	90
G2	$\mu = 100$	$\mu = 88$	$\mu = 100$	$\mu = 112$	100
G3	$\mu = 90$	$\mu = 110$	$\mu = 110$	$\mu = 130$	110
Means	$\mu_{E1} = 100$	$\mu_{E2} = 99.333$	$\mu_{E3} = 98.333$	$\mu_{E4} = 102.333$	$\bar{X} = 100$

Table 2.3 Data for Interactive Reaction Norm.

Following the formulas used in section 2.4.1, V_G is calculated:

$$V_G = \frac{(\mu_{G1} - \bar{X})^2 + (\mu_{G2} - \bar{X})^2 + (\mu_{G3} - \bar{X})^2}{n_G}$$

$$V_G = \frac{(90 - 100)^2 + (100 - 100)^2 + (110 - 100)^2}{3}$$

$$V_G = 66.67$$

As is V_E :

$$V_E = \frac{(\mu_{E1} - \bar{X})^2 + (\mu_{E2} - \bar{X})^2 + (\mu_{E3} - \bar{X})^2 + (\mu_{E4} - \bar{X})^2}{n_E}$$

$$V_E = \frac{(100 - 100)^2 + (99.33 - 100)^2 + (98.33 - 100)^2 + (102.33 - 100)^2}{4}$$

$$V_E = 2.17$$

Assuming additivity, both are combined to give V_P :

$$V_P = V_G + V_E$$

$$V_P = 68.84$$

When these numbers are factored into a heritability model:

$$H^2 = V_G / V_P$$

$$H^2 = 66.67 / 68.84$$

$$H^2 = 0.968$$

This is an example of a non-additive norm of reaction, where there is an interaction of gene and environment ($V_{G \times E}$) that has not been accounted for using the additive model (formula 1).

When referring to genes and environment, interaction is a word that has two distinct meanings, apt for confusion in the nature-nurture debate. One sense of the term refers to the dependence of genes and environment to produce phenotypes, mentioned earlier as the 'interactionist consensus'. For example, to produce the phenotype of language ability an individuals' genome, which includes genes for the fine motor control of tongue, lips and larynx, and possibly other genes related to language comprehension³⁶, must interact with environmental cues for the learning and development of speech. Even genetically determined Mendelian traits such as blood type or Huntington's disease require an environment in which they can be expressed.

The second use of the term is the formal statistical concept. When two variables interact in this sense, the effect of a change in value of one variable varies depending on the values of

³⁶ The existence of these kinds of genes is subject to debate. See for example Bishop (2002).

the second variable. For example variation in genes (V_G) may affect emotional stability (V_P), but the effect could be mediated depending on the level of stress in an individual's environment (V_E). It is possible to have two variables which interact in the common sense use of the term, but do not interact in the statistical sense; yet it is not possible to have variables which interact in the statistical sense without interacting in the common sense also.

When data like this is computed additively, as shown in the equations above, the resulting heritability estimate does not accurately reflect the causes of phenotypic variance. The estimate attained ($H^2 = 0.968$) indicates that the variance in IQ is almost solely due to variance in genotype, however, the norm of reaction demonstrates that changes in environment also have a strong phenotypic effect.

This is because, unlike in Figures 2.4-2.6, variance in genotype does not produce a consistent change in phenotype. $V_{G \times E}$ accounts for the modifying effect of environment upon how genes influence phenotypes, and occurs when the same environment has differential modifying effects on individuals of different genotypes. $V_{G \times E}$ has been relatively well discussed (Griffiths & Tabery 2008; Moffit, Caspi & Rutter 2005; Rutter & Silberg 2002; Tabery & Griffiths 2010), and has shown to be important in evolutionary contexts such as mate-quality signalling (Kokko & Johnstone 2002).

$V_{G \times E}$ demonstrates that phenotypic variance does not always result from the additive effects of V_G and V_E , as shown in equation 1. Thus heritability models must include an additional variable to account for the statistical interaction ($V_{G \times E}$):

$$V_P = V_G + V_E + V_{G \times E} \quad (7)$$

$V_{G \times E}$ has been the source of considerable debate regarding the efficacy of heritability estimates. The debate concerns the statistical power to detect interactive effects, and the

consequences of interaction for extrapolating heritability results. These issues are discussed in section 3.5 of the next chapter.

2.7 Missing Heritability

Significant heritability has been found for a large range of human traits. For example human height has a heritability of approximately 0.8 (Visscher 2008), ADHD of 0.7 (Grunblatt et al. 2013), insomnia 0.48 (Wing et al. 2012), hair curliness between 0.85 and 0.95 (Medland, Zhu & Martin 2009), and alcoholism between 0.50 and 0.60 (Stacey, Clarke & Schumann 2009). Turkheimer (2000) claims that ‘genetic variance is an important component of variation for all behavioural outcomes’ (p.160), and has called for the ‘first law of behavioural genetics’ to state that all human behavioural traits are heritable.

However, there has been little success establishing the molecular genetic basis of V_P . Genome wide association studies (GWAS) examine the correlations of a large number of alleles with different phenotypes. This is generally done using single nucleotide polymorphisms (SNPs), which are common sequences that vary by a single nucleotide. On the basis of survey sequencing results it has been estimated that the human genome contains at least 11 million SNPs, making them the most prevalent class of genetic variation among individuals in human populations (Frazer et al. 2009). The HapMap Project, which began in 2001, aims to catalogue a set of SNPs which can be used as markers for phenotypes. Groups of SNPs that are likely to be inherited together (linked), and are therefore statistically associated, are called a haplotype. GWAS correlate particular haplotypes to phenotypes at a population scale, allowing for the statistical association of genetic variation between hundreds of loci (Gibbs 2003).

The total SNPs identified in GWAS account for only a small fraction of the variation of V_P that V_G is estimated to generate (Fraser et al. 2009; Maher 2008). An oft cited example of this is human height (Griffiths & Stotz 2013; Manolio et al. 2009; Nelson, Petterson & Carlborg 2013), which has a heritability of 0.80 (Visscher 2008), yet a GWA study spanning 200 000 individuals and 180 loci could account for only 10% of the phenotypic variance (Allen et al. 2010). Yang et al. (2010) managed to recover a larger proportion of V_P (45%) by accounting for the combined effects of multiple SNPs, yet this is still a far cry from the widely repeated 80% found in heritability estimates. For intelligence, the discrepancy is similarly problematic. The heritability of IQ is estimated between 0.5 and 0.8 (Plomin & Spinath 2004), but GWAS have only been able to recover 40% of phenotypic variance at a molecular level (Davies et al. 2011).

The discrepancy between the genetic variance estimated by heritability and the genetic effects of loci at a molecular level is called the problem of ‘missing heritability’. One proposed explanation for this discrepancy is that the effects of single alleles are too small to be detected by GWAS (Goldstein 2009; Monolio et al. 2009; Rockman 2012). Others have suggested that the studies are absent of rare variants which may have large effects (Eichler et al. 2010; Pritchard 2001). Others still have pointed to non-additive genetic effects, such as V_D and V_I (Bloom et al. 2013; Eichler et al. 2010; Frazer et al. 2009; Zuk et al. 2012), epigenetic variation (Richards, Bossdorf & Pigliucci 2010; Slatkin 2009), parental effects (Eichler et al. 2010; Nadeau 2009), and $V_{G \times E}$ (Eichler et al. 2010; Frazer et al. 2009).

No-one to date seems to have properly investigated G-E covariance as a potential explanation for missing heritability. One of the aims of this thesis is to draw attention to the impact of G-E covariance on V_P . Chapters 4 and 5 will argue for the prevalence and magnitude of G-E covariance, and chapters 6 to 8 will suggest factors that contribute to an

interpretation of these effects. As G-E covariance has been demonstrated to inflate heritability estimates, and is currently overlooked by many behavioural and quantitative geneticists, it is likely to be one of many contributing factors to missing heritability.

2.8 Summary and Conclusion

Heritability (H^2) estimates measure the relative contribution of genetic variance (V_G) and environmental variance (V_E) to phenotypic variance (V_P), within a population. When computed additively, V_P is calculated by the addition of V_G and V_E (equation 1). Because of this population relativity, a heritability estimate for a given phenotype may change depending on the genetic and environmental variation present in a population. This is referenced further in section 3.5 of the next chapter, where the extrapolation of heritability estimates are considered.

The ANOVA example used in section 2.4.1 will be drawn upon in subsequent chapters in this thesis, concerning the heritability of IQ. Now that I have laid the foundation needed for a statistical understanding of heritability, and demonstrated some of the methods used for its estimation, the remainder of this thesis shall look at scenarios where a high H^2 discords with intuitions about genetic and environmental causation: when G-E covariance occurs.

In order to assess the causal intuitions that seem to conflict when G-E covariance is present, the next chapter will look at how heritability estimates can be used to make (limited and specific) causal claims, in accordance with the interventionist account of causation. I assess the explanatory depth of these claims using two dimensions of causation which feature in the interventionist account: invariance and stability. These dimensions can also shed light on the debate surrounding the applicability of heritability estimates to other

populations. This causal ground work will frame the discussion of G-E covariance cases presented in chapter 4, where I describe examples where high H^2 conflicts with ‘common sense’ accounts of genetic causation. The significance of this problem is argued for in chapters 4 and 5, while chapters 6 to 8 consider the factors which shape their interpretation.

Chapter 3 Causation and Causal Dimensions

The previous chapter illustrated the details of heritability as a statistical parameter.

Heritability estimates are often used to make causal claims (Okasha 2009, p.722; Sesardic 1993; p.399), yet strict definitions of heritability do not go beyond non-causal, statistical relations. G-E covariance situations, described in the next chapter, are also often referenced in causal terms (Eaves et al. 1977; Jencks et al. 1972; Jinks & Fulker 1970; Roberts 1967; Sesardic 2003; 2005). The covariance term alone, however, does not necessitate a causal relation –therefore the exact meanings of such claims are not clear. One of the aims of this thesis is to clarify the causal relations involved in heritability studies, especially to make sense of the role that causation plays in G-E covariance.

This chapter begins by outlining some of the major conceptual issues in the field of causal explanation and the metaphysics of causation (section 3.1). I then introduce the interventionist account of causation (section 3.2) and describe the criteria required for a causal relationship, which I apply to heritability estimates (section 3.3). In this section I also outline the criteria for an indirect causal relationship, which I apply in chapter 6 to G-E covariance. The interventionist account has been selected for its merits in addressing some of the conceptual issues introduced in section 3.1, because it allows for a variable view of relata which is compatible with the components of heritability, and because it best parallels the accounts of causation used currently within the sciences.

Section 3.4 introduces a related nature-nurture debate in the philosophy of biology, which concerns privileging genes over other phenotypic causes. One way to causally privilege something is to measure it along a dimension of causation. While many factors can be identified as causes under the interventionist account, some may be considered more important than others, depending on these other causal dimensions. Two such dimensions

are introduced in this chapter: invariance and stability. These tools are used to analyse the causal claims made regarding heritability estimates generally, and in later chapters, in reference to G-E covariance.

Section 3.5 introduces the concept of invariance, and shows that it is sometimes used as an amalgamation of two distinct concepts: invariance under interventions on the causal relationship (termed invariance simpliciter), and invariance under interventions on causal background conditions (termed stability). These concepts are applied to understand the norm of reaction, which was introduced in the previous chapter. Invariance is also referred to in chapter 6 to show one way in which the proximity of causes to their effects may be reason to privilege those causes above another.

Section 3.6 turns to an alternative way to make causal attributions, by appealing to psychological or conceptual factors. I examine three factors that have been shown to affect causal reasoning: agency, blame, and norms. I review the empirical and theoretical work involving the three, and show how they are linked.

3.1 Conceptual Issues in Causal Explanation

The philosophy of causation can be defined by two main questions: What is a cause? and What is causation? The first refers to the *causal relata* – the kinds of things that are related by causation. For example in the causal relationship ‘eating bread crusts causes curly hair’ the causal relata are ‘eating bread crusts’, and ‘curly hair’ – the causes and effects involved. The second question concerns the *causal relation*, which is the thing that holds between the relata. What is it that connects bread crust eating and curly hair? What does it mean for one thing to cause another?

Before questions of relata and relation can be addressed, it must be determined what kind of causal relationship is being referred to. These are usually divided into two: type and token. A type (sometimes called general) causal relationship would be like the one mentioned above: eating bread crusts causes curly hair. This refers to a class or kind of causal scenario which could span multiple instantiations of bread crust eating and hair curling, each figuring in the one same causal generalisation. In contrast, a token (sometimes called singular) causal statement refers to a particular causal relationship, defined over a precise time and space. For instance, ‘Holly’s eating of bread crusts caused her to have curly hair’ is a token causal claim.

For causal talk in genetics, this distinction is also useful. Simply replace ‘eating bread crusts’ with ‘gene *X*’, and you will see that the claim ‘gene *X* causes curly hair’ and ‘Holly’s gene *X* caused Holly’s curly hair’ are different causal claims. In the previous chapter I described an additional causal relationship used in genetics; one concerning the study of heritability. I will argue in section 3.3 that this is best understood as a token causal claim. But in order to get to these points, a specification of the causal relata is needed.

3.1.1 Causal Relata

Causal relata are the ‘causes’ and ‘effects’ that are referred to in a causal relationship. In the nature-nurture debate more generally, the relata in question are: genes or genotypes and the environment (or some environmental facet) as causes, and a phenotype (for instance height, aggression, intelligence or a disease) as the effect. The relata in heritability studies are variance in genotypes (or genetic differences) (V_G), variance in environment (V_E), and variance in a phenotype (V_P).

One approach to causal relata is to consider them as objects (see for example: Swinburne 2000; Lowe 2002). As mentioned in section 1.2.1, when referring to variance in genotypes, the Mendelian gene concept is being used. However, in order to more clearly illustrate the

various relata theories, it is often best to start with an example using a molecular gene concept. As the molecular gene refers to a physical stretch of DNA on a chromosome, it may seem that the object view of causal relata is appropriate. Take the recent finding that an area of chromosome 20 causes male pattern baldness (Richards et al. 2008). Under this account the gene refers to an object which has a physical location in the genome (20p11.22), although the phenotype ‘baldness’ does not. It is hard to spatially locate ‘baldness’ in the world, and thus consider it as an object. This seems to be the case for many phenotypes, whether they are a physiological trait, a disease, or behaviour.

The object view also says nothing about the timing involved in the causal relation. The claim that Richards et al. (2008) make refers to a genetic background which is associated with baldness developing at a particular age³⁷. An allelic variant of 20p11.22 does not cause baldness in infancy, even though the gene as an object exists during this period (and many carriers of this gene may be bald during this period also). This demonstrates that under an object view of causal relata there is an under-specification of the phenotypic relata referred to. In regards to heritability, it makes little sense to term genetic, environmental or phenotypic variance as objects in the world. This is because it is the variances themselves which are the relata concerned (and not the genes, phenotype or environment), and variance cannot be considered as an object. Therefore for causal claims involving the molecular gene or variance in the Mendelian gene, the object view of relata does not seem appropriate.

An alternative view³⁸ of causal relata is to consider causes and effects as events (Davidson 1969; Kim 1973; 1976; Lewis 1986). This overcomes the problem of time-specification –

³⁷ According to their study, between 35 and 60 years old.

³⁸ Additional alternative concepts of causal relata exist that are not discussed here. These include ‘property instances’ (Paul 2000) and ‘facts’ (Bennett 1988; Mackie 1974; Mellor 2004). Others believe that there can be asymmetrical causal relata, or relata pluralism. A relata pluralist allows for different kinds of relata to be

as events have defined spatio-temporal properties. However, event causation is not without its own problems. To return to the case above: ‘gene 20p11.22 causes baldness’, the phenotype event is clarified by explaining the time that baldness refers to. But it must still address which event ‘gene 20p11.22’ refers to. Does it refer to the time of first expression of the gene, when transcription initially takes place? Or does the event stretch over the entire time period that 20p11.22 is expressed? Similarly, although one could define the event as the time and place that V_P is measured, it is not clear which event(s) the relata V_G or V_E refer to for heritability studies.

This problem concerns the individuation of events (Schaffer 2003). Philosophers have attempted to resolve this problem by opting for a fine (Dretske 1977; Kim 1973) or coarse grained approach (Davidson 1969). But what if expression varies over time? Say, it begins during an early developmental period, halts, and then starts again. Such expression profiles are common for genes. Androgenic genes are expressed at certain stages of early development, and then again at puberty, when hormonal changes trigger transcription. These types of genes, called facultative genes (as opposed to constitutive genes, which show constant expression) are turned on and off depending on environmental conditions, and are common features of the human genome. Thus like the object view, event relata does not appear to sufficiently capture genetic causation for claims involving the molecular gene or the relata concerned in heritability estimates.

A third alternative is the variable view of relata. This is the view that I will consider in this thesis. First, it fits better with the issue of heritability, and second, it avoids several strong objections against the other two views.³⁹ Variables are thought to be a property, magnitude,

factored in to one causal relationship (Mellor 1995; Menzies 1989). As the variable view of relata is the endorsed view in this thesis, these ideas shall not be further discussed.

³⁹ This view is also useful in that it accommodates for absences as causes. For instance a deletion mutation in the *FIX* gene causes haemophilia B in dogs, and possibly also in humans (Mauser et al. 1996). This means that it is the absence of the functional gene product which is the cause of the phenotype- meaning that the

or quantity which can take on at least two different values. For instance the variable for colour may have the values [red], [purple] and [green], and the variable for mass may have a range of values between 5kg and 10kg. For the example of ‘gene 20p11.22 causes baldness’, the variable ‘gene 20p11.22’ could have values corresponding to different allelic forms of the 20p11.22 locus. The variable baldness could have the values: [bald] and [not bald] (a binary response), or could be separated into discrete variables of distinctive baldness patterns. Alternatively, one could measure a degree of hairlessness, with multiple continuous values. It is by far the broadest way to conceptualise causal relata.

For heritability, the relata V_G , V_E and V_P are all appropriately considered as variables. They take numerical values, which are determined by the data in the heritability model. The gene concept that figures in heritability studies is the Mendelian gene – which is defined by a statistical relation, and may not be grounded in an object or event. Thus a variable view of causal relata is the most appropriate for assessing heritability and is the view that shall be adopted in this thesis.

3.1.2 Causal Relations

The bulk of philosophical work has focussed not on causal relata but the causal *relation* – more often referred to as simply as theories of causation. Theories of causal relation aim to characterise what it is for some sequence to be causal. When the heat is turned up on the stove and the water inside a pot starts to boil, we are confident in saying that the increase in temperature *caused* the water to boil. But what exactly does this say about the relation between the temperature and the water in the pot?

causal relata could be neither an object nor an event. As such the variable *FIX* could be conceptualised as having the values of [functionally absent] or [functionally present], and the phenotype could be conceptualised as the variable ‘blood clotting property’, with the values of [haemophilic] or [non-haemophilic].

When Hume addressed this question in 1739, he arrived at three conditions under which causation occurs: the cause is contiguous to the effect in space and time, the cause occurs prior the effect in time, and all events of a particular type C, are regularly followed by events of type E⁴⁰ (Psillos 2009). Note that the third condition implies a reference to type causation – as multiple instantiations of types of causes and effects are considered. What is notable about this theory is that there is no extra property of the world that is distinctly causal. Causation is defined using purely non-causal terms, and as such can be reduced to things which are regularly observed as occurring together – the cause before the effect. In other words, there is no necessary connection between the cause and effect over and above their regular association (Psillos 2002).

A major problem for the regularity view is that of spurious causation; the conditions given are not on their own sufficient for a relationship to be causal, as some non-causal relationships also fulfil these criteria. Non-causal correlations such as the mercury dropping in a barometer regularly happening before a storm occurs, fulfils the priority, contiguity and constant conjunction conditions. However, mercury dropping in a barometer does not cause storms to occur, both are effects of a common cause: a drop in barometric pressure (Kitcher & Salmon 1962).

This problem demonstrates the adage ‘correlation does not equal causation’- a point widely recognised in the sciences. As such, a regularity view is not sufficient for the study of causation within science, including genetics. An alternative view is the counterfactual account of causation – made famous by David Lewis (1973). Under this theory causal relations are analysed in terms of counterfactual dependence. The claim ‘Gene X causes

⁴⁰ When referring to causal variables in text, the upper case C shall be used for causes and E for effects. When there are multiple causes and effects, these variables will be numbered (C1, C2, C3...Cn). For the values of variables, lower case letters (c and e) shall be used. When there are multiple values, numbered values (c₁, c₂, c₃...c_n) will be used. Square brackets are used to designate other listed values.

Disease Y' means that if gene X occurs then Disease Y would occur, and if X had not occurred, then Disease Y would not have occurred either. In other words, C causes E when 'if not C, then not E'. Counterfactual conditionals refer to how the world would have been had the cause had not occurred. If the effect would also not have occurred, then C and E are joined by a causal relation.⁴¹ However, this theory still presents some problems. Like the spurious cause problem for regularity theories, there appear to be non-causal correlations that fit the counterfactual criteria. Say an individual gets infected with the measles virus (C). He gets a fever (E) and then shortly thereafter gets a rash (F). It seems reasonable to assert that if he had not gotten a fever, he would not have gotten a rash (if not E then not F)⁴². But we cannot make the claim that it was the fever that *caused* the rash, as this fits a common cause relation, where C causes both E and F, rather than E causing F (Scheines 2004).

The theories above demonstrated the problem of spurious causes – where correlations appear as causal under the given theoretical definitions. To overcome these types of problems, philosophers have taken alternative approaches, focussing on the perception that causal connections are potentially available to manipulate – intervening on causes seems to alter their effects. In the sciences researchers attempt to isolate causes from correlations by manipulating variables - whilst keeping the causal background constant - to see if a change presents in the effect. This associated change implies a causal link between the two. Thus a

⁴¹ Counterfactual accounts of causation rely on two additional concepts: possible worlds and a similarity metric. Possible worlds are worlds in which alternative states of affairs occur, and just what these states of affairs are is determined by how similar the possible worlds are to the actual world. Here are two examples of possible worlds: world one is a possible world in which I am wearing a red shirt (instead of the white shirt I am wearing in the actual world), and that is otherwise identical to the actual one. World two is a world in which that last glaciation event did not occur. Which of the two possible world is more similar to the actual world is determined by a similarity matrix, and most would agree that the former – in which the colour of my shirt changes, is more similar to the actual world. So the claim 'if not C then not E', strictly means 'if not C, then not E holds in possible worlds closer to the actual world than ones in which E does occur'. Criteria for similarity between worlds is specified in Lewis (1979, p.47).

⁴² And that this would hold true in a closer possible world in which the rash occurred without the fever (or vice versa).

cause is taken to be something that, if manipulated, would bring about some change in the effect. This idea has given rise to manipulationist accounts of causation, which are related to counterfactual theories, as they describe what would happen to an effect in a different possible world: one where there is a manipulation of the cause (Woodward 2007).

3.2 The Interventionist Account

One such theory is the interventionist account of causation. Under an interventionist account a cause (C) causes an effect (E) if an intervention on C, changing the nature of C, produces a change in the nature of E (Woodward 2003). This is best understood when considering causal relationships in which the relata are variables, as introduced in section 3.1.1.

3.2.1 Causes

Take two variables, C and E, where C has the possible values c_1 and c_2 and E the values e_1 and e_2 . For C to be a cause of E, an intervention on C, changing its value (e.g. from c_1 to c_2), results in a change in the value of E (e.g. from e_1 to e_2). Thus the expression ‘C causes E’ is true if an intervention on C changes the value of E.

This can be illustrated using an example of a ‘genetically caused’ phenotype in monkeyflowers. Variations in the *YUP* locus in *Mimulus lewisii* results in two colour morphs. The wild type flowers are pink, while those with a mutant *YUP* allele are orange (Bradshaw & Schemske 2003). To show that *YUP* is a cause of flower colour under the interventionist account, an intervention on this gene (C), changing its value from the wild type allele (c_1) to the mutant allele (c_2), results in a change in flower colour (E), from pink (e_1) to orange (e_2), as shown in Figure 3.1.



Figure 3.1. *Mimulus lewisii* alternate alleles at the *YUP* locus a) shows the wild type, and b) the mutant orange form (Image adapted from Bradshaw & Schemske 2003, p.177)

It must be noted that for C to be a cause of E under an interventionist account *one* intervention on C must result in a change in E. In the example above a change from [allele 1] to [allele 2] may change the flower colour from pink to orange, however, a change from [allele 2] to [allele 3] may not produce any change in flower colour, as both alleles result in orange flowers.

I have used the term intervention so far in the sense of manipulation: however, an intervention is a particular kind of manipulation. The change of value for variable C must occur without changing the value of any other variable, Z, which could itself be a cause of E. In this way the change in the value of E is fully accounted for by the change of the value of C (Woodward 2003). This illustrates the abstract concept of intervention as an idealised manipulation, bringing about changes to the value of C and C only, resulting in no other changes in the causal background conditions (Z). This caveat ensures that there are no confounding variables, and allows investigators to make conclusions about the causal relationship under investigation.

3.2.2 Interventions

It is for this reason that interventions are described as ‘idealised’ experimental manipulations. In real life it is difficult to alter the value of an experimental variable without also altering some other factor in the causal system. Not only is the nature of interventions idealised in the sense that no other variables are affected by the manipulation, but the pragmatic and human aspects of intervention are also abstracted. Thus the term intervention is used throughout this thesis to refer to the change of some variable, even if there is no possible mechanism for changing that variable that a human may be able to produce in an experimental setting. For example, the causal generalisation ‘the collision of tectonic plates causes the formation of mountain ranges’ is true under the interventionist account. In this case an idealised intervention can be made on the variable representing tectonic plates, changing its value from [not colliding] to [colliding]. This intervention changes the value of the effect variable – from [no mountain range present] to [mountain range present]. This is a sense of intervention separate from human involvement, eliminating the anthropomorphic sense of intervention which was seen in earlier manipulation theories, where manipulations were accounted for by human agency and action (see Menzies & Price 1993). A useful way of capturing this notion was expressed by Strevens (2006, p.2), who describes an intervention ‘as the result of the hand of God descending and directly tweaking the relevant factor’.

Causal relationships are often thought of in an interventionist sense within biology. For instance, Green and Wright (1977) in their studies on *Pinus ponderosa* investigated the causal relationship between carbon dioxide (CO₂) and rate of photosynthesis. In these studies the cause variable, CO₂, held two values: [ambient (300-350 ppm)] and [enhanced (450-500ppm)]. The effect variable, photosynthetic rate, was represented in mg of CO₂ respiration per gram of dry leaf weight, a quantitative variable which took on many values.

In the experiment an intervention was made on the CO₂ variable changing the value from [300ppm (the default ambient value of CO₂)] to [450 ppm.]. This resulted in a change in the effect variable: the photosynthetic rate of plants in this condition was different from that in the ambient condition. From this result Green and Wright (1977, p. 689) concluded that ‘carbon dioxide enhancement caused a significant increase in total daily net photosynthesis’.

In this example the intervention is not an idealised one, it was human-mediated in order to carry out the study. However, biologists continue to talk of causation in circumstances where human intervention is not possible. For instance, causal claims about the effects of CO₂ on photosynthesis have been made about the past in palaeobiological settings (e.g. Cerling, Ehleringer & Harris 1998; Surge et al. 1997), and predictions have been made about the future within the climate science literature (e.g. Manning & Tiedemann 1995; Polley et al. 1997), showing that within both disciplines causal claims are made about situations in which manipulation of the causal variable is not possible.

It comes as no surprise then that the interventionist account was initially inspired by the treatment of causal relationships within the sciences (Woodward 2003, p. 12), and fits with the way that causes are discussed in social and behavioural sciences, as well as in biology (Woodward 2007, p. 20). However, even the most carefully controlled experimental manipulation in these fields of study may result in changes of other causal variables. Not only this, but as illustrated above there are some causal variables which are impossible for humans to manipulate. It is because of these limitations that it must be emphasised that an intervention is envisaged as an *idealised* experimental manipulation, not dependent on the practices or abilities of human activity.

3.2.3 Indirect Causes

The transitivity of causation appears to be a natural feature of causation (Carroll 2009), and has been explicitly endorsed by causal theorists (Lewis 1973; 1979; 2000). The transitivity of causation entails that when C causes I , and I causes E , then C causes E ⁴³. In chapter 6 I examine indirect causal relationships that map to cases of reactive and active G-E covariance. However, a formal basis of indirect causes under the interventionist account is needed in order to make a credible comparison.

The causal relationship $C \rightarrow E$ is assessed by the interventionist account as a change in the value of C from c_1 to c_2 , resulting in a change in the value of E from e_1 to e_2 . This becomes an indirect causal relationship if some intermediate variable I stood between C and E , such that $C \rightarrow I \rightarrow E$.

According to Pearl (2001; 2009) an indirect effect of the transition from a prior variable C from values c_1 to c_2 is defined as the expected change in E (the effect) by holding C (the prior cause) constant at some value c_1 , ($C = c_1$), and changing I (the intermediate cause and effect) to whatever value would have attained had C been set to c_2 . So in order to determine if a variable E is an indirect cause of C , such that $C \rightarrow I \rightarrow E$, we must first look at what value the intermediate variable I would have if C was intervened on, changing its value from c_1 to c_2 . If C had the value c_2 post intervention, then I would have the value i_2 , as C is a cause of I , meaning that changing the value of C produces a change in the value of I from i_1 to i_2 .

To determine if C is an indirect effect of E , C is held constant at c_1 , while I is intervened on and changed to the value that would have obtained if C was set to c_2 , which is i_2 . If i_2 produces a change in E which corresponds to the change that would have presented if C

⁴³ Some (Hall 2000; Hesslow 1981; Hitchcock 2001; Lowe 1980; McDermott 1995) have disputed this assumption, as it can entail strange counterexamples.

was set to c_2 , that is, if E is set as e_2 , then C can be said to be an indirect cause of E. Thus $C \rightarrow I \rightarrow E$ occurs when a change in C to c_2 produces a change in I to i_2 , and a change in I to i_2 produces a change in E to e_2 . This is the same as saying that $C \rightarrow I$, as an intervention on C changing c_1 to c_2 produces a change in I from i_1 to i_2 .

3.3 Heritability and Causation

As mentioned at the beginning of this chapter, causes can be divided into two classes: type and token. I used the example ‘gene X causes curly hair’ for a type causal claim, and ‘Holly’s gene X caused her to have curly hair’ as a token causal claim. Upon closer inspection one can see that these claims differ subtly in their effect relata. The type claim refers to ‘gene X’ and ‘curly hair’, while the token claim refers to ‘Holly’s gene X’ and ‘Holly’s curly hair’. Heritability estimates concerns a third type of causal claim, as they differ from the first two in its causal relata.

As described in chapter 2, heritability concerns the causes of differences within a population. For the hair-curling example, an appropriate causal question in the domain of heritability would be: ‘Does variation in genes cause variation in hair shape within a population?’ In this case the effect relata is no longer ‘curly hair’ but ‘variation in hair shape’.

The heritability model is considered as a causal (rather than simply correlational)⁴⁴ model (Block 1995, p.116; Fisher 1918, p.399; Keller 2010, chapter 2; Lush 1940, as cited in McClearn & DeFries 1973, p.201; Lynch & Walsh 1998, p.13; Okasha 2009, pp.722-723; Roberts 1967, p.217; Sesardic 1993, p.399; 2005, p. 22; Tabery 2014, p.37) although often

⁴⁴ Some such as Feldman and Lewontin (1975) and Sarkar (1998) have criticised the causal nature of heritability. The basis of this criticism is addressed in section 3.5.

geneticists replace the word cause with synonymous terms such as ‘determined by’ (Roff 1997, p.24), ‘contribute’ (Plomin et al. 2008, p.82; Roff 1997, p.24), ‘influences’ (Bazzett 2008, p.204; Griffiths, A et al. 2005, p.643), ‘due to’ (Plomin 1990, p.43), ‘responsible for’ (Plomin et al. 2003, p.7), and ‘attributable to’ (Falconer & McKay 1996, p.160).

Like type causation, a heritability claim refers to a population, albeit a narrower one. For type causal claims, one is presumably referring to the entire population of curly-haired people. Although data from a heritability estimate is derived from a single population, the scope of heritability studies can be more contentious as some use the derived data to make claims about larger populations that have not been factored into the analysis. This debate is explored in more detail later in this chapter (3.5.3). For token causation the question applies to one individual only, and thus has an extremely limited scope. These features of different causal claims are summarised in Table 3.1

	Developmental (Token)	Developmental (Type)	Heritability (Variance)
Example	What causes Holly's hair to be curly?	What causes hair to be curly?	What causes variation in hair shape within a population?
Application	Individual level	Population level	Population level
Cause Relata	Holly's genes and her environment	Genes and Environment	Variation in genes and / or variation in environment
Effect Relata	Holly's curly hair	Curly hair	Differences in hair shape within a population
Makes Sense to Apportion Causal Responsibility?	No	No	Yes

Table 3.1 Type, Token, and Variance Causation

Both the type and token questions refer to the development of a trait, and under an interventionist account of causation both genes and the environment are causes of phenotypes. For example, in a developmental token trait (Holly's curly hair), intervening on both her genotype (C_1) and her environment (C_2) would produce a difference in her hair shape (E). Remember that under this account of causation, *some* intervention on C must produce a change in E, not all interventions. Thus if any intervention on C_1 or C_2 produces a change in E, then they should be considered as causes of E. One could intervene on Holly's genotype changing the value from [complete genotype] to [missing or interrupting all the sequences that code for keratins⁴⁵] and the value of E would change from [curly hair] to [no hair]⁴⁶. Thus C_1 is considered a cause of E. Similarly, changing the value of C_2 from [Holly's normal developmental environment] to one in which she [receives no nutrition] would also change the value of E from [curly hair] to [no hair], as Holly would not live long enough to develop hair at all. The same logic can be applied to type developmental causes. Changing the value of genetic or environmental variables more generally (even if this is done in a far-fetched way, as in the examples above) would also change the value of the phenotype of curly hair.

For heritability estimates the question is a little different. As the effect relata is variance in a phenotype, the amount of causal influence from genetic and environmental differences can be quantified. Details of how these estimates are made have been described in chapter 2. For heritability, genetic (or environmental) variance can either completely or partially account for phenotypic variance, or not at all. V_G or V_E can completely cause V_P , partially

⁴⁵ A group of proteins required for the composition of hair, skin and nails.

⁴⁶ It is likely that Holly would also suffer changes to many other phenotypes if this intervention were to take place.

cause V_P , or not cause V_P , depending on the data collected and the population studied⁴⁷ (see Figure 3.2 below).

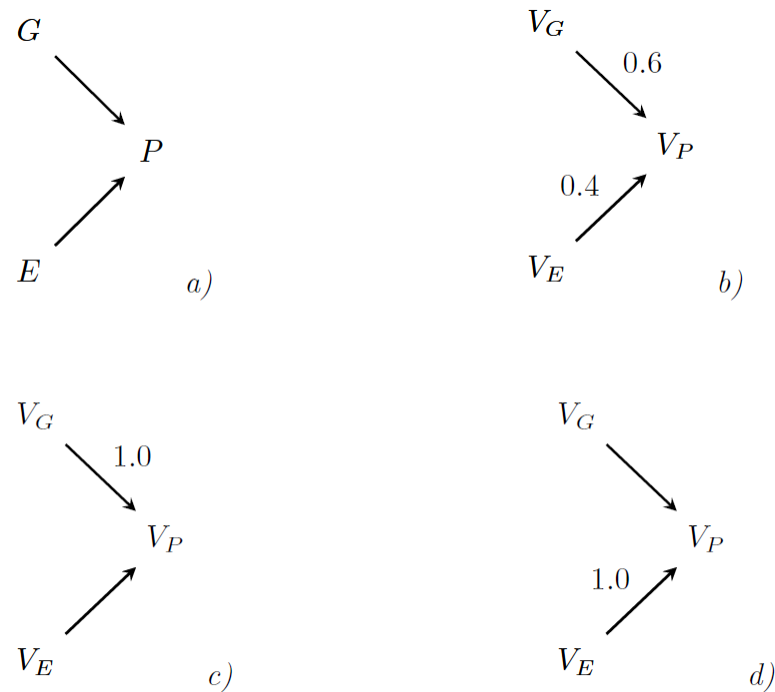


Figure 3.2 Causal Structures of Type, Token and Variance Claims a) represents the causal relationship for both type and token causal claims, where both genotype (G) and environment (E) are causes of phenotype (P). b)-d) represent the kinds of causal relationships that can occur in heritability. It is possible for both variance genotype (V_G) and variance in the environment (V_E) to cause variance in phenotype (V_P), and make relative quantitative contributions, for example 0.6 and 0.4 (b), for just genotypic variance to cause V_P (c) or for just environmental variance to cause V_P (d)

An example of such a case would be the phenotype of skin colour in humans. Human skin colour is somewhat determined by the genes an individual possesses, but environmental influences like the amount of UV radiation received (from sunshine or other sources such as tanning beds), also affect how light or dark a person's skin is. Within a given population

⁴⁷ It is worth noting that V_G or V_E almost never completely cause V_P , generally V_G and V_E are both contributors.

the variation in people's skin colour may be accounted for both by variation in their genetics, and variation in how much UV radiation they have received (their environment). For instance, a H^2 of 0.6 indicates that both V_G and V_E are causally responsible for the trait (see Figure 3.2).

3.4 Dimensions of Causation

In heritability studies, it is not enough to say that both V_G and V_E cause V_P , we want to know which one causes *more* variation than the other. This is done by a numerical partitioning of phenotypic variance, illustrated in chapter 2. For other kinds of causal relationships, different dimensions of causation have been invoked in order to prioritize some causes over others. I wish to show how some of these dimensions map to the numerical attributions provided with heritability estimates.

Identifying dimensions of causation is a response to what Menzies (2004) terms the problem of profligate causes. Using a philosophical account to identify the causes of an effect leads to a plethora of candidate causes. This problem appears rife no matter the philosophical account of causation presupposed. For instance under an interventionist account the causes of my writing this chapter would include my motivations to complete a PhD thesis. If I intervened on that motivation, altering its value so that I was no longer, or at least less, motivated, then this chapter would not be here to read. However, the writing of this chapter also depends upon my being born, every person in my family's lineage being born, and acting in such a way that brought about the precise ancestral history that resulted in my birth, as well as each specific environmental factor which contributed to my existence and motivations up until the very point that I wrote this chapter. Intervening on my great-great grandmothers marriage and changing this event to one in which she does

not marry my great-great-grandfather would result in a changed effect where I would not be writing this chapter (as I would not exist). An intervention on any one of these could alter the effect of this thesis being written.

Yet common sense and causal intuitions suggest that neither the creation of the universe nor my great-great-grandmother's marriage to my great-great-grandfather are causes of my writing. Or at the least that these are different kinds of causes to the motivation to complete a PhD thesis. While much philosophical discussion has focussed on the fine-tuning of criteria to distinguish causes from non-causes, surprisingly less has been said about distinguishing between kinds of causes. What, if anything, makes one cause different from another? For instance, what makes my motivations to write a different kind of cause from the meetings of my distant relatives? This is the problem of causal selection – where one cause is selected among many as *the* cause of an effect; or causal privileging – where one or more causes are considered *more of a cause* or a *more important cause* than other causes of the same effect.

This problem has been considered in related facet of the nature-nurture debate. Proponents of Developmental Systems Theory (DST) have argued that biologists are too 'gene-centric', causally privileging DNA as more important than other factors that are also required for the production of phenotypes (Griffiths & Gray 1994; Griffiths & Knight 1998; Kitcher 2001; Oyama 2000; 2001). They have argued for the importance of modifying effects of the environment (Griffiths & Gray 1994; Kitcher 2001), developmental feedbacks (Griffiths & Gray 1994; Oyama 2000), other cellular machinery (Griffiths & Gray 1994; Oyama 2000; 2001), as well as emphasising the role of non-genetic inheritance, described in section 1.2.2 (and further discussed in sections 4.1.3, 5.3 and 5.4).

Kitcher (2001, p.404) has gone as far as calling for a 'causal democracy' within the study of biology, where:

...if the effect E is the product of factors in a set S, then, for any $C \in S$, it is legitimate to investigate the dependence of E on C when the other factors in S are allowed to vary.

Oyama (2001), Griffiths and Gray (2005), Stotz (2006) and Griffiths and Stotz (2013) defend a more moderate view of causal parity, stating that whatever criteria are applied to privilege a causal factor should be applied consistently. The causal role of genes is to specify the linear sequence of gene products. However, other causal factors, among them splicing and editing factors and environmental signals activating or recruiting these elements, also share this causal role of informational specificity. Whether a cause is informational depends on whether it is specific, not on whether it is genetic. DST simply criticises the unfair division among causes to privilege genes or DNA above other contributing causes.

Criteria for causal selection have been applied to the nature-nurture debate, though to the likely dismay of DST theorists, most often the target is genes or DNA. These criteria have been used to differentiate between different types of causes and causal relationships concerning genetics. I will discuss just two of these: invariance and stability. It should be noted, however, that other dimensions of causation have been invoked to support or at least explain the causal privileging of genes, genomes, and DNA. These include specificity (Waters 2007; Weber 2006; Woodward 2010; 2011)⁴⁸, actual difference making (Waters 2007)⁴⁹ and proportionality⁵⁰ (Woodward 2010). An alternative approach has been to justify gene-privileging on pragmatic grounds (see Gannett 1999; Kronfeldner 2009). These shall not be considered here as I do not think they apply in the same way to causal claims regarding heritability.

⁴⁸ See Stotz (2006) and Griffiths and Stotz (2013) for a counter to some of these arguments.

⁴⁹ See footnote 48.

⁵⁰ This dimension is referenced in chapter 7.

3.5 Invariance

One of these causal dimensions is invariance. Broadly speaking, an invariant causal relationship is one which continues to hold under a range of interventions. The more interventions it can withstand, the more invariant the relationship is. There are two senses of invariance used within the causation literature, although they are sometimes conflated. Both apply to type-causal relationships in an interventionist framework. One concerns the relationship that holds between the causal variables, namely the extent to which the causal dependencies hold between these two variables under interventions on C. The other regards the range of background conditions under which a causal relationship can be maintained. In this section I will show how both can be related to the norm of reaction in heritability studies, and how applying these features to heritability can help to inform us about what kind of causal relationship heritability refers to.

3.5.1 An Amalgamation of Invariance Concepts

Woodward (2000, p.205) distinguishes between two ‘sorts of changes that are relevant to the assessment of invariance’. The first are changes to the background conditions of a causal relationship, which he later renames sensitivity (2006) or stability (Woodward & Hitchcock 2003; Woodward 2010). The second are changes to some factor explicitly present in the relationship itself, termed invariance under interventions (2000), or just invariance simpliciter (Woodward 2001a; 2003; Woodward & Hitchcock 2003).

Invariance (simpliciter) refers to a dimension of a causal relationship in which the causal generalisation continues to hold under interventions on the causal variable. That is, the relationship between C and E is invariant if it continues to hold under interventions on C. A minimal criterion for the relationship ‘continuing to hold’ is that at least one ‘testing intervention’ produces a change in the value of the effect. That is, at least one intervention

upon C must produce some change in E. Minimal invariance is a requirement for causal relationships, as a single testing intervention demonstrates that a change in the value of C produces a change in the value of E (Woodward 2003, p.250; Woodward & Hitchcock 2003). When a relationship holds under multiple testing interventions, the degree of invariance can be used to measure a dimension of causation, which Woodward (2001a; 2003; 2010) and Woodward and Hitchcock (2003) regard as an indicator of explanatory depth. The more testing interventions that produce changes to E, the greater degree of invariance this causal relationship possesses.

For relationships that are maximally invariant, a change in the value of C always produces a change in the value of E. Maximal or largely invariant relationships are often observed in scientific laws. Woodward (2001a, pp.10-11) uses the example of Hooke's Law, which describes the action of a spring when extended. The causal generalisation is: $F = kX$, where X represents the extension of a spring, F the restoring force it exerts, and k a constant specific to springs of type S. An intervention on the spring, extending it in a way that changes the value of X would produce a change in F under many different interventions on X. However, there would still be some interventions, such as extending the spring so far that it breaks, which would cause the generalisation to break down. Thus this is a highly, although not completely, invariant relationship.

Take another example, of the effect of nutrient level on bamboo growth, where C is the level of nitrogen, and E the height of the bamboo. Intervening on C to increase the nutrient load will result in an increase in the height of the bamboo (a change in the value of E). This is likely to be true for many values of C and E— the more nutrients, the taller the bamboo grows. However, there will be a point at which a change in C, a further increase of nitrogen, will not result in a change in E. This is because bamboo can only grow so tall; it will reach

a point at which additional nitrogen will make no difference to height. In this case, as in the one before, not every intervention on C results in a change in the value of E.

Woodward (2001a; 2003) has argued that this form of invariance helps to identify the explanatory depth of a causal generalisation. The more invariant the generalisation, the more valued the causal explanation (2003, p.257).⁵¹ However, an issue for determining the invariance of the relationship is defining the values that the cause and effect variables take. If the variables are defined to have a very fine-grained set of values, then it may be that many interventions on C produce many changes in E. If the values are more coarse-grained, fewer interventions on C and E will be counted. Woodward also describes greater invariance as holding when generalisations hold under ‘more important set[s] of changes’ (2003, p.257), although it is not clear how the importance of these values should be determined. So while this sense of invariance may play a useful explanatory role for partitioning causes for their explanatory depth, it is worth noting that a determination of value relevance and fineness of grain is implicit in this assessment.

The second notion of invariance concerns the degree to which the relationship between two variables holds under changes to the values of *other* variables. That is, variables within the causal background that do not factor into the causal relationship under investigation. This type of invariance is often referred to as ‘stability’ and from here on shall be referred to in this way.

For example, imagine that allele *a* of gene *A* causes hairy toes. All individuals who possess variant *a* have hairy toes, despite differences in their genetic background and environment. Conversely, those with variant *b* of gene *A* do not have hair on their toes, no matter the differences in other variables. The relationship between gene *A* and toe hairiness is

⁵¹ He also makes the point that it matters most that generalisations are invariant in this sense rather than the stability sense, explained below (Woodward 2000, p. 208; 2003, p.248).

relatively stable, as the relationship continues to hold across a large range of background circumstances. If one were to intervene on a background variable such as the latitude in which an individual lives, or allelic forms of other genes within an individual's genome, the causal relationship between gene *A* and toe hairiness would continue to hold.

Contrast this with another gene *R*, which is the cause of reading (hypothetical example adapted from Woodward 2010). Individuals who possess variant *r* are able to learn how to read, and individuals who do not possess this variant (perhaps possessing other variants *p* or *q*) are not. However, reading ability only occurs given particular background circumstances; such as education availability or the presence of a written language. This particular causal relationship is far less stable than that between gene *A* and toe hairiness. Should the values of variables in the background change, such as the world no longer having a written language, or the individual's community not containing educational support, the causal relationship between gene *R* and reading would fail to hold.

Like with invariance under interventions, stability is a feature of a causal relationship that comes in degrees. A causal relationship is more or less stable than another depending if it continues to hold under greater or lesser changes in background conditions. In the example above, the relationship between gene *A* and toe hairiness is more stable than that of gene *R* and reading, as the former produced the same effect under a wider range of background circumstances than the latter.

The stability concept was proposed by Mitchell (1997; 2000) as an alternative to the strict criteria for a dichotomous conception of law hood. Traditionally in the literature on laws, generalisations were considered to be laws if they were naturally necessary, exceptionless, and/or universal. The consequences for this view was that generalisations usually termed biological laws, such as Mendel's law of segregation, were no longer considered law-like,

as they did not fulfil the normative criteria for law hood. Mitchell proposed that laws instead should be considered along a continuum, assessed by their stability.

While neither Woodward nor Mitchell claim that more stable causal relationships are more ‘important’ than those which are less stable, Woodward (2006) does believe that the stability of a causal relationship may help to explain why people hold different attitudes towards different causes of the same effect. He contends that stability can (at least partially) account for why some causes are regarded as ‘defective, nonstandard, or at least importantly different from less sensitive [more stable] causal claims’ (p.2) and ‘less important or salient than others’ (p.47). This, he believes, may at least partially account for why a relationship such as the one between gene *A* and toe hairiness appears more acceptable as causal than the relationship between gene *R* and reading.

The reason for this intuition may be that the notion of stability captures how easily the causal relationship can be altered (Woodward 2001b; 2010). Highly stable relationships cannot be altered as easily or through as many different avenues as relationships which are less stable. Consequently, less stable relationships may be more susceptible to alteration, either by human interventions or evolutionary processes such as natural selection. Thus the stability of the causal relationship may be able to tell us something biologically important about the relationship itself.

3.5.2 Invariance, Stability, and the Norm of Reaction

In chapter 2 I introduced the norm of reaction. One feature of reaction norms is that they nicely illustrate how stability and invariance relate to heritability estimates, as well as the relationship between the two causal dimensions. Norms of reaction represent the same data as a heritability estimate, but because the representation is slightly different, it can be said

to include information about causal relationships with slightly different variables and values.

Recall from chapter 2 that a norm of reaction illustrates the effect of each genotype (curves) on the expression of a phenotype (y-axis), against differences in an environmental background variable (x-axis). As such it shows how variance in genotype (V_G) effects variance in phenotype (V_P) across various environments (V_E). But it also gives information about particular genotypes and particular environments. Because of this more detailed information, one can consider two different, but related, causal relationships. The first is the causal relationship between a particular G (line on the graph) and P (point on the y-axis), or between an E (point on the x-axis) and P. These causal relationships regard the effects of just one genotype or just one environment on a phenotypic outcome. An example of this kind of relationship would be that G1 causes the P value of 120 when the background condition of E1 is satisfied. Or alternatively that E1 causes P to be 120 when the genetic background is G1.

The second causal relationship is the more general one between V_G , V_E , and V_P . Instead of the values of these variables being numerical, as they are in a heritability claim, the values of V_G would be the genotypes represented, and of V_E would be the environments represented. The V_P variable is determined by a range of quantitative values that are represented on the y-axis. For example in the norms of reaction displayed in chapter 2, the values of V_G are G1, G2 and G3, the values of V_E are E1, E2, E3 and E4, and the values of V_P are IQ points between the range of 75-125.

In the example introduced in the section above, gene A causes the phenotype hairy toes in a stable manner. Given a certain value of A, toe-hairiness will be the same no matter the differences in environment. This parallels a norm of reaction where heritability is high, such as the one presented in Figure 2.4. The flatter the reaction norm, the more stable the

causal relationship. That is, the relationship between each genotype (G_1 , G_2 , G_3) and P is stable, as background conditions (V_E) do not perturb this causal relationship. Conversely, a graph like Figure 2.5, where heritability is low and the reaction norm changes over environmental conditions, displays a relatively unstable relationship between each genotype and P .

It must be noted that in the norm of reaction the background conditions are represented by a single variable. While this is labelled generally as ‘environment’ it does not canvass all the possible interventions that could be made on environmental background conditions. In Figures 2.4-2.7 (pp. 62, 63 and 65), the environment is limited to just one variable with four possible values. This demonstrates the limits of the analogy between the norm of reaction and the broader stability concept. Stability is meant to incorporate considerations of variations across a large range of background variables (Woodward 2010, p.296), while the norm of reaction only allows for a single quantitative (if the environmental variable exists along a continuum, such as temperature or nutrient load), or qualitative variable for the environment (if the environments are discrete variables encompassing a multitude of factors, such as the environmental treatments in the example in section 2.4.1). As such the degree to which stability can be determined is limited by the experimental investigation by which heritability has been estimated. So while the norm of reaction may be a useful heuristic for representing the stability of a causal relationship, it is not nearly as broad as the philosophical stability concept proposed by Mitchell (1997; 2000) and Woodward (2006; 2010) that are applied to type-causal claims.

If one were to assess the stability of the relationship between the second kind of causal relationship: V_G and V_P , then Figures 2.4, 2.5 and 2.6 all display stable relationships, as the variation in genotype predicts the same amount of variation in phenotype across each environment (considered here as causal background conditions). As long as the lines in the

norm of reaction graph do not diverge or cross, as seen in Figure 2.7 where $V_{G \times E}$ is present, then the relationship between V_G and V_P is stable, which corresponds to additivity in the heritability model. Changes in the environment do alter the phenotype in Figures 2.5 and 2.6, but they do not change the way that variation in genetics predicts variation in the phenotype.

Reaction norms not only give us information about the stability of the causal relationship between genotype and phenotype, but also, to some degree, its invariance. Whenever multiple genotype values are given in a reaction norm, one can see how changes to the value of the genotype produce changes to the values in the phenotypic effect variable. From this, one could see whether changes to the genetic variable result in a causal relationship being maintained with the phenotype. The relationships represented in Figures 2.4 and 2.6 show invariant causal relationships between the variables V_G and V_P . This is because the causal relationship between genotype and phenotype ‘continues to hold’ in the sense used by Woodward, whereby an alteration of the value of a genotype (corresponding to a testing intervention) results in a change in the value of phenotype. Different genotypic values (G_1 , G_2 , G_3) map to different phenotypic values (y-axis). A less invariant relationship between V_G and V_P is shown in Figure 2.5, where different values of V_G result in the same values of V_P . This reflects the strength of the effect of V_G on V_P . Figure 2.5 represents a low heritability estimate, where very little of V_P is accounted for by V_G . Conversely, Figures 2.4, 2.6 and 2.7 all show a V_P for which V_G had a significant effect.

In parallel with its analogue to stability, the norm of reaction gives a limited amount of information regarding invariance, due to the ranges of values that the genotype variable takes within the graph. In Figures 2.4-2.7 just three genotype values are considered, which is due to the limitations inherent in the experiment employed to attain an estimate. While general type-causal claims consider a range of possible values factoring into the causal

relationship, heritability studies are limited by the number of genotypes and environments that are actually studied in an experiment.

Notice that I have only examined the stability of the causal relationships concerning genetic causes: $G \rightarrow P$ and $V_G \rightarrow V_P$. What happens when $E \rightarrow P$ and $V_E \rightarrow V_P$ are investigated instead? For stability, the opposite result occurs. For a high heritability estimate (Figure 2.4), the relationship $G \rightarrow P$ is relatively stable, as demonstrated above. But the relationship $E \rightarrow P$ is unstable, as now the causal background conditions are differences in genotypes (V_G), rather than the environment. The same occurs for low heritability estimates. Corresponding reaction norms (Figure 2.5) show that $G \rightarrow P$ is relatively unstable, as the relationship changes as background conditions (V_E) change. Yet $E \rightarrow P$ is a stable causal relationship, as changes to E produces changes in P , despite differences in the background, V_G .

In other words, when the relationship $G \rightarrow P$ is stable, then V_G is high and heritability is high. When $E \rightarrow P$ is stable, V_E is high and heritability is low. This same switch can be done for invariance. In Figure 2.4, where heritability is high, the relationship between V_G and V_P is invariant, but the relationship between V_E and V_P is not, as different values of V_E do not produce changes to V_P . Conversely, in Figure 2.6, changes to V_E do produce changes to V_P , while changes to V_G do not. Thus the relationship between V_G and V_P is not invariant, while the one between V_E and V_P is.

3.5.3 Invariance, Extrapolation and Explanatory Depth

In section 2.6 I introduced $V_{G \times E}$ as a problem for heritability estimates that can be illustrated with a reaction norm. $V_{G \times E}$ reflects a wider problem with heritability estimates concerning the extrapolation of heritability claims. This is sometimes termed the locality objection (Sesardic 1993; 2005).

Recall that when $V_{G \times E}$ is present environmental effects on the phenotype are modified depending upon the genotypic background (and vice versa). When this happens V_G and V_E no longer behave additively, and as such an extra variable ($V_{G \times E}$) needs to be factored into the heritability model. In order to extrapolate outside of the population and environment(s) studied, it must be assumed that the contribution of V_G and V_E remain additive, that is, the effect of a particular genotype relative to another is maintained across other environments (see Figures 2.4, 2.5 and 2.6 in chapter 2, pp. 62 and 63). Lewontin (1974) has argued that the absence of interaction across the range of environments and genotypes studied for a particular estimate does not demonstrate that there is no interaction at other, unobserved genotypic and environmental values. For instance, genotypes that appear to have performed consistently better than others across some environments may perform more poorly in a different environment, but this interactive effect would not be considered if that kind of environment had not been measured. Lewontin (1974) also suggests that additivity of V_G and V_E is rare in nature. He bases this on empirical studies in plants and *Drosophila* where a large amount of $V_{G \times E}$ is present for various traits. Sesardic (2003, citing Jensen 1981 and Plomin 1986), Herrnstein (1973) and Crow (1990) have all argued that $V_{G \times E}$ rarely accounts for a large portion of V_P in human studies. This debate is as yet unresolved, as norm of reaction data is hard to obtain for humans (Ofstedal 2005) and others have noted that this may be due to a problem with the statistical power and design methodologies to detect such interactions (see Wahlsten 1990 and commentaries; Griffiths & Tabery 2008; Tabery & Griffiths 2010.)

Say an experiment is conducted in which the results from Figure 2.4 are attained, and the corresponding H^2 of 0.9948. Based on these results geneticists may publish claims that this phenotype (intelligence) is highly heritable, and that G1 individuals are more intelligent than their G2 and G3 counterparts. However, if one were to extend the study to include

more genotypes (G4, G5, G6 ...) and/or more environments (E5, E6, E7 ...) one might find other genotypes, environments, or combinations of the two that fare better in intelligence tests, and that this might occur in way that deviates from the observed function (linear in Figure 2.4) from the genotypes and environments already studied. They may also find that G1s perform worse under particular environmental conditions than G2s ($V_{G \times E}$). As a result, after considering these new values, the amount of phenotypic variance that can be accounted for overall by V_G or V_E could be considerably lower (or higher) than has been estimated using the original limited set. For example see Figure 3.3.

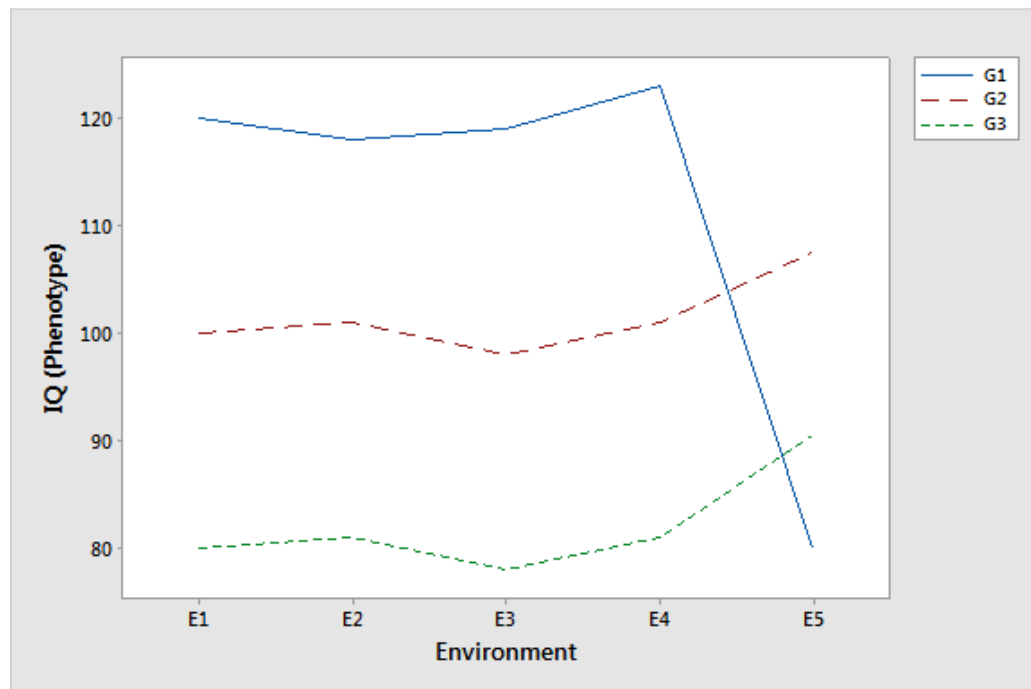


Figure 3.3 Norm of Reaction Displaying Locality Problem

Thus Lewontin's locality objection becomes a problem regarding extrapolation. Generally, the types of conclusions that quantitative and behavioural geneticists make based on heritability analyses are extrapolated to general or type-causal claims. They make causal

claims in the form of ‘phenotype x is highly heritable’ or ‘phenotype x has a heritability of 0.67’. Rather than the more conservative, token-sounding claim ‘phenotype x is highly heritable in this population of particular subjects and limited environmental variables and values’. In addition to this, the term reaction *norm* is used to refer to the graphical representation of a single heritability estimate, implying a more general causal relationship. So are behavioural and quantitative geneticists playing fair? Lewontin (1974; 1983) and others (Block & Dworkin 1976; Feldman & Lewontin 1975; Gottlieb 2003; Layzer 1974; 1976; Lewontin, Rose & Kamin 1984; Wahlsten 1990) think not, and have argued that this problem undermines the utility of causal claims made in light of heritability studies.

Griffiths and Tabery (2008) contribute to the debate by distinguishing between two interpretations of the graphs shown in Figures 2.4-2.7 and 3.3: the reaction norm and the reaction range. This is motivated by work by Platt and Sanislow (1988), who have argued that the original graphical representation from Dobzhansky (1955) displayed a sample from a distribution of possible phenotypes. Dobzhansky himself seems to have understood the locality problem, yet claims that a reaction norm refers to a broader generalisation, even though it is one that is never completely known. Under this view, graphical representations like those shown in Figures 2.4-2.7 act as representatives of the more general causal relationship that is the theoretical reaction norm.

The norm of reaction of a genotype is at best only incompletely known. Complete knowledge of a norm of reaction would require placing the carriers of a given genotype in all possible environments, and observing the phenotypes that develop. This is a practical impossibility. The existing variety of environments is immense, and new environments are constantly produced. Invention of a new drug, a new diet, a new type of housing, a new educational system, a new political regime introduces new environments. (Dobzhansky 1966, as cited in Platt & Sanislow 1988, p.254)

A reaction range on the other hand is a concept that was later introduced by Gottesman (1963a; 1963b, as cited in Griffiths & Tabery 2008). His interpretation of the same

graphical representation includes the limits of genotypes and environmental values studied within a given experiment. Thus the reaction range refers only to the particular genotypic and environmental values studied, and the population used to generate such results.

This debate relates to an issue introduced in section 3.3 – concerning the nature of the causal claim heritability maps to. On the Dobzhansky reaction *norm* side of the debate, the representation is meant to refer to a broader generalisation, spanning multiple genotypes, environments, and populations. Presumably, the corresponding heritability estimate is also thought to refer to more general causal claims about the effects of V_G and V_E on V_P .

On the Gottesman reaction *range* side of the debate the norm of reaction refers only to the genotypes and environments that have been factored into that heritability analysis, and as such, claims about the heritability of such traits are true only relative to some particular population. This is closer to a token-causal claim – where V_G and V_E are causally responsible for some components of V_P in one particular instantiation. Sesardic (1993) has made a convincing argument that heritability analyses track causal claims in a local sense, which goes against claims by Lewontin (1974), Feldman and Lewontin (1975, p.1163) and Sarkar (1998) that heritability estimates correspond to *no* claims about genetic causation. Responding to Lewontin’s locality criticism, he states:

It is, however, wrong to suggest (as Lewontin does) that by making this causal inference one is committed also to a “general”, “functional” relation between G and P... (p.403)

Others have agreed that heritability estimates (where interaction is not present) can be used to make this kind of type causal claim (Jencks 1980; Wahlsten 1990), but have concluded that this undermines the explanatory utility of the estimates, as they are too restricted to be of any interest. So Sesardic takes this claim further, in order to preserve the utility of heritability, and argues that in some situations extrapolation is permissible. That is, some heritability estimates can be used to make both token and broader type causal claims. He

argues that while a heritability analysis cannot convey the impact of V_G on V_P in every possible environmental background condition, having to do so is too much to ask of any causal claim. More general type causal claims of the form ‘C causes E’ are also not assumed to hold under *all* background conditions. Those claims that do are considered to have special epistemic features, like lawlikeness, as was discussed in the sections above. Thus asking for a maximally invariant basis for causal claims $V_G \rightarrow V_P$ is too great a requirement.

Sesardic points to causal mechanisms as a way of determining the extrapolation-worthiness of a heritability estimate. He believes that the more that is known about the causal mechanisms involved, the more reliable the extrapolation (1993, pp.404-405). I believe that a different approach, to look at invariance and stability, can help inform this debate. I demonstrated in section 3.5.2 that both invariance and stability can be applied to the norm of reaction. Yet I also showed that this application is more limited to the way in which these concepts are applied for type-causal claims. This is because there are less values for the variables, and less background variables (and their values) that factor into the causal relationships under study. These variables and their values are determined empirically by the experimental design of particular heritability estimates.

For a type-causal claim to have explanatory depth, Woodward and Mitchell assert that high degrees of invariance and stability are needed. Thus it may be useful to think of the results of heritability studies as having greater explanatory depth – and thus greater potential for extrapolation to type causal claims, depending upon the degree of invariance and stability that they display. This, as mentioned, is related to the number of variables and values studied in a particular experiment or experiments. Thus multiple studies over many populations, genotypes, and environments which display similar results (and no $V_{G \times E}$) lend greater support for extrapolating claims than those which do not.

So perhaps, the question about type and token claims, and the extent to which they can be extrapolated, simply ‘depends’. What it depends upon is the amount and extent of research done on the heritability of a particular phenotype. The more that a phenotype has been studied - in terms of different genotypes and environments factoring into heritability estimates - the more reasonable it will be to take causal claims about the heritability of this trait as type or general. As such, heritability claims *should* be regarded as concerning type-causation, although the types that it applies to are extremely limited, and the claims are usually explanatorily shallow, as they are confined to the population(s) studied.

3.6 Psychological Dimensions of Causal Attribution

An alternative approach to differentiating between causes is to consider the conceptual and psychological factors that play a role in selecting and privileging causes. This section will examine three factors that have been thought to contribute to causal selection: agency, blame, and norms. I will show how agency is not sufficient to explain common-sense causal selection, and that an additional factor, blame is needed. I will then detail how blame and norms are related, when contrasts or counterfactual reasoning is used.

3.6.1 Agency

Agency has been used as a feature in causal theories that aim to distinguish causes from non-causes. The early manipulationist accounts were agency accounts, where A causes B ‘...just in case bringing about the occurrence of A would be an effective means by which a free agent could bring about the occurrence of B.’ (Menzies & Price 1993, p.187). In this account a ‘free agent’ is required to bring about change, and so causation is assessed relative to the capabilities of agents. This theory was replaced with the agent-free interventionist account of causation, which retained the manipulability aspect of the

account, without the concerns that come with an appeal to human agency. These concerns included defining what a ‘free agent’ may be, and accounting for apparent causes which an agent may not be able to bring about (see section 3.1.2).

Alicke (1992) looked at the role that agency plays in selecting causes from a causal background. The study presented vignettes about the cause of a car accident where the driver, John, was speeding home and was involved in an accident. These scenarios varied so that some examples included the involvement of another agent in the car accident. The motivations of John also varied in these vignettes (discussed below).

Oil spill. As John came to an intersection, he applied his brakes, but was unable to stop as quickly as usual because of some oil that had spilled on the road. As a result, John hit a car that was coming from the other direction.

Tree branch. As John came to an intersection, he failed to see a stop sign that was covered by a large tree branch. As a result, John hit a car that was coming from the other direction.

Other car. As John came to an intersection, he applied his brakes, but was unable to avoid a car that ran through a stop sign without making any attempt to slow down. As a result, John hit the car that was coming from the other direction. (Alicke 1992, p.369)

Alicke found that even when John’s own actions and motivations were held fixed, the inclusion of an additional agent into the system (the driver of the other car) led to a decrease in the causal attributions made to John compared to the ‘oil spill’ and ‘tree branch’ scenarios. Thus ‘the intervention of another human agent similarly influenced judgments of responsibility, avoidability, and award of compensation’ (Alicke 1992, p.370). This study demonstrates that the presence of human agency can be a determining factor for attributions of causation.

3.6.2 *Blame*

Agency alone does not appear sufficient to explain the selection of some causes above others. An example from Hart and Honore (1985) helps to illustrate why. Imagine a householder who is prudent in storing firewood in his cellar, only to facilitate a pyromaniac an opportunity to burn it down. Here both the householder and the pyromaniac are agents, and both have causally contributed to the burning down of the house (under an interventionist account of causation both would be considered as causes). Yet it seems clear that the pyromaniac is causally responsible for the house-burning, and not the householder.

Feinberg (1970) has argued that agency plays an important role in causal attribution, but that agency alone is not sufficient in explaining the selection of causes. Instead the motivations and actions of the agent are subject to moral judgements, and these are what determine which factors are selected as salient causes. In other words, whether the agents are *blameworthy* or not appears to play a role in the way that causes are attributed. Causal responsibility has been repeatedly shown to be a precondition for assigning blame (Alicke 1992; Shultz, Schliefer & Altman 1981; Sloman, Fernback & Ewing 2009), but more interestingly, Feinberg and a host of empirical studies indicate a bi-directionality in this relationship: that blame-worthiness can act as a presupposition for people's causal judgements.

Driver (2007a) thinks that when people causally reason, they employ the entailment claim: 'that moral responsibility entails causal responsibility' (p.423). This is supported by Alicke's (1992) empirical research, where causation is attributed to the actions of an agent when there is a negative outcome and the agent acts in a morally undesirable way, or is 'culpable'. In one version of the scenario presented earlier the reason for John's speeding was so he could hide an anniversary present he had bought for his parents before they got

home. In the alternative scenario he was speeding home to hide some cocaine that he had left out so that his parents would not find it. Although the speeding and the outcome were the same in each case, John was identified as being causally responsible for the car crash more often in the cocaine-hiding scenario than in the present-hiding one. Alicke (1992, p.370) concluded that the study:

... provided a clear demonstration of the culpable causation principle: With causal necessity, sufficiency, and proximity held constant, the more culpable act was deemed by subjects to have exerted a larger causal influence.

Alicke (1992) concluded that when there is a harmful outcome, the most blameworthy actor is assigned as the cause. Feinberg (1970) similarly argues that when an outcome is negative the cause is usually attributed as the person at fault – and so moral judgements are conflated with causal ascriptions.

3.6.3 Norms

While Knobe (2006, p.62) believes that ‘ ... people’s willingness to say that a given behaviour caused a given outcome depends in part on whether they regard the behaviour as morally wrong’, he expands this account to emphasise the role of contrast classes in causal reasoning. Knobe believes that when determining a salient cause from a set of contributing causes, the factor(s) that exhibit a deviation from what is contrasted as a normal state of affairs are selected as causes. To demonstrate this he uses the following example:

George and Harry both work in a large office building. George is the janitor; Harry takes care of the mail. Every day, George goes through the entire building and empties all of the garbage baskets. Since the building is large, this task normally takes him about one half hour. One day, George is feeling tired and decides not to take out the garbage. Harry sees that the garbage hasn’t been taken out. He doesn’t go to take it out himself, since that is not his job. But it turns out that the company is extremely lucky. An accountant had accidentally thrown out an important document, and everyone is overjoyed to find that the trash hadn’t been taken out and hence that the document is still there. (Knobe 2006, p.75)

Knobe argues that George is attributed as causing the letter to be saved, although he is not blamed for it. Rather, the deviation from a normal state of affairs (taking out the garbage) is what explains the causal attribution. This theory has been extended by Hitchcock and Knobe (2009) who argue that people's causal intuitions are determined (at least in part) by judgments about the relevance of counterfactuals, and that these judgements are determined by an appeal to norms.

This account can be used as an alternative explanation for Alicke's results also. Instead of the salient factor determining the cause of the car crash being blame-worthiness or moral responsibility, it is deviation from the norm. Knobe and Fraser (2007) tested this possibility by using a different vignette:

The receptionist in the philosophy department keeps her desk stocked with pens. The administrative assistants are allowed to take the pens, but faculty members are supposed to buy their own. The administrative assistants typically do take the pens.

Unfortunately, so do the faculty members. The receptionist has repeatedly emailed them reminders that only administrative assistants are allowed to take the pens. On Monday morning, one of the administrative assistants encounters Professor Smith walking past the receptionist's desk. Both take pens. Later that day, the receptionist needs to take an important message... but she has a problem. There are no pens left on her desk. (Knobe & Fraser 2007, p.443)

Participants were asked whether they agreed or disagreed with the following statements:

Professor Smith caused the problem.

The administrative assistant caused the problem. (ibid)

If atypicality or norm deviation is the driving factor for causal attributions, then there should be no difference in agreement between Professor Smith and the administrative assistant. However, the study found more agreement with the statement that Professor Smith caused the problem than the administrative assistant, suggesting the ascription of blame-worthiness does play a role in causal attribution.

Although, it has been argued that moral culpability can be viewed as a norm deviation in this and the above cases – as blameworthy acts diverge from what is morally normal (Driver 2007b). This is compatible with a contrastive account of causation (Schaffer 2005), where counterfactual reasoning is used to compare a given causal scenario to another in order to identify the salient cause. Knobe (2009) argues that counterfactual reasoning is used to make causal judgements, and that this type of reasoning can explain the results in vignettes of the type presented above. This is supported by causal theories that suggest counterfactual reasoning is used in causal reasoning, including Woodward's (2003) interventionist account. According to Hitchcock and Knobe (2009), which counterfactual is deemed a relevant contrast is determined by an appeal to norms. Relevant counterfactuals are those in which a 'normal' state of affairs occurs.

This can be further related to the interventionist account of causation. Menzies (2009) suggests that one of the reasons that norms are used is that one's intuitive folk concept of causation is related to interventions and interventions bring about changes in what are otherwise a *normal* course of events. Thus if a cause is an intervened upon and set to an abnormal factor in a situation, it must be contrasted with the normal ones.

3.7 Summary and Conclusion

Although heritability estimates are often interpreted in causal terms, the nature of the causal relationship referenced is unclear. This chapter described the interventionist account of causation, in which a causal relationship obtains between two variables when an idealised manipulation on the cause variable produces a change in the effect variable. This account is useful for the analysis of heritability because it considers causal relata as

variables, and the manipulation of a cause to bring about an effect reflects common usage of causation in the sciences.

The causal relationship concerned in heritability is the causes of variance or differences in a phenotype (V_P). The cause relata considered are variables, namely, variance in genetics (V_G), and environment (V_E). When conceptualised in heritability models, these variables can take on different numerical values between 0 and 1. When represented in a norm of reaction, these variables illustrate the particular genotypes and environments that have been studied in a given experiment.

The norm of reaction is a useful tool for heritability claims as it provides information about the stability and invariance of the causal relationships involved. These dimensions of causation have been used within the nature-nurture debate to grant causal privilege to genes or DNA, but have not yet been applied to heritability claims. I have shown how these relate to heritability, and how they helped to elucidate the explanatory depth of the causal relationships involved. As the causal claims are not particularly explanatorily deep, heritability claims should be regarded as concerning type-causation, although the types that it applies to are extremely limited, as they are confined to the population studied.

The purpose of this chapter has been to provide a causal framework in which to assess G-E covariance in regards to heritability. These tools shall be used to provide a systematic framework to account for the discord of interpretations for G-E covariance cases. The criteria for causes, indirect causes, and common cause scenarios, outlined in section 3.2, shall be drawn upon in chapter 6. Invariance and stability are referenced in chapters 6 and 7 and chapters 6 and 8 both consider conceptual factors that contribute to causal attributions. Agency, blame and an appeal to norms become important in chapter 7, where I show that the difference between two types of G-E covariance cases rests on the presence of another agent, who is in most cases thought to be blameworthy.

Chapter 4 Gene-Environment Covariance

Gene-environment covariance, or correlation, occurs when different genotypes assort non-randomly among different environments: that is, when there is a relationship between the genotype of an individual and their environment. These cases are important because they challenge our intuitions concerning heritability and genetic causation.

Although covariance embodies a non-causal function, G-E covariance is typically presented causally. Jaffee and Price (2007) distinguish between causal and non-causal cases of G-E covariance. An example of non-causal G-E covariance is geographical association with variation at the haemoglobin locus. Two alleles, sickle cell (*HbS*) and normal (*HbA*) are inherited in a Mendelian fashion. *HbS* carriers (heterozygotes for both *HbS* and *HbA*) have a greater resistance to malaria, because the *HbS* allele confers resistance to the *Plasmodium* parasite which causes the disease. Populations where malaria is prevalent such as West Africa and parts of India have evolved to have a larger amount of *HbS* carriers in the population, compared to non-malarial areas (Piel et al. 2013). This has led to a large-scale correlation of environments and genotypes, where the *HbA* allele covaries with malarial environments.

Causal cases of G-E covariance are those of interest in this thesis. In these examples a covariance or correlation occurs because individuals with a certain genotype are predisposed to develop in a particular environment. This has been described as people having ‘genetic control’ over their developmental environment (Jaffe & Price 2007; Kendler & Eaves 1986). That is, possessing a particular genotype in some sense *causes* an

individual to live and develop in a certain environment. G-E covariance is a process therefore akin to nature ‘via’ nurture (Figure 4.1)⁵²

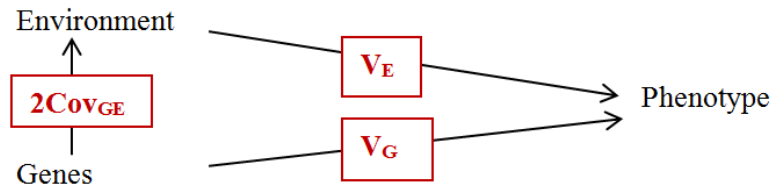


Figure 4.1 Nature –via –Nurture: Causal Interactions in G-E Covariance Cases
 2Cov_{GE} represents genetic variance being expressed via differences in environment, or nature ‘via’ nurture.

In chapters 2 and 3 I stated that when a large amount of trait variation is due to variance in genotypes, heritability is high, which is thought to correspond to some notion of genetic causation. This is one sense of the term ‘genetically caused’. Likewise, if variability in a trait is due for a large part to differences in environment, and heritability is low, then the trait is said to be determined by the environment, and thus would be considered as ‘environmentally caused’.

However, G-E covariance cases can present highly heritable traits in which the variance in the phenotype does not appear to be directly due to variance in genotypes. Therefore, despite a high heritability estimate, the story behind the sources of variance for a phenotype conflicts with the causal intuitions that usually accompany a high heritability estimate. The role of intuition and the attributed ‘common sense’ causality in this problem shall be discussed in section 4.3. But first, section 4.1 presents some examples of G-E

⁵² It has also been termed the ‘nature of nurture’ (Plomin et al. 2008, p.306).

covariance, and section 4.2 describes the responses to, and debate surrounding this problem.

4.1 Reactive, Active and Passive G-E covariance

Causal cases of G-E covariance are conventionally separated into active, reactive, and passive forms (Plomin, DeFries & Loehlin 1977). Active G-E covariance occurs when the carrier of a particular genotype is more likely to place *themselves* in a particular kind of environment than those with a different genotype – and this environment has a measurable difference on their phenotype. This can be contrasted with reactive G-E covariance, where the environment is altered or imposed upon the subjects by *others* as a result of their original genetic difference. Additionally, there is passive G-E covariance, whereby a genotype and environment are correlated because parents tend to pass on both their genes and a developmental environment to their offspring. Details of these different types of G-E covariances are outlined below.

4.1.1 Reactive G-E Covariance

Reactive G-E covariance occurs when an individual's developmental environment is altered by others as a result of the subject's initial genetic difference (Scarr & McCartney 1983). This is sometimes also referred to as evocative covariance. Extreme versions of reactive G-E covariance are illustrated in a macabre series of thought experiments about red-haired children. In these examples, a hypothetical society singles out children with red hair and subjects them to abuse based on their hair colour. The children are starved (Block & Dworkin 1976), beaten (Sesardic 2005), or in a comparatively kinder scenario, denied educational access (Jencks et al. 1972). As a result of the abuse other phenotypes are affected in the children, such as reading scores (Jencks et al. 1972), IQ (Sesardic 2005),

and height (Block & Dworkin 1976). To further illustrate, here is one of the (less extreme) examples from Jencks et al. (1972, pp.66-67).

If, for example, a nation refuses to send children with red hair to school, the genes that cause red hair can be said to lower reading scores... If an individual's genotype affects his environment, for whatever rational or irrational reason, and if this in turn affects his cognitive development, conventional methods of estimating heritability attribute the entire effect to genes and none to environment.

In reactive cases, genotypic differences which manifest themselves physiologically, such as in hair colour, result in the children being exposed to different kinds of environments. Thus there is a covariance of G and E, and in a population, of V_G and V_E . These differences in environment in turn impact on differences in other phenotypes, such as reading scores in the example above. Thus in a heritability analysis, variation in genotype, at least at the locus responsible for red-hair colour, results in variation in reading scores, through this environmental reaction. This means that the V_G influence for reading score differences (V_P) would be high, corresponding to a high heritability estimate.

These examples suggest that the differential treatment of any individual based on some expression of genetic difference; be it skin colour, hair colour, gender, size, or shape, can play a part in the apparent heritability of phenotypes. Gibbard (2001, p.169) presents a particularly gruesome example:

Imagine blue-eyed children are fed to lions, but some of them survive, maimed. If eye colour is inherited and this grim ritual is the predominant cause of anyone lacking a leg in that population, then non-two-leggedness in that population has substantial heritability.

As far-fetched as these examples might sound, they provide an illuminating analogy to the influence that a reactive society may have on heritability estimates when the covariance concerns racial or gender-based differences. By reacting to people of a given race, and then

comparing racial groups based on ‘genetic differences’⁵³, the appearance of phenotypic traits arising from this reaction would appear as highly heritable. This is one of the central criticisms of assertions by such authors as Arthur Jensen (1969), Richard Herrnstein (1973) and Herrnstein and Murray (1994) that genetic variance is a cause of racial differences in IQ, made by Block (1995), Block and Dworkin (1976), Jencks (1980), and Sober (2001). When discrimination is triggered by an initial genetic difference⁵⁴, then under a heritability estimate the consequences of this discrimination appear to be caused by genetic differences. Sober (2000; 2001) has pointed out that these kinds of G-E covariance cases may account for some of the apparent heritable differences between people of different races.

If blacks are treated badly because of their skin color, and their skin color is genetic, then the lower IQ will be assigned to genes, not to environment. (Sober 2001, p.74)

The outcomes of sexual discrimination could be interpreted in the same highly heritable way. Gender is (commonly) determined genetically – by the presence of either two X (female) or X and Y (male) chromosomes. This genetic difference causes differences in physical appearance and identity, which in turn can cause differences in the way that the individuals are treated, including the amount they get paid or the kinds of opportunities they receive.

For instance, using a traditional heritability estimate hair length would appear to be heritable in many cultures, if the genotypic variance measured related to, or included the sex chromosomes. The same goes for being paid less, time spent doing house work, and the ability to drive in Saudi Arabia. All of these phenotypes are highly heritable in a statistical sense, as the variation in phenotype is explained in some sense by variation in

⁵³ Lewontin (1972) has pointed out that the majority (85.4%) of genetic diversity in humans can be found within racial groups, rather than between them. Thus there is good reason to view race as social construct, rather than a biological one that corresponds to distinct genotypic groups representative of V_G . For a response to this argument see Sesardic (2010), and for a response to Sesardic see Hochman (2014).

⁵⁴ See footnote 53.

genotype. The phenotypic variation in these examples would all intuitively be considered as socialized environmental responses, and not due to genetic differences, however, under a heritability estimate the opposite is true. As there seems to be something wrong about labelling ‘time spent doing housework’ or ‘exposure to sexual assault’ as being determined by genetic differences, the covariance of genes and environment in the reactive case is problematic for behaviour genetics.

In chapter 2 I used an example where a population of individuals of three different genotypes were raised over four environments in a fully factorial design. When measured on IQ tests, G1 children outperformed G2 children, and G3 children performed the most poorly, independent of the environment in which they were raised. In this example a high heritability was given ($H^2 = 0.9948$). This indicated that a large amount of variation in phenotype could be accounted for by genotypic differences, whereas variation in the environment produced hardly any effect. This example was given as a straight-forward (and purely hypothetical) case of high heritability, where V_G accounted for most of V_P .

Here is one possible developmental story as to why G1 children performed better on the IQ test: The G1 children inherited genes that made their brains develop in a certain way. This meant that their cognitive abilities were better adapted to answer the questions presented in the IQ test than those of G2 or G3 genotypes. This would be the ‘genetically determined’ interpretation of such results – a large amount of variation in phenotype is explained purely in terms of the genotype: G1 ‘just does’ endow children with superior abilities to succeed in an IQ test. This is the scenario presented in Figure 4.2a). Under this developmental story, it would seem that attributing intelligence as highly heritable⁵⁵ is a reasonable conclusion,

⁵⁵ For the sake of this example I am assuming that IQ scores are reflective of human intelligence, although I recognise the problems surrounding the representation of intelligence by IQ. This problem can be avoided if instead of intelligence IQ scores are taken as the phenotype under investigation.

and would support the hereditarian standpoint. But as Block and Dworkin (1976, p. 483) put it:

Heritability has the virtues of its vices. We can calculate the heritability of a characteristic without knowing anything about the causal mechanisms involved in the development of the characteristic.

Given reactive G-E covariance, this result could also be explained by the G3 children having genes for red hair – thus being discriminated against and hindered in their education, resulting in the poorer scores. G1 children could have the alleles for brown hair, receiving no such prejudice and thus being able to access ample educational resources. Perhaps G2 children have genes for auburn hair (an intermediate of red and brown), receiving some intermediate abusive treatment between G1s and G2s. With this extra information about the causal story behind the experimental results, the high heritability estimate attained no longer looks as clearly ‘genetic’ as it did in chapter 2.

Behavioural geneticists strive to partition the relative contribution of genetic and environmental variation on phenotypic differences. If the story above was true for the data presented in chapter 2, then attributing 99.48% of V_P to V_G seems strange, if not unacceptable. This is because the V_G term appears to have been inflated by the covariance of genes and environment, represented as $2Cov_{GE}$ in heritability models. There are two ways in which G-E covariance can inflate heritability results by virtue of $2Cov_{GE}$.

The first is the situation described above, in which children of different genotypes are treated differently by society because of their different hair colours. In this case the reactive covariance of genes and environment (V_{E1}) fully accounts for all of the phenotypic variance attributed by the V_G term, while some other environmental variance (V_{E2}) makes a negligible contribution (Figure 4.2b).

The alternative situation is one in which the children still differ in hair colour, and society reacts to them based on these differences. But additionally, different genotype groups differ in their cognitive abilities. G1 individuals are on average more intelligent than those with a different genotype, due to some genetically based variation, which facilitates brain development. They also possess the genes for brown hair, which means that society allows for and even encourages their educational attainment. G2 individuals possess genotypes which lend themselves to average cognitive abilities, and additionally, they have the genes for auburn hair, meaning that they are not deprived of educational resources, but they are also not as encouraged as the brown haired children are. Lastly, G3 children have some mild form of mental retardation, due to genetic mutations. As a result of both neurophysiological differences (caused by V_G) and differences in encouragement and educational resources (V_{EI}), there are differences in IQ between the genotype groups.

Although far-fetched, there are a few ways that this correlation between cognitive abilities and hair colour could arise. The first is via pleiotropy, where one gene influences multiple unrelated phenotypes, so that the same alleles for brown hair also enhance cognitive development. The second is epistatic mechanisms, where the expression of some genes are modified by others – so that the hair colour alleles interacted with the expression of genes needed for cognitive development. Finally it could arise if genes at the hair colour locus were linked (located close together on a chromosome, so have a higher probability of being inherited together) to genes for cognitive development. These kinds of genetic associations are unlikely to occur in phenotypes as complex as intelligence, but lie within the realms of possibility required for this thought experiment.

In this example when the phenotypic correlation is present, phenotypic variance for IQ is accounted for by both genetic variance alone (V_G) and a covariance of genes and environment ($2Cov_{GE}$) from a reactive society (Figure 4.2c).

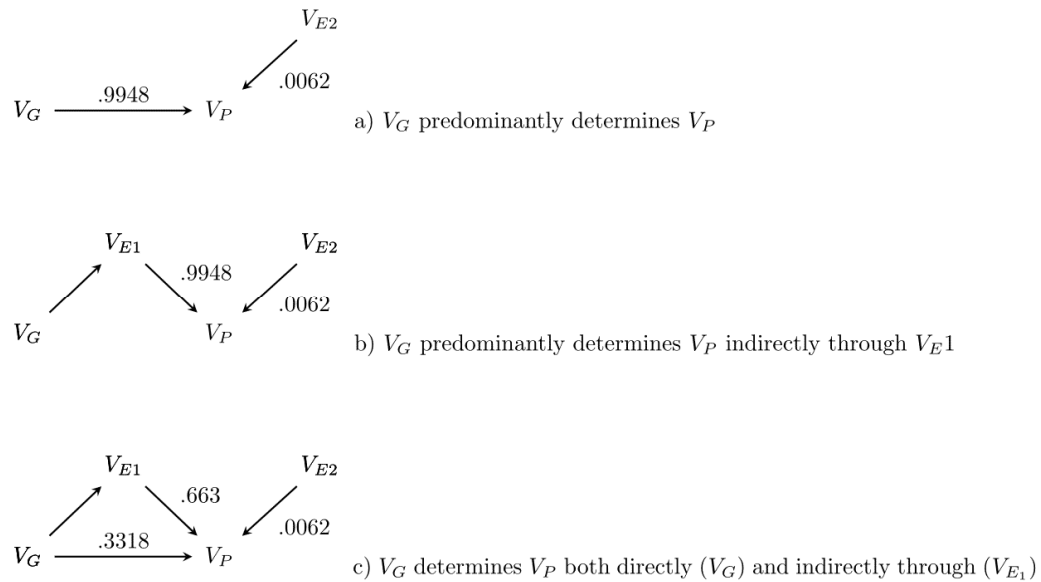


Figure 4.2 Causal Structures for Active and Passive G-E Covariance Cases. V_G represents genetic variance, V_{E1} represents an environmental variable that covaries with genetic variance, and V_{E2} represents some other independent environmental variance.

4.1.2 Active G-E Covariance

Active G-E covariance occurs when an alteration of the environment is due to the motivation of the individual possessing the genotype. In these examples individuals modify their own environment, and differences in environmental modification are caused by differences in genotype. Like with the reactive cases, genetic covariance with the environment can lead to high heritability estimates despite the causal work done by the mediating environmental variance.

In keeping with the example used above, we could consider now a causal story inclusive of active G-E covariance that explains the results given in chapter 2. An alternative active G-E covariance account is that at a young age children with genotype G1 had a negligible genetic advantage compared to G2 and G3 children in terms of intelligence. Because of

this small advantage G1 children modified their environment in a way to intellectually stimulate themselves, by seeking out books, taking extra classes, and working on problems. Consequently, by the time they reached 10 years of age and were given an IQ test they had reached a stage of measurable intellectual advantage, which allowed them to better answer the questions on the test (example adapted from Jensen 1972). Thus ‘small genetic differences may therefore end up producing big environmental differences’ (Jencks 1972, p. 110), which lead to large scale phenotypic differences.

This is an example of G-E covariance, as variation in genetics is correlated (or covarys) with variation in the environment. This situation fits the same picture as that shown in Figure 4.2, where the phenotypic effects of genetic variance are either completely (4.2b) or partially (4.2c) mediated by differences in the environment. In this case the G1 genotype is correlated with a more stimulating environment. This means that when phenotypic variance (in this case IQ) is accounted for, one will see a relationship with genetic variation. However, because this genetic variation appears to have in some sense caused these differences in environment, resulting phenotypic variation will be counted as genetic in the heritability estimate. This result has led some (Block 1995; Gibbard 2001; Jencks 1980; Sober 2001) to believe that heritability estimates are of no use for partitioning environmental and genetic causes:

Until we know how genes affect specific forms of behaviour, heritability estimates will tell us almost nothing of importance. (Jencks 1980, p .723)

Here is another example of how these results may have occurred. Imagine now that the G1 children not only have better genes for cognitive development, they possess genes which engender a love for the musty smell of books. Based on this, they are compelled to seek out and surround themselves with books. Already these children are developing in a different, more book filled environment, than the others. Because of this, these children

spend a larger amount of time reading and learning, which aids them in the skills needed to perform in intelligence tests. As a result these children are measured as being more intelligent than those with a different genotype, resulting in an H^2 of 1. In this case the V_P that is accounted for by V_G in the heritability estimate appears to be a mixture of genetic (V_G) and environmentally mediated ($2Cov_{GE}$) influences, corresponding to Figure 4.2c). The same story could be told where the only difference between genotypes was the children's book smelling preference (Figure 4.2b). In either of these last two cases the genetic basis of a phenotype is either accentuated (4.2c) or driven (4.2b) by environmental effects, and the causal effects of V_G and V_E appear conflated.

In these examples, like the reactive ones, the resulting heritability estimates are inflated by a covariance between V_G and V_E . However, it is possible for G-E covariance to have the opposite effect where V_G is deflated instead. For example imagine a case in which G1 children that are more intelligent for some 'genetically determined' physiological reason decide not to try as hard at school, as they can get away with studying less than other children and achieving the same result. Other children who do not find the work so easy try especially hard and seek out extra stimulation and study materials. When both groups are tested for IQ, the variation between them is small. As such, less of the overall V_P can be accounted for by V_G , because of a covariance between genes and environment.

In the reactive case something similar could occur, where parental or teacher encouragement is bestowed upon children who are initially struggling, evening out the differences between genotype groups (Plomin et al. 2008, p. 319). Thus G-E covariance should be generally thought of as having the potential to bias heritability estimates, and not necessarily inflating or deflating them.

4.1.3 Passive G-E Covariance

There third type is passive G-E covariance. Individuals who are raised by their biological parents not only inherit genes, but also part of their environment from them. For example, parents with high IQ's tend to pass on not only a genetic endowment to their children, but they shape their child's environment to allow better development of phenotypes, such as intelligence. Thus a child's phenotype is the result of both their own genotype and the environment that they inherited from their parents. Although it appears very different from the other two cases, this is also a form of G-E covariance as the child's genotype is correlated with a particular environment, due to the (at least in part) genetically determined phenotype of their parents in shaping that environment. The difference is that the shaping of the child's environment is in no way due to his or her own genotype, but is instead due to the actions of his or her parents. As Plomin, DeFries, and Loehlin, (1977, p. 310) note:

This conjunction exists prior to and independently of the particular phenotypic characteristics or activities of the child in question.

Block and Dworkin (1976, p. 480) refer to passive G-E covariance as either a 'double advantage' or a 'double disadvantage', where children inherit either higher genotypic intelligence and a better environment, or lower than average intelligence and a less stimulating environment. Under this picture it appears that passive covariance will always inflate heritability, as it magnifies the phenotypic effects between genotypic groups (thus inflating the impact of V_G on V_P). However, passive G-E covariance, like the other forms, can also deflate estimates. Scarr and McCartney (1983, p. 427) point to the following example:

Parents who are skilled readers, faced with a child who is not learning to read well, may provide a more enriched reading environment for that child than for another who acquires reading skills quickly.

Although presented as a passive case, this example is much more like the reactive case described in section 4.1.1, as it also includes a reaction from the parents to the child's phenotype (not learning to read well). So in this example, the child's phenotype is still causally involved with the covarying environment, meaning that it is more than just passive G-E covariance. A more appropriate example of a passive case where heritability is deflated would be if a family with a genetic predisposition to gain weight passes on those genes to their children, but also passes on an environment in which high calorie foods are restricted, as they are aware of their own propensity to weight gain. In this situation genes for a high body weight are negatively correlated with an environment for high body weight, leading to a deflation of the effects of V_G on V_P .

Although these examples typically refer to genetic correlations with post-natal environments, the pre-natal environment is also inherited from the mother, along with 50% of her (nuclear) DNA. As discussed in chapters 1 and 2, influences in the prenatal environment such as exposure to nutrition, hormones, and other cues have been shown to influence phenotypic variation for a range of traits.

4.1.4 Niche Construction

Parallels can be drawn between the different G-E covariance cases and types of niche construction. Ecological or selective niche construction is the process whereby organisms modify their niches, through their activities and choices. This can occur in the form of the building of nests, dams, and burrows, which are environments that are then passed on to offspring through a process of 'ecological inheritance' (Odling-Smee 1988; Odling-Smee, Laland & Feldman 1996; 2003). For example, leaf cutter ants have a symbiotic relationship with a fungus which breaks down leaves collected by the ants, and provides them with nutrients. In return the ants propagate and care for the fungus. The fungus garden niche and hence the mutualistic relationship between ant and fungus is transmitted to future

generations (Sterelny 2001). Odling-Smee (1988) notes that niche construction does not need to imply the modification of the environment. Instead, an organism could for instance chose to move to a particular new environment, instead modifying the environmental experience of that organism, and of its offspring.

Active G-E covariance also involves the modification of one's own environmental experience, either by actively constructing a certain niche or preferring to spend time in a selected niche. Reactive G-E covariance can occur when a subject is involved in somebody else's niche construction, and passive G-E covariance exemplifies the inheritance of a constructed niche from a family member. In humans complex niches are inherited within the family and from the greater social environment. These kinds of factors, which change the heritable features of the phenotype during development, have been termed developmental niche constructions, which refers to an extended inheritance comprising epigenetic, behavioural, ecological and social developmental resources (Griffiths & Stotz 2013; Stotz 2010; 2012).

Both selective and developmental construction have important evolutionary implications: with respect to the former, instead of organisms adapting to static, externally determined environments, they are thought to actively influence their environments, contributing to the selection pressures of current and subsequent generations. With respect to the latter, non-genetically inherited developmental resources, which comprise the developmental niche, create new phenotypic variation above and in interaction with genetic resources. Thus there exists a bi-directionality of causal influences between organism and environment in regards to evolutionary adaptations (Laland & Sterelny 2006), and a range of inheritance systems other than genetics, such as epigenetic, behavioural, ecological, socio-cultural, and symbolic inheritance (Avital & Jablonka 2000; Jablonka & Lamb 1995; 2005; Griffiths &

Stotz 2013; Odling-Smee, Laland & Feldman 2003; Oyama, Griffiths & Gray 2001; Stotz 2012).

4.2 Evidence and Estimation

The G-E covariance examples presented above have all come from within the philosophical literature, but some empirical work in the behavioural sciences has also demonstrated the importance of G-E covariance. While some quantitative geneticists (Falconer & McKay 1996) have dismissed G-E covariance as unproblematic for heritability analyses⁵⁶, some psychologists recognise the concern for the estimation and control of G-E covariance for heritability estimates.

4.2.1 Passive Cases

Passive G-E covariance is not extensively discussed as a criticism of heritability measures, for it can in principle be controlled for by methodological means, as acknowledged by critics of heritability analyses (Block 1995; Jencks 1980; Sesardic 2005; Sober 2001). One such method of control is to compare the correlations of environmental conditions and children's phenotypes in adoptive and non-adoptive families (Plomin, DeFries & Loehlin 1977; 1994; Plomin et al. 2008). The adoptive families demonstrate that if there is a correlation between a child's phenotype and its family environment, it could be attributed purely to environmental variance (V_E) as there is no shared genetic variance between parents and offspring. The same correlation in non-adoptive families should be accounted for by both V_E and any covarying V_G of the passive form. Thus a comparison of these two correlations would allow researchers to infer the passive $2Cov_{GE}$ term. This method has

⁵⁶ Although it is likely that they are referring to animal and not human studies in this dismissal. In the next chapter (5) I demonstrate how this assumption about animal research is incorrect.

uncovered a significant passive G-E covariance for behavioural problems, temperament, and mental and language development (Plomin, Loehlin & DeFries 1985)⁵⁷.

However, it must be noted that this method does not take into account the passive covariance with the maternal environment – which would still be inherited by adopted children, and so all children would experience a maternal environment that is correlated with their genotype (although there would be no correlation with their later developmental environment). As mentioned in section 1.2.2, the maternal environment can have a significant impact on phenotypic variation in both humans and animals. This has been demonstrated for physiological traits such as obesity and cardiovascular disease, and for a wide range of behaviours, e.g. in mice (Vickers et al. 2000; Vickers et al. 2003) as well as other organisms (Mousseau & Fox 1998; Maestripieri & Mateo 2009). Devlin, Daniels and Roeder (1997) suggest that maternal effects could account for a significant amount of variation in IQ, and Eichler et al. (2010) and Nadeau (2009) point to maternal effects to account for ‘missing heritability’.

Moffitt (2005) has speculated that passive G-E covariance (of the post-natal kind) impacts on child aggressiveness, through a correlation of genotypes which predispose to aggressive behaviours, and a ‘bad parenting’ environment. Similarly, Rutter, Moffitt and Caspi (2006) have suggested that these sorts of mechanisms could contribute to the heritability of psychiatric disorders. However, empirical work in this area is still limited. While it has been demonstrated that more aggressive children often become bad parents themselves (Caspi et al. 2001 as cited in Moffitt 2005), and there are associations between parental psychopathy and the environments that they provide (Rutter, Moffitt & Caspi 2006),

⁵⁷ In animals similar studies have been conducted in a manipulative fashion, where offspring are ‘cross-fostered’ to determine the relative impacts of genetics and environment. For example see Norris (1993).

studies have not yet been carried out that test the prevalence of passive G-E covariance directly for these phenotypes.

Another method of estimating passive G-E covariance is to look at twins (see chapter 2 for details on these methods). MZ twins reared together should inherit both their environment and genetics from their parents, and as such V_P can be attributed to environmental differences, including the inherited environment. MZ twins reared apart no longer inherit an environment from their parents, and as such the resulting V_E does not include any inherited environmental influences. Using this method passive G-E covariance has been detected as a cause for early age school performance differences (Hay 1985, chapter 6). However, there are limitations to this method, which were discussed in section 2.4.2.

Although some studies have been conducted to identify and estimate passive G-E covariance, they exist only for a limited set of phenotypes. Many heritability studies do not control for passive G-E covariance in such a way. This is because the method relies on a population consisting of twins or adoptive children, which is not representative of, or easy to obtain in a large amount of the population. Thus while passive G-E covariance can be controlled in principle it is not always controlled for in practise. Additionally, this ‘in principle’ control neglects the covariance of maternal effects. If the prenatal environment is thought to be subsumed under the V_E term⁵⁸, then some passive G-E covariance is likely to occur even in experiments which seek to identify and control for it.

4.2.2 Reactive and Active Cases

Active and reactive forms of G-E covariance cannot be separated experimentally. In chapter 6 I argue that they both conform to the same causal structure, which can account

⁵⁸ It is a consequence of the way that the terms ‘gene’ and ‘environment’ are used within behavioural genetics that V_E includes these first 9 months. The methods used in behavioural genetics, where inferences are made based on the percentage of genetic relatedness, also infer that this period is part of V_E .

for why they are empirically inseparable. There is good evidence that children actively shape their environment (Ambert 1997), and others have shown that some self-mediated environmental alterations are based on genetic differences. For example, Plomin and Bergmann (1991) found significant effects of V_G on 'family environment' variables such as socioeconomic status, television viewing, quality of social support, and family 'warmth', and Plomin et al. (1994) demonstrated that parent-child interactions and parental tactics for dealing with conflict were also heritable. Plomin, Owen & McGuffin (1994) found an average heritability of 0.27 for these kinds of family environment measures. Differences in stressful life events as well as socioeconomic, educational, and occupational status have all been shown to be somewhat genetically mediated (Plomin et al. 2008; Rutter & Silberg 2002).

Rutter, Moffitt and Caspi (2006) and Rutter and Silberg (2002) have proposed that active and reactive covariance (along with the passive forms) contribute significantly to the heritability of psychiatric disorders. For instance, aggressively prone offspring are likely to promote harsher treatment from others, compounding their development along a psychiatric trajectory. This work has been extended by Jaffee and Price (2007) who have identified particular allelic variations and their associations with environments, such as parental rejection. These associations are then predictive of later psychiatric illness, indicating that genetic variation may account for active, reactive and/or passive forms of covariance with parental engagement.

Meek et al. (2013) have suggested that heritability estimates for autism may also be largely accounted for by active and reactive G-E covariances. Children who begin as mildly autistic are likely to select environments lacking in social stimuli (active), and others around them can react to them in a way which compounds both their autistic phenotype

(reactive), and their subsequent environmental selection (further compounding the active covariance pathway).

Active and reactive forms of G-E covariance are even more difficult to estimate directly than passive forms, and as such, are likely to go undetected to an even greater degree.

Plomin, DeFries and Loehlin (1977, p.321), in a seminal paper on G-E covariance, have written:

Because it is not possible to measure all aspects of the environment (including everybody and everything) that might correlate with childrens' genotypes, it will probably never be possible to assess completely the effects of active and reactive genotype-environment correlations.

Block and Dworkin (1976, p.482) are even more pessimistic about the potential for reactive and active estimation:

...no one knows *how* to separate the variance due to indirect genetic effects from the variance due to direct genetic effects, at least within the constraints on human experimentation. Such a separation would involve investigation of the details of the mechanism by which genes affect psychological characteristics, a task which is well beyond present knowledge.

Block (1995, p.118), Feldman and Lewontin (1975), Jencks (1992), and Layzer (1974; 1976) have come to similar conclusions, stating that reactive and active G-E covariance are empirically inseparable. This claim has partially shaped the way in which these cases are interpreted, as discussed below.

4.3 Interpretations and Intuitions

If we imagine that G-E covariance situations could be identified, the question is how then to treat them? Is the variation in these cases legitimately due to genetic variance, simply expressed or in some mediated way through the environment? Or is it constitutive of environmentally caused variance? Or should we instead consider covariance as a separate source of variation from either genetic or environmental sources of variance?

Recall from chapter 2 that in order to arrive at a heritability estimate, measures of phenotypic variance are partitioned into genetic and environmental components. The two components are then assumed to combine additively to arrive at V_P (equation 1), with the addition of $V_{G \times E}$ if there are interactive effects (equation 7).

These models give us two of the above three options. The V_P resulting from G-E covariance is attributable to either variation in genetics (V_G) or variation in the environment (V_E).

The third option is to consider G-E covariance as a separate source of variation. This augments models 1 and 7:

$$V_P = V_G + V_E + 2\text{Cov}_{GE} \quad (8)$$

Or when $V_{G \times E}$ is present:

$$V_P = V_G + V_E + V_{G \times E} + 2\text{Cov}_{GE} \quad (9)$$

But these new heritability models do not solve the problems of interpretation for G-E covariance. Scholars have interpreted different types of G-E covariance in different ways, and there is still disagreement as to what is the best interpretation.

4.3.1 Passive Cases

The interpretation of passive G-E covariance is uncontroversial. The general consensus is that any variation that is accounted for by an inherited environment should be subsumed under V_E (Block 1995; Roberts 1967; Sesardic 2005; Sober 2001). Clearly, the effects of the parental phenotype should not be encompassed in the child's V_G . However, when unidentified, these can inflate V_G estimates. Instead, the influences on behaviour that stem from an individual's parents are generally considered in sum as an environmental source of

variation, which is in line with the gene concept used in behavioural and quantitative genetics (chapter 1). This also concords with the assumptions used in behavioural genetic methods, such as inferring the degree of genetic similarity (which is used to compute the V_G estimate) by biological relatedness. However, as demonstrated in section 4.2.1, passive G-E covariance is sometimes partitioned as an additional variable to V_E ($2Cov_{GE}$), to allow researchers to separate out the influences of the greater environment versus the inherited family environment. The issue in these cases is a pragmatic one, namely of how to distinguish these types of causes from genuine genetic ones, and of partitioning the different environmental sources that are of interest.

4.3.2 Reactive Cases

As noted by Sesardic (2005), much of the controversy surrounding G-E covariance regard examples of reactive G-E covariance, as is seen in the red-haired children example (section 4.1.1). It seems evident that the creators of these more extreme examples believe that the resulting variance should not be subsumed under V_G . Some of these authors have accused Roberts (1967) of defending the subsumption of reactive cases under genetic variation, due mostly to this quote:

...it matters not one whit whether the effects of the genes are mediated through the external environment or directly, through, say, the ribosomes. (Roberts 1967, p. 218)

However, Sesardic (2003; 2005) points out that this allegation is misconceived, and Roberts in the above statement is referring to active G-E covariance cases. In fact there have been no philosophers or biologists who defend the claim that reactive G-E covariance should be considered a component of V_G (Sesardic 2005). Instead disagreement for reactive cases is more subtle. Fuller (1979, p. 427) is explicit in claiming that the resulting variation in these cases should be considered as part of V_E , for example:

In our human societies discriminatory practices are often based upon superficial physical characteristics or upon cultural stereotypes. In these instances a G-E correlation will result if, and only if, the criterion for discrimination is heritable in the genetic sense... Any correlation between it and behaviour is logically attributable to environmental influences.

But most others believe that these examples identify a source of variation that is attributable to neither V_E nor V_G , and instead should be encompassed under the $2Cov_{GE}$ term (Block 1995; Eaves et al. 1977; Jencks 1980; Jensen 1969; Jinks & Fulker 1970; Loehlin & DeFries 1987; Loehlin & DeFries 1981; Loehlin, Spuhler & Lindzey 1975; Plomin 1987). Many though, do not specify how this source of variation should be treated, only that it should not be considered as genetic variance (Block & Dworkin 1976; Feldman & Lewontin 1975; Gibbard 2001; Sober 2000; 2001).

While everyone seems to agree that the resulting phenotypic variation in reactive G-E covariance cases should not be ascribed to V_G , and most that a separate $2Cov_{GE}$ term should be used, very little is said about why this conclusion has been reached. Evidence does not seem to go beyond appeals to common sense and intuition. For example:

Attributing redheads' illiteracy to their genes would probably strike most readers as absurd under these circumstances. (Jencks et al. 1972, pp. 66-67)

Sesardic (2003; 2005) has been careful to point out many of these appeals to common sense and intuition, but instead of questioning their validity as a basis for heritability analyses, he endeavours to support their claims that heritability estimates cohere with common sense causal attributions. For example, after discussing a reactive G-E covariance case in which the different genders are paid less due to sexual discrimination, he writes:

I will try to show that far from being so semantically perverse, the term "heritability", when properly understood, actually accords quite well with our common-sense etiological ascriptions. (2003, p.1004)

Sesardic successfully argues that behavioural geneticists generally attribute reactive G-E covariance cases to non-genetic factors, cohering with genetic effects ‘in our usual sense of the word’ (Sesardic 2003, p.1004) that are ‘not really anomalous or aberrant’ (Sesardic 2005, p.104). They appear to do this by using their best common-sense causal intuitions, however, he does concede:

This is all admittedly pretty vague, and I am not sure how intuitions underlying our different approaches to these two kinds of cases [active versus reactive] should be refined further and made more precise. Fortunately this doesn’t really matter, for I only want to claim that in dealing with G-E correlations, behaviour geneticists are by and large guided by the common-sense considerations about causality, with all their characteristic vagueness and ambiguities. (2003, pp. 1012-1013)

My contention in this thesis is it *does* matter, and chapters 6 through 8 are devoted to getting at the bottom of the common-sense ascriptions of causality that are currently being used to assess G-E covariance cases. Thus, I attempt to fill a gap in Sesardic’s assessment, concerning how an approach to G-E covariance should be ‘made more precise’. Before embarking on this, it is necessary to consider the less publicised, but much more contentious active form of G-E covariance, where intuitions about ‘common sense ascriptions’ of causation appear to be divided.

4.3.3 Active Cases

Agreement largely exists for the interpretation of reactive cases; that is, that the resulting phenotypic difference should be attributed to $2Cov_{GE}$, rather than being subsumed under V_G . However, there is great controversy over how to interpret active cases. Some feel that the resulting phenotypic variance from active G-E covariance should be treated as genetically caused (Eaves et al. 1977; Jencks 1980; Jensen 1969; Jinks & Fulker 1970; Roberts 1967; Rowe 1994; 1997). They argue that genetic differences in environmentally modifying behaviours can be thought of as part of the differences in the phenotype that one

is measuring. That is, they feel that these cases are simply a reflection of the expression of genetic variation, that the environmental causes are a natural extension or expression of the phenotype under study, which ‘...present(s) no more of a dilemma than the observation that fast growing genotypes eat more.’ (Eaves et al. 1977, p.9). This is supported by the idea that some environmental modification appears to be an inherent part of human development (Lerner 1995), meaning that environmental modifications in an active G-E covariant form are ‘a more or less inevitable result of genotype’ (Jinks & Fulker 1970, p. 323). As Jinks and Fulker (1970, p. 323) put it: ‘To what extent could we ever get a dull person to select for himself an intellectually stimulating environment to the same extent as a bright person might?’

Others (Block 1995; Block & Dworkin 1976; Feldman & Lewontin 1975; Gibbard 2001; Layzer 1974; 1976; Loehlin & DeFries 1987; Loehlin, Lindzey & Spuhler 1975; Plomin 1987; Plomin, DeFries & Loehlin 1977; Sober 2001) think that any resulting variation from active G-E covariance should be treated as deriving from a separate source of variation ($2Cov_{GE}$).

As with the reactive cases, Sesardic (2003; 2005) and Emigh (1977) believe that the partitioning of variance must be interpreted commonsensically. This time, however, Sesardic believes that what is commonsensical will differ depending on the nature of the particular active G-E covariance case. Thus:

...active G-E covariance is occasionally subsumed under genetic variance, and passive covariance is assigned to the environmental side of the equation. However, it is important to stress that this redistribution is not a necessary consequence of some esoteric methodology for calculating heritability. Rather, it is a practical decision primarily guided by an attempt to follow the commonsense way of apportioning causal responsibility. If there happens to be any doubt about how to classify G-E correlation, the regular fallback position is just to treat it as a distinct component of variance, separate from heritability and environmentality. (2005, p.104)

This thesis aims to uncover a more principled way to determine how to interpret active G-E covariance cases, by looking at what factors drive the common-sense causal ascriptions that seem to be motivating this debate. This will be the subject of chapters 6, 7 and 8.

4.4 Summary and Conclusion: What to do with Cases of G-E Covariance?

While there is a general consensus about how to interpret reactive and passive G-E covariance cases, active cases are a source of disagreement among scholars. In terms of empirical estimation, passive G-E covariance is in principle estimable, while active and reactive forms are not. These issues can be summarized in Table 4.1 below. Here you can see that while both reactive and active G-E covariance pose problem for methodology such as the control of variables, of the three types of G-E covariance, it is only the active case which poses real controversy in terms of interpretation and the appropriate variables to use in a heritability model to partition phenotypic variance.

Type of G-E Covariance	Appropriate model	Methodological Considerations
Passive	Consensus	Partially Controllable
Reactive	Consensus	Difficult to control
Active	Uncertain	Difficult to control

Table 4.1 The Current State of G-E Covariance Considerations

As noted in the previous section, one of the aims of this thesis is to go beyond the common sense solution and offer some principled way of interpreting G-E covariance cases. What is it that makes scholars agree upon the interpretation of reactive and passive cases, but not

active ones? Chapters 6 and 7 turn to the causation literature for answers, by examining the differences in causal structure and background conditions between cases. These chapters attempt to determine the differences between active, passive and reactive cases in a causal sense. While passive cases are easy to causally distinguish from the other two, I show that a particular description of background variables and/or an appeal to agency is needed in order to make principled distinction between reactive and active cases. Chapter 8 focuses on the differences in interpretation for active cases, and demonstrates that the phenotype under consideration plays a part in the resulting differences in causal intuitions. This can help to account for the division in opinions for active cases, as the field in which this problem is situated concerns phenotypes with ambiguous and hotly debated reference classes.

But before turning to these interpretations, it is useful to take a quick detour into the field of animal research. Some effort has gone into the estimation of G-E covariance, although the results have been limited to the passive form. In quantitative genetic animal research G-E covariance is not thought to offer a widespread problem for heritability analysis. The next chapter argues that there is good evidence for G-E covariance in animal research, which is currently being overlooked. As animal research offers empirical opportunities that human research cannot (e.g., developmental manipulation), the ability to estimate covariances in animal populations may help to fill the gap in human research for the estimation of active and reactive G-E covariance cases.

Chapter 5 Gene-Environment Covariance in

Animal Populations

When characterising G-E covariance, the previous chapter (4) used examples concerning human subjects which either inherited, actively modified, or evoked from others, an environment which correlated with their genotype. These scenarios are thought to lead to either inflated or deflated heritability estimates in behavioural genetic studies, which have been claimed by some to contribute to the hereditarian assertion that there are genetic causes of phenotypic dissimilarity between races, particularly in the intelligence debate.

To address this, a few studies in psychology and psychiatry have attempted to estimate or infer G-E covariance, although estimation has only been possible for the passive form and excludes the prenatal environment (Hay 1985; Jaffee & Price 2007; Jinks & Fulker 1970; Plomin & Bergmann 1991; Plomin et al. 2008; Plomin, Lohelin & DeFries 1977; Plomin Owen & McGuffin 1994). Generally though, the empirical foundation for G-E covariance is limited in human heritability studies, and is not accounted for in most research designs.

While the majority of this thesis focuses on human behavioural genetics, this chapter highlights the application of the G-E covariance discussion to animal studies. Generally, G-E covariance is thought not to occur in quantitative genetic animal studies (Plomin 2013), and as such is not paid attention to or taken account of in their heritability models. For instance Falconer and MacKay (1996, pp. 131-132), in their highly cited textbook, refer to G-E covariance as ‘seldom an important complication, and can usually be neglected in experimental populations’. To really emphasise the neglect of G-E covariance in animal populations, one need only to look at the comments from Robert Plomin, the leader in the field of G-E covariance estimation in human populations, who has argued that

the phenomenon is unlikely to occur, and in principle inestimable in animal studies (Plomin 2008; 2013).

I will show that it is not only possible, but likely that G-E covariance occurs in animal research, particularly in studies where there is an enriched and social environment. I show, using evidence from recent empirical work in mice, that large amounts of resulting V_P may occur even when initial variations in genetics (or other covarying factors such as epigenetics and early environmental experience) are quite small. Although this highlights a major problem for animal studies, it also comes with a benefit. Active and reactive forms of G-E covariance are inestimable in human populations, as we are not able to manipulate or control an individual's developmental environment (section 4.2.2). However, in animal studies it is possible to impose these kinds of controls. This chapter suggests alternative methods of estimating G-E covariance using animal populations, which may help to shed light on the magnitude and scope of the problem in human research.

I shall begin by distinguishing two uses of heritability estimates, which map roughly to their uses in animal versus human studies (5.1). I then look at the different methods used in quantitative genetic studies between human and animal populations (5.2). Sections 5.3 and 5.4 go on to show, using an empirical example in mice, how active and reactive G-E covariance can occur in controlled experimental animal studies, leading to an elevated V_P . Section 5.4.1 will forecast ways in which G-E covariance could be estimated in animal populations, as a contrast to section 4.2, which outlined the limited ways in which G-E covariance is estimated in human populations.

I conclude that since G-E covariance is not limited to research in human behavioural genetics, but is also present in animal studies, animal researchers in quantitative genetics should be made aware of this limitation. While active and reactive G-E covariances pose a problem for research designs in animal quantitative genetics, the advantage is that they

may be estimated more easily in animal populations. While each estimate would remain phenotype- and species-specific, large amounts of empirical estimates in animals may enable a broader understanding of the impacts of G-E covariance generally, including in human behavioural genetics.

5.1 The Uses of Heritability Estimates

Before delving into when and how G-E covariance can impact animal heritability studies, it is useful to have an understanding of what heritability studies are *for*. Why do scientists bother making these measures in the first place?

In chapter 2 I described two different types of heritability estimates: broad (H^2) and narrow (h^2) heritability. These two types of heritability represent slightly different measures, and as such, have different uses within genetic research.

5.1.1 The Utility of Broad-Sense Heritability

Broad-heritability (H^2) is the type of estimate most often used in the social sciences, focussing on human populations. It is particularly utilised to study the genetic basis of human behavioural or personality traits, the field of behavioural and psychiatric genetics.

Broad heritability concerns the proportion of phenotypic variance (V_P) that can be accounted for by total genetic variance (V_G), and includes epistatic and dominance effects (see equation 4)⁵⁹. As described in chapter 2, broad sense heritability is estimated in human behavioural genetics because the total genetic contribution to these traits is of interest (Ofstedal 2005).

⁵⁹ It also includes maternal effects, which are not recognised in the equation, but potentially confound heritability estimates. These are discussed further in section 5.3.1.

Some have opposed the notion that broad heritability estimates reflect information about causal strength or importance because of the existence of gene-environment interaction (chapters 2 and 3) and covariance (chapter 4). Opponents include (but are not limited to): Burian (1981; 1982, both cited in Sesardic 1993); Crusio (1990); Feldman and Lewontin (1975); Gottlieb (1995; 2003); Hirsch (1976, as cited in Sesardic 1993); Kempthorne (1997); Kitcher (1990); Lewontin (1974; 1983); Sarkar (1998); Wahlsten (1990) and Wahlsten, Douglas and Gottlieb (1997).

However, others defend the notion of H^2 as explanatorily useful. They believe that the measure gives an explanation of the causes of variation in a particular trait (Griffiths, A et al. 2005; Jensen 1972; Pearson 2007; Sesardic 1993). The utility of broad heritability has been defended from a purely explanatory standpoint. By knowing the broad heritability of a trait, we get some information about the causal strength of genetic influences on V_P (Cheverud 1990; Crow 1990). For example Freeman (1973, p.202) writes: 'Thus, heritability in the broad sense may be thought of as an index of the relative importance of gene differences as a cause of individual differences in a population...'. Roff (1997) has suggested that broad heritability is a useful measure of setting an upper limit of h^2 (explained below), when h^2 cannot be in practise estimated.

Additional to the pure explanatory utility of heritability estimates, broad-sense estimates can be used as a tool to investigate the causes of phenotypic variation in detail (McGuffin & Katz 1990). For example, they may be used as justification for the search for genetic markers which are the first step of genetic mapping, and can lead to the cloning of genes which are responsible for less complex traits (Bazzett 2008; Pearson 2007; Tenesa & Haley 2013).

Broad heritability estimates can also be used to estimate and predict the phenotypes of families and offspring, including complex diseases and behaviours (Griffiths, A et al. 2005;

Lynch & Walsh 1998; Tenesa & Haley 2013). This information can be utilised for preventative procedures and genetic counselling strategies, as well as to provide extra intervention and support for those who may be genetically susceptible to undesirable phenotypic variants (Mann 1994).

Preventative procedures represent one other important aspect of heritability estimates. Crow (1990) emphasized the importance of broad heritability as it enables one to judge the efficacy of potential environmental interventions. If a phenotype is highly heritable within a certain range of environments, then manipulation of those environments (whilst staying within the range)⁶⁰ is not likely to have much of an impact on phenotypic variance. If, however, the heritability of a trait is low, then manipulations of the environments under study are likely to produce changes in the phenotypic differences observed. Thus broad-sense heritability can be used to identify difference makers, which may or may not be amenable to interventions to V_P .

The heritability of a trait has also been invoked to discuss broader philosophical issues such as free will and moral responsibility. For instance Kaebnick (2006) raises the question: If no environmental interventions (that have yet been studied) seem able to alter the V_P of a trait, how responsible are individuals possessing a certain variant? Kaebnick (2006) believes that heritability analyses help to inform, or at least introduce, some of these broader philosophical questions and should be considered by ethicists. Others such as Parens, Chapman and Press (2006) have similarly theorised that knowledge about the heritability of a trait is can impact on individual feelings of blame, responsibility, and human identity.⁶¹

⁶⁰ For more detail see section 3.5, on reaction ranges and norms, or Griffiths and Tabery (2008).

⁶¹ However these researchers need to be careful they are not conflating the causal claims made by heritability about variation in a population to phenotypic causes in individuals. These issues were discussed in chapters 2 and 3.

All of these interpretations and uses of broad-sense heritability of course rely on the fact that the estimate is (at least to some extent) methodologically accurate⁶², and G-E covariance is one phenomenon which may undermine this assumption.

5.1.2 The Utility of Narrow-Sense Heritability

Another use for heritability analyses not listed above is that they can be used to predict evolutionary adaptation. For a population to adapt to environmental change it must possess variation in relevant traits which have some heritable basis. This follows from the basic tenets of evolution by natural selection (Darwin 1859). Therefore, in order to forecast how much a trait can evolve in a given number of generations (its adaptive potential), an estimate of heritability is needed. Firstly, there must be variation in the trait of interest (V_P). Secondly, the traits must have some heritable basis (V_G). And lastly, individuals that are better suited to their environment due to some trait variation will produce more offspring than those that do not carry the same variation. This encompasses a selection pressure an organism may experience, which is represented by the selection differential (S).

Because of dominance and epistasis, the phenotypic effects of particular genotypes does not follow an invariant inheritance pattern, and the estimation of H^2 includes the effects of some alleles and other modifying genes dominating over and interacting with others. This means that the phenotypic outcome of subsequent generations cannot be accurately predicted, as it is unknown how much of V_G is due to dominance and epistasis⁶³. In order to predict the phenotypic consequences of future generations, additive genetic variance

⁶² Because of the methodological limits associated with broad-sense heritability estimation, some (for example Crusio 1990; Hirsch 1990; Kempthorne 1997; Sarkar 1998; Wahlsten 1990) believe that narrow heritability measures (h^2) are the only heritability measures which are of any use, as they can be used to decide which environments should be controlled, and to predict future outcomes for a population (see section 5.2).

⁶³ Maternal effects are also potentially included in the broad heritability V_G term.

(V_A) alone needs to be estimated. The proportion of phenotypic variance accounted for by V_A is represented by narrow heritability, h^2 (equation 5). The forecasting of adaptive potential is confined to this type of heritability. This is because additive genetic variance responds to natural and artificial selection, and thus can be used in evolutionary prediction.

The heritability of a trait determines its ‘ability’ to respond to selection (S), according to the aptly named breeder’s equation, which serves as a predictor of evolutionary change (Lush 1937):

$$R = h^2 \times S \quad (10)$$

Where R = response to selection, S = selection differential (difference between selected mean and population mean) and h^2 = narrow-sense heritability. The response to selection gives an indication of how much a trait will increase or decrease along a quantitative continuum in the next generation, given selection in a particular direction. The direction of selection is encompassed in the selection differential (S), which represents the mean difference between the population and that subpopulation comprising the selected parents of the next generation.

This is best illustrated by way of an example. If one wanted to breed animals to run faster or grow taller they would start with a pool of animals, and then select a subset of the fastest or tallest to breed for the next generation. The desired result is dependent on the fact that the selected animals were at least partially faster or taller because of their genetic endowments, and that the responsible genes would be passed on to subsequent generations, making them faster or taller still.

For example, imagine a rabbit owner who has taken an interest in kaninhoppning (Figure 5.1), and wants to breed his rabbits to jump higher in order to compete. He currently has a

large population of adult rabbits (F0), and has a single generation to create a population of rabbits (F1) that can jump higher than his F0s.



Figure 5.1 Kaninhoppning (Image from Swedish Federation of Rabbit Jumping, <http://skhrf.com/englishsit>, Retrieved April 2014)

Our competitor is also taking bets as to how high he can get his F1 rabbits to jump.

Therefore it is in his interest to be able to predict the mean jumping height of his F1 rabbits – the ones that will compete in the kaninhoppning competition.

To do this he first measures the height that his current rabbits (F0) can jump, and finds that they have a mean jumping height of 20cm. He also knows from research conducted by other rabbit breeders that the narrow heritability of jumping ability is $h^2=0.3$. This means that 30% of the variation in jumping height can be attributed to additive variation in genes.

The next step is to select a sub-population of F0s that jump the highest. From a total F0 population with a mean height of 20cm he selects a subpopulation of F0 with a mean jumping height of 30cm (Figure 5.2).

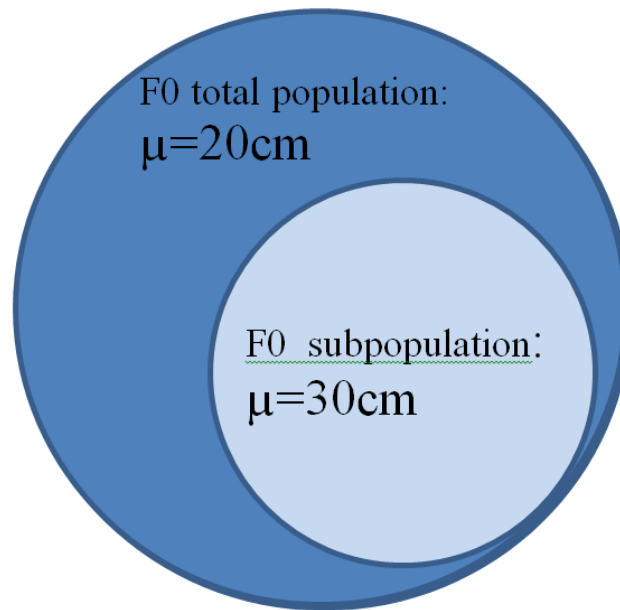


Figure 5.2 Means of Jumping Height for F0 Rabbits.

As our breeder wants rabbits that will jump the highest, he breeds only the higher jumping subpopulation. In this case the selection differential is the difference between the original mean ($\mu=20\text{cm}$) and the selected mean ($\mu=30\text{cm}$): 10cm. The subpopulation here is artificially selected by our breeder, however, the breeder's equation can also apply to populations in which natural selection occurs. Just imagine instead that a population of wild rabbits are under pressure to find food. An abundance of food lies over a high barrier, and so only the highest jumpers are able to forage there. We may find in this instance that from a F0 population with a mean jumping height of 20cm, the subpopulation of rabbits that were able to survive and reproduce had a higher mean jumping height of 30cm.

In both cases the selection differential (S) = $30 - 20 = 10\text{cm}$.

In order to forecast how high the rabbits in F1 (the offspring of the F0 subpopulation) will jump, the selection differential is multiplied by the narrow sense heritability of the trait, 0.3:

$R = h^2S$, therefore = $0.3 \times 10\text{cm} = 3\text{cm}$.

The response to selection forecasted is 3cm, meaning that the expected mean jumping height of F1 rabbits is the original mean (20cm) plus the response to selection (3cm): $(20 + 3) = 23\text{cm}$. So if our breeder is wise and has done his calculations correctly, he will be betting that the mean height of the next generation of rabbits will be 23cm high.⁶⁴

Adaptive potential and narrow heritability are used amongst animal and plant breeders, as well as conservation geneticists, to forecast the potential of specific traits to evolve under natural selection pressures. This information is especially pertinent at the moment, as it can be used to predict the adaptive response to large-scale environmental changes that may occur under rapidly changing climates. For example, traits such as desiccation and cold resistance have been shown to be highly heritable in some species, whilst low in others, reflecting differences in adaptive potential under these kinds of environmental changes (Kellerman et al. 2009). Given this, species with a stronger additive genetic basis for these kinds of traits are more likely to survive in climates changing in respect to temperature and humidity, as they will be able to respond to selection at a faster rate. Other climate-impacted traits that have been shown to be heritable include seasonal timing, stress, and thermal responses (Hoffman & Sgro 2011). This kind of information can be used by geneticists to formulate management plans, and prioritise the conservation of species in need of most protection, given forecasted climactic change.

However, an inaccurate h^2 estimate will impair the accuracy of adaptive potential predictions. Specifically, an inflated h^2 estimate may lead to a prediction that animals are

⁶⁴ To further illustrate, imagine a trait that had a heritability of zero. This means that variation in the trait cannot be explained by variation in genetics. If this is the case, then there can be no response to selection, as there is no heritable basis to the trait. No matter which individuals were selected for the next generation, the traits that these individuals possess will not be passed on to their offspring. This is reflected in the breeder's equation. When $h^2=0$, the response to selection (R) is also always zero, no matter the selection differential. $R = h^2S$, $h^2=0$. $R = 0 \times S = 0$.

capable of adapting to environmental change when in fact they lack the adaptive potential to do so. Conversely, a reduced estimate would lead to the conclusion that these animals are unable to adapt to environmental change. As a result these animals are likely to be mismanaged by conservationists, or overlooked as low-priority organisms for conservation planning.

Heritability estimates have been made for a huge amount of traits in a substantial number of different animal species. Many of these estimates have focused on agricultural animals, such as cattle, pigs and poultry, and concern agricultural needs, such body weight, milk-yield, life-span, fecundity, and litter size (Falconer & MacKay 1996; Roff 1997). However, a large amount of work has also been done using other species such as fish, birds and insects (Merila & Sheldon 1999). More recently, researchers have begun to estimate the heritability of animal behaviours. For instance heritability estimates exist for alarm reaction in honeybees (Collins et al. 1987), exploratory behaviour in the great tit (Drent, van Oers & Noordwijk 2003), boldness in the zebrafish (Ariyomo, Carter & Watt 2013), courtship behaviour in fruit flies (Aragaki & Meffert 1998), docility in cattle (Le Neindre et al. 1995), parental care in sparrows (Freeman-Gallant & Rothstein 1999) and many other dimensions of personality in rodents, birds, fish, sheep, dogs and chimpanzees (van Oers et al. 2005).

As I have shown in chapter 4, G-E covariance has the potential to inflate or deflate heritability estimates. If it is demonstrated that G-E covariance may be occurring in animal populations, some of the above estimates may not give as accurate an interpretation of adaptive potential as originally thought.

5.2 Animal and Human Populations

These days, we are not so concerned about breeding humans, or forecasting their adaptive potential⁶⁵. As such, the use of the breeder's equation and the forecasting of adaptive potential are confined to animal studies. Animal and plant⁶⁶ studies differ from heritability studies in human populations as the environment can be carefully controlled. For ethical and societal reasons, we cannot raise a child, or population of children, in particular controlled environments, as was given in the hypothetical example in chapter 2. However, in animal studies this is possible and it is very commonly done.

While animal heritability studies still have the problem of $V_{G \times E}$ to deal with, G-E covariance is not thought to impact upon them. This can be illustrated by quoting three prominent quantitative and behavioural geneticists:

Animal model research focuses on GE interaction because of the ability in the laboratory to impose exactly the same environment on each individual animal. GE correlation is not studied in the laboratory because the need to give animals environmental choices defeats the purpose of experimental control provided in the laboratory. (Plomin 2013, pp. 1148-1149)

Correlation between genotype and environment is seldom an important complication, and can usually be neglected in experimental populations, where randomization of environments is one of the chief objects of experimental design. (Falconer & MacKay 1996, p. 131)

Described in chapter 4, active G-E covariance, referred to in these texts as correlation, arises when an individual can personally modify their environments, and that modification occurs in part due to a genetic predisposition. In the reactive case, one individual or group modifies another individual's environment, based at least in part on a phenotypic

⁶⁵ However, it must be noted eugenicist motivations were part of the driving force at the conception of behavioural genetics. See chapters 1 and 2 for more detail.

⁶⁶ Plants have been well-used for heritability studies also, although this thesis shall not be focusing on plant studies.

expression of their genetic background. Lastly, passive G-E covariance cases occur when an individual inherits both their parent's genotype and environment.

As mentioned in chapter 4, passive cases are easy to control for using adoption and cross fostering experimental designs – where an individual is not raised by their biological parents, and thus does not inherit an environment from them.⁶⁷ Reactive cases are unlikely to occur in most experimental situations, so long as the animals in questions are kept in isolation. If animals are housed in groups, then there is the possibility that animals in that group could treat each other differently, based on some phenotypic manifestation of each other's genotypes. For example mice with genotypes that make them smaller on average may be bullied or face aggression from other mice. This could lead to variation in behaviour, such as exploration tendency and ability, or cognitive development. In this case the phenotypic variation would be due to a correlation of genes and environment. Neither Plomin, nor Falconer and MacKay appear to have accounted for such possibilities. Lastly, active covariance could occur if there were a variety of environments available for individuals to choose from. Those with particular genotypes may gravitate towards a particular environment, correlating the two. This could in turn, lead to phenotypic differences, which would arise from differential environmental exposure.

It is not commonplace for animal experiments to allow individual animals to elect from a variety of environments the one in which they wish to live. As mentioned by Plomin above, quantitative genetic studies generally aim to carefully control environments between groups and between individuals, varying only the variables which they wish to investigate.

However, there are some issues that arise with strictly controlled environments.

Traditionally, a controlled environment was one in which very little other stimulation was

⁶⁷ As mentioned in chapter 4, this does not eliminate the fact that a prenatal environment is inherited from the mother, and thus could covary with their inherited genotype even in controlled studies.

available. Even today, many laboratory animals are kept in small cages with minimal environmental stimulation, so as not to confound the effects of the treatment being tested. While this may sound in principle a good way to ascertain the effects of V_G , these are very different kinds of environments to the animal's natural habitat, and the animals may experience distress in this kind of situation (Newberry 1995).

This has lead Young (2008) and others (Beattie, O'Connell & Moss 1995; Shepherdson et al. 1998; Wells 2004) to argue for the implementation of enriched environments on ethical grounds. This is supported by studies showing that animals raised in enriched environments displayed behaviours and physiological traits indicative of improved welfare (Beattie, O'Connell & Moss 1995).

While some have argued that environmental enrichment can decrease the statistical power of detecting genetic effects (Blackie et al. 1977; Gartner 1999, as cited in Wolfer et al. 2004), it has been shown empirically that this is not the case (Wolfer et al. 2004). To the contrary, many have argued that impoverished environments, or environments dissimilar to an animal's natural settings have a negative impact on empirical studies, resulting in altered brain function and behaviours (for example see Laviola et al. 2008; Wurbel et al. 2001).

In support of this, many studies have found significant phenotypic differences between animals in enriched versus non-enriched environments. In rats, enriching environments have been shown to promote drug resistance (Bezard et al. 2003), spatial memory (Nilsson et al. 1999) and neurogenesis (Nilsson et al. 1999). The latter has also been shown in mice (Kempermann, Kuhn & Gage 1997), insects (Scotto Lomassese et al. 2000), and crayfish (Sandeman & Sandeman 2000). The interactive effects of enriching environments has also been demonstrated on rats (Cooper and Zubek 1958)

One notable example is Alexander, Coombs and Hadaway (1978) and Alexander et al.'s (1981) 'rat park' experiment. In this experiment two populations of rats were compared. One population was confined in isolation to the 'standard' wire mesh cages, typical of experiments with lab rats at the time. The other population were contained in a larger, more spacious arena, complete with sawdust and a climbing pole, and most importantly, were housed with other rats. As rats are social animals with large ranges, Alexander, Coombs and Hadaway (1978) believed that this form of housing was more reflective of their natural habitat.

Both groups of rats were then subjected to morphine exposure – which varied between being the only fluid available, and available as a choice between morphine and water. This exposure was varied over cycles which had been previously shown to initiate addictive behaviours in rats.⁶⁸ In previous studies of opiate addiction in lab rats (Stolerman & Kumar 1970; Ternes 1975), these procedures produced self-administration of the drug, even when the choice of water as an alternative was available, indicating opiate addiction.

In the experiments from Alexander and colleagues rats housed in Rat Park self-administered significantly less morphine than those in the isolated cages. This has been cited as evidence for impoverished environments mediating addictive behaviour - findings that have more recently been applied to models of human addiction (Alexander 2008).

Since the rat park experiments environmental enrichment has been seen as essential for the wellbeing and successful study of laboratory animals. However, I wish to show that an emphasis on environmental enrichment has opened the door for limitations in quantitative

⁶⁸ These cycles were broken into four experimental periods. The first was a limited access period, in which a 3 day cycle of water only access (day 1) and water and morphine choices (days 2 and 3) were repeated 9 times. The second was a forced consumption period, in which the rats were given only morphine laced liquid for 53 out of 57 consecutive days. The third was the Nichols cycle period, in which a 3 day cycle of no liquids (day 1), morphine only (day 2) and water only (day 3) were repeated 8 times, with morphine versus water-choice days after cycles 2,4,6 and 8. Lastly, there was a 7 week abstinence period, in which only food and water were freely available, although two morphine versus water-choice days occurred in week 2 and week 5. See Alexander, Coombs and Hadaway (1978, p. 1976) for more detail.

genetic research, which has gone unrecognised. Specifically, I believe that enriched environments in experimental settings can allow for G-E covariance to occur, which may bias heritability estimates. While I do not propose that enriched environments should be scrapped in the scientific domain, as the benefits seem clear, I do believe that geneticists should be aware of the disadvantages offered by enriched environments and potential interference due to active and reactive G-E covariance.

5.3 An Example from Inbred Mice

In the previous section I outlined the case for enriched environments in laboratory animal studies. Controlled environments and enriched environments are not in principle at odds with one another. Two different treatment groups of animals could be subjected to the same enriched environment; thus controlling for differences between the groups. However, in this section I wish to argue that an enriched environment, even if homogenous between groups or individual animals, can lead to phenotypic divergence. Recently this point has been empirically demonstrated by Freund et al. (2013).

Due to the demands of accurately estimating variances, quantitative geneticists have traditionally estimated H^2 by exposing diverse pedigrees to one or few discrete environments. The focus of this approach is to isolate the phenotypic effects of V_G by standardising environmental backgrounds (thus reducing V_E). In a recent study, Freund et al. (2013) inverted this focus to examine the genesis of phenotypic individuality in mice. Instead of studying mice of varying genomes, they used highly inbred mice that were so genetically similar that they could have varied across only 8-12 SNPs (Bailey 1982)⁶⁹.

⁶⁹ To put this number in perspective, the current estimate for the number of nucleotide bases in the mouse genome is 2.5 billion (Chinwalla et al. 2002).

Freund et al.'s data introduce intriguing new considerations by demonstrating significant phenotypic individuality even in the absence of initial V_G . They exposed these 40 highly inbred (referred to in the paper as 'genetically identical') individuals to the same complex environment, enabling individual variation in environmental experience, and effectively magnifying V_E against a background of negligible V_G . This environment embodied a modern day 'rat park': it contained 5 levels, each connected with glass tubes, two nesting boxes, as well as toys, cardboard tubes, wooden scaffolds, and plastic flower pots (Freund et al. 2013, sup.) (see Figure 5.3).

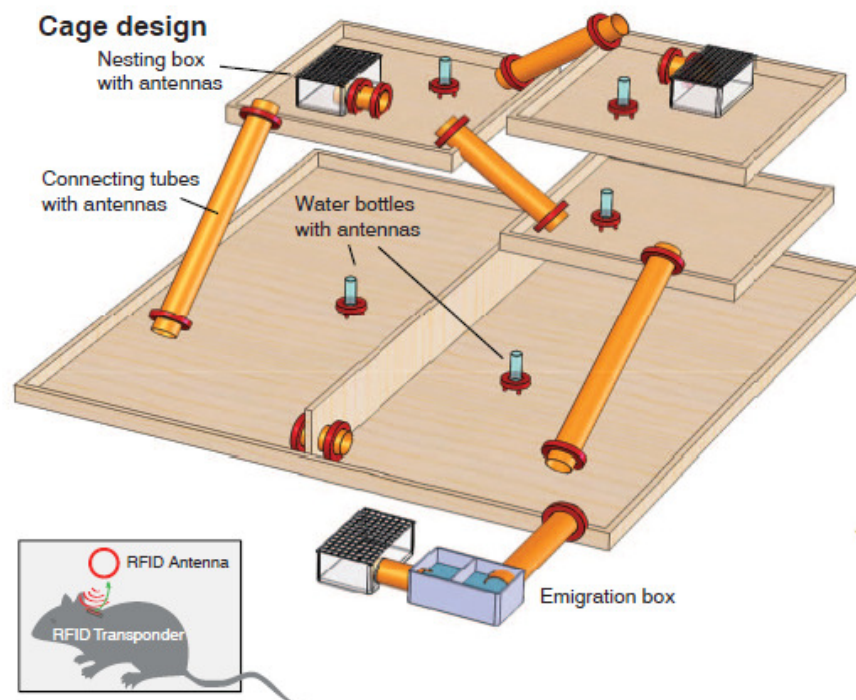


Figure 5.3 Cage Design for Enriched Environment (Adapted from Freund et al. 2013, p. 757).

Each subject's movements was then tracked using RFID transponders, and computed to calculate 'cumulative roaming entropy' (cRE) as an index of accumulated behavioural experience and activity. Results showed that, intriguingly, even without genetic differences individual mice diverged substantially and consistently in cRE over time. This divergence represented phenotypic individuality in the tendency for environmental exploration (as measured by cRE) (Figure 5.4). It was also correlated with features of brain development, measured at the end of the study as hippocampal neurogenesis (Figure 5.5).

Interestingly, post-experiment variation in individual cRE was independent of early cRE, yet strongly predicted by both linear and exponential rates of early cRE change. This indicates that once released into the experimental environment, individuals pursued unique and consistent developmental trajectories. After 3 months this had generated over 20-times the observed starting variance in cRE, an effect accompanied by correlated changes in hippocampal neurogenesis. That early cRE did not predict developmental trajectory is particularly salient in showing how phenotypic individuality was largely driven by each individual's experience in (and of) its enriched developmental environment (see Figure 5.4).

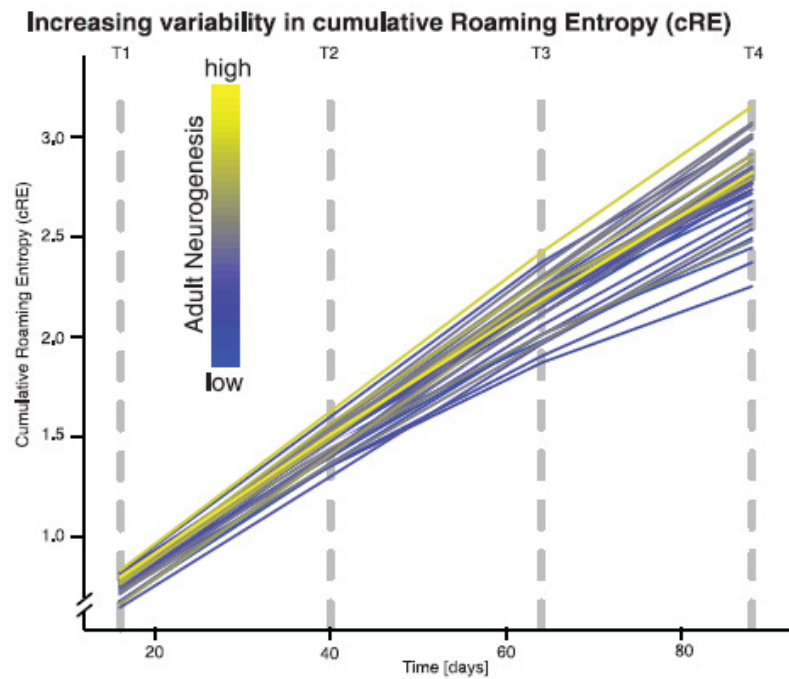


Figure 5.4 Increases in Variation of Cumulative Roaming Entropy (Adapted from Freund et al. 2013, p.758)

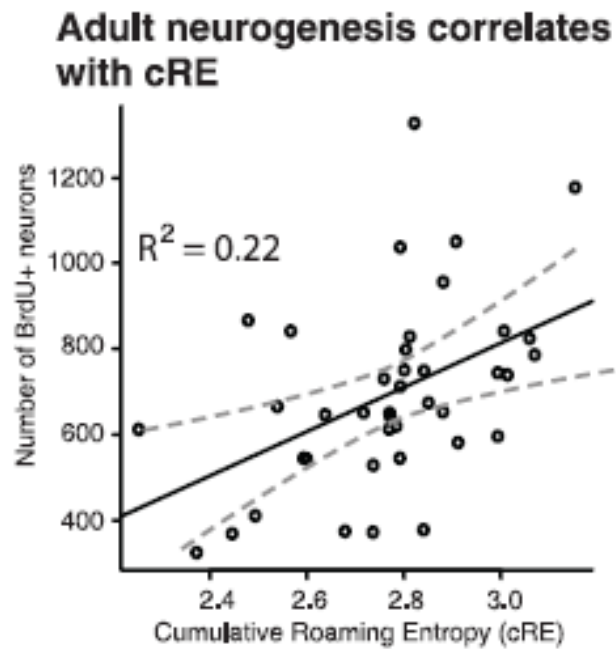


Figure 5.5 Adult Neurogenesis Correlates with Cumulative Roaming Entropy (Adapted from Freund et al. 2013, p.758)

Freund et al. attribute this result to the formation of a ‘personalised life space’, a process whereby micro-habitat selection shaped subsequent development, reinforcing future microhabitat choice and compounding the development of individuality. This life space or habitat selection parallels the ‘non-shared environment’ concept in quantitative genetics.

5.3.1 Sources of Divergence

Whereas Freund et al.’s mice were nearly genetically identical, wild and many laboratory populations typically harbour abundant V_G . Through biasing early life experiences, any genetic pre-disposition towards particular microhabitats could propel individuals along unique phenotypic trajectories, illustrating G-E covariance. However, in this study little to no V_G was present. This presents a question concerning the source of initial microhabitat biases. What was responsible for initiating the process of self-reinforcing individuality?

I suggest five possible influences.⁷⁰ The first is that the environments that each mouse was exposed to were not in fact identical. Each could have experienced variation in intrauterine environments (parental effects) and early experience such as handling and transportation. They were obtained from breeders at 4 weeks of age, and so environmental information for this early period of development is not recorded. The effects of early and pre-natal experience have been shown to be significant in humans (Gluckman & Hanson 2004; Gluckman, Hanson & Pinal 2005), and early experience has been long known to affect behavioural traits in mice (Beach & Jaynes 1954; Denenberg et al. 1964; 1981; Eklund 1997; King 1957; King & Gurney 1954; Mothes et al. 1996). More recently Francis et al. (2003) investigated the effects of early experience in mice independent of genetic variation by using inbred strains. They cross-fostered mice from different strains both prenatally (via

⁷⁰ The first, second and fifth influences have all been recognised by Freund et al. as potential direct effects, although were not considered in a covariance framework.

embryo transfer) and post-natally, and found that strain differences that were once thought of as genetic appear to result from differences in pre- and post-natal early experience.

So it is certainly possible that these kinds parental effects may have directly impacted upon the final measured phenotypes, and could account for the variation present at the end of the study (i.e. V_{earlyExE} causes V_P). It is also possible that these small initial differences impacted on the types of environments that each mouse chose to select for itself in later development. This in turn could affect subsequent exploratory behaviour, and this accumulation of behavioural differences and differential environmental experiences could have contributed to differences in hippocampal neurogenesis. This would be a case of active covariance of early and later environments ($2\text{Cov}_{\text{earlyExE}}$).

The second possibility is that the mice used were not 100% genetically identical. As mentioned above, there is the possibility of small amounts of genetic diversity between inbred individuals. If this is the case, and if there is some genetic basis of exploratory behaviour (as has been shown in mice (DeFries, Gervais & Thomas 1978) and other animals (Ariyomo, Carter & Watt 2013; Dingemanse et al. 2002; Van Oers et al. 2005)), then small genetic variations could either be directly responsible for the behavioural variation measured ($V_G \rightarrow V_P$), or this variation may have contributed to variation in micro-habitat selection by way of active G-E covariance (2Cov_{GE}). In turn the selection of a micro-habitat could have caused variation in behavioural and physiological phenotypes – in this case exploratory activity and hippocampal neurogenesis ($V_G \rightarrow V_E \rightarrow V_P$). However, as the genetic differences between the mice were extremely small, this explanation is unlikely.

A third potential candidate is simply the stochasticity in initial conditions of each subject's formative experiences. Stochastic influences of the enriched environment may have propelled mice in particular directions, initiating variation in environmental experience.

One mouse may have happened upon a cardboard tunnel which it enjoyed, and habitually returned to the spot, shaping its particular environmental experience. The only reason that this mouse rather than another experienced the developmental environment in such a way was because of this chance happening, perhaps due to the order or location of which the mice were first placed in their cages. Like the G-E covariance and early environment-later environment covariance cases above, small initial variations of these kinds could have placed mice in an environment which fed back on their development and behaviour, reinforcing a particular developmental trajectory, as is seen in the cRE results in Figure 5.4.

The fourth possibility is that the mice within the enriched and social environment reacted to each other, based on small differences arising from genetic, stochastic, or early experience variations. Like the possibilities above, this would mean a covariance between either genes or early environment, however, in this case it would be a reactive covariance. For instance a mouse that happened to find itself in a particular tunnel may be bullied by other mice, reinforcing its habitat choice and shaping its exploratory behaviour and future environmental experiences. The social impact on behaviour has been demonstrated in rats by Thullier et al. (1992). When rats are arranged into groups and given access to food via difficult routes, behavioural differentiation develops where some rats are sent to forage and the others steal from these ‘carrier’ rats. To demonstrate that this is not a purely genetically determined behavioural difference, the study removed the carrier rats from the group, and observed that others filled that behavioural niche, succumbing to a social hierarchy within the rat group. Social hierarchies of this kind would have also been possible in the Freund et al. study, which exemplify a form of reactive covariance, with genes and/or early experience.

The fifth suggestion is even more interesting. Instead of small pre-existing genetic variations in the mice, it may have been that the mice varied in respect to their epigenome.

The epigenome consists of the collective inherited chromatin modifications which regulate gene expression, but do not involve altered DNA base sequences (Jablonka & Lamm 2012) – such as the methylation of cytosine bases and histone modifications (see section 1.2.2). Variation among epigenomes is thought to account for significant variation in measurable phenotypes (Bossdorf et al. 2010; Dias & Ressler 2013; Jablonka & Raz 2009; Robinson 2004; Turan et al. 2010), often attributed to ‘developmental noise’ (Robinson 2004). Similarly to cases of G-E covariance, it may be that epigenetic factors influence an organism’s environmental choice at an earlier developmental stage which consequently influences the micro-habitat construction at later stages. This could happen in both an active or reactive fashion, as explained above. This would be a case of *epigenome-environment covariance* (2Cov_{EpE}), a yet unexplored source of variance in quantitative genetic models.

This is related to the first possible cause, as early exposure to parental effects can lead to behavioural changes which are mediated by epigenetic modifications. For example rat pups who have been licked by their mothers have changed methylation patterns on genes in their hippocampus (see section 1.2.1).

Epigenetic sources of variation may help to explain other apparent anomalies in animal research with genetically similar organisms. Another study yielded similar results – where genetically similar⁷¹ mice displayed individual differences in exploratory behaviour, anxiety, maze and swimming performance that could not be accounted for by obvious environmental differences in the laboratory (Crabbe, Wahlsten & Dudek 1999).⁷² In this experiment, multiple environments were tested, and it was found that individual mice

⁷¹ This study used inbred strains similar to those in Freund et al.’s (2013) study, where minimal genetic variation is present.

⁷² As mentioned above, it is possible for early pre- and post-natal environment to still have made a difference to phenotypic divergence, despite genetic homogeneity.

performed differentially in a range of phenotypic assays, even though they had been subjected to the same laboratory environments, and had negligible genetic differences. This indicates a potential interaction effect between environment and the epigenome – whereby individuals with one particular epigenome show a particular phenotypic behaviour in a certain environment that others do not.

Epigenetic variation, along with its covariation and interactions with other sources of phenotypic variance, may also help to account for the ‘missing heritability’ of many traits, as explained in chapter 2. As mentioned in chapter 1, epigenetic variation, caused by parental effects (caused by the parental phenotype but experienced by the offspring as parental environment), clearly impacts on phenotypic variation, and may also interact and covary with later environmental influences (Bossdorf et al. 2010). However, to tackle such issues properly would require an additional thesis at least. For this reason this thesis will concentrate only on genetically and environmentally caused variation (V_E and V_G) and their covariance.

What I can show in this chapter is that *some sort* of covariance is likely to be occurring in animal studies. The processes described in each of the above options are possible sources of phenotypic variation on their own, and of covariance with the environment. Small initial differences in genetics, epigenetics, and early developmental or stochastic experiences can place individuals in particular environments which feedback on behaviour and future environmental preference. Options 1 to 5 exemplify the same kind of causal story involved in G-E covariance, whereby experience in a personalised life space, or non-shared environment generates self-reinforcing runaways and results in large scale phenotypic variation. It may be that these runaways are initially caused by variation in genotype, epigenotype, early experience, or stochastic variation; and the runaway may be due to both active and/or reactive mechanisms.

As Freund et al.'s data illustrates an increasing divergence in exploratory behaviour over time, it seems likely that some type of covariance with the environment is occurring, although the initial sources of variation remain a mystery. It is possible that a combination of the above factors was responsible for initial experiences of the enriched environment, and as such many variables covaried with the environment in this study.

This is further supported by the fact that initial variations in cRE were not predictive of the final V_P and unique individual developmental trajectories. Roaming entropy from T1 was not predictive of cRE T2-4, which then started to reliably and significantly diverge (see Figure 5.4). Instead, to account for the magnitude of divergence, it appears that initial variation was magnified by additional sources of variance. Individuality in exploratory behaviour emerge, as part of what seemed to be a feedback from an individual's environment. It could not be predicted simply from initial differences alone. These trajectories increasingly diverged over time, possibly due to the self-reinforcing effects of past experience. The emergence of such individuality highlights the hidden potential for small-scale initial variation (environmental, stochastic, epigenetic or otherwise) to generate large scale-phenotypic variation.

5.4 Consequences of Covariance

The amazing thing about Freund et al.'s study is that such variation was generated without any (or very little) initial V_G . Given this, imagine the potential for additional covariance, and thus additional resulting phenotypic variation, if substantial genotypic variation were initially present to further bias habitat choice (see Lynch & Kemp 2014).

Figure 5.6 illustrates this point. 5.6(a) shows a scenario in which genetically identical organisms (represented by the single circle) experience small initial differences (for

instance stochastic, or early environmental experience) that lead to phenotypic divergence early in development (coloured bar at E1), which are maintained in later development (coloured bar at E2). This is the kind of situation that could occur if small initial differences impacted on V_P directly, without affecting the micro-habitat selection of the individual. Figure 5.6(b) shows a covariant example reflective of Freund et al.'s study. Small initial differences at E1 lead individuals to select their own environmental experience, leading to feedbacks and further phenotypic divergence at a later time (E2). Figure 5.6(c) illustrates a covariance example where genetic differences are initially present. It is predicted that this extra initial variation would magnify the effects further, leading to even more phenotypic divergence at E2.

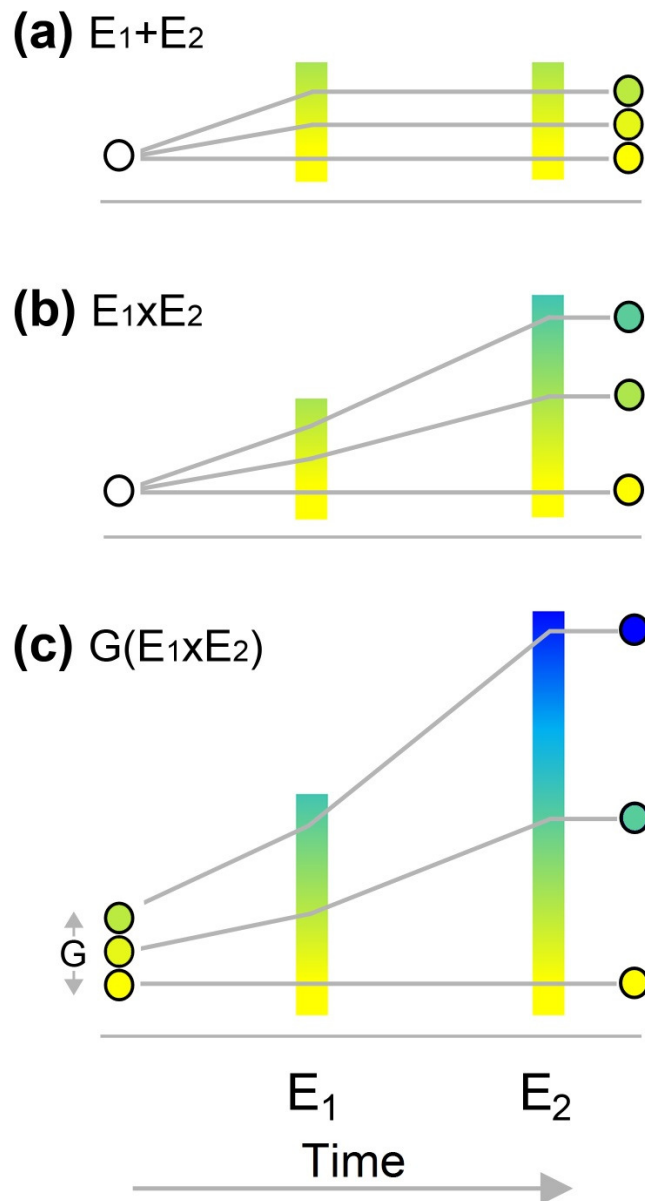


Figure 5.6 Developmental Trajectories How developmental trajectories might generate phenotypic variance. Environmental effects are for simplicity levied at two discrete stages (the coloured bars at E_1 and E_2). In panels (a) and (b), small stochastic effects drive genetically-identical organisms into slightly different initial environments (E_1), which generates phenotypic variation at and after E_2 (indicated by the differently coloured circles). In (a), the initial environment does not bias subsequent environment choice. In (b), experiences at E_1 bias the environments experienced at E_2 , thereby magnifying overall divergence. This illustrates the reciprocal feedback between phenotype and environment envisaged by Freund et al. (2013). Panel (c) then considers the potential for initial genetic variation (V_G) to compound this process even further, through biasing environment choice in both E_1 and E_2 (Adapted from Lynch and Kemp 2014, p.3)

Thus it is interesting to consider the broader potential for covariance and causality between early experience, stochasticity, epigenetics (V_{Ep}), V_G and V_E in other populations - animal and human, as Lynch & Kemp (2014) predict that this would lead to even more phenotypic variation than observed in Freund et al.'s study.

As noted above, epigenomic variation could bias formative (postnatal) environmental choice and thereby influence phenotypic development through the covariation between epigenetics and environment. This is consistent with work on monozygotic twins, where phenotypic divergence increases over a twin-pairs life time (Turkheimer 2011), and may shed light on some of these results. The fact that epigenetic change is itself mediated through environmental experience raises additional possibilities for reciprocal feedbacks. If V_G serves to bias the selection of early developmental environments, correlated changes to the epigenome could reinforce habitat biases even further, thereby accelerating phenotypic development along unique trajectories.

Further, if this variation is itself heritable, these biases could go as far as to influence the evolutionary trajectory of a species. Such self-reinforcing 'runaways' remain speculative, yet the intriguing recent findings from Freund et al.'s paper suggest how examination of such processes could prove key to unravelling the true genesis of phenotypic individuality.

Epigenetics aside, this finding demonstrates the large-scale phenotypic variation (V_P) that can result from the selection of one's own environmental experiences, even when housed communally in a single larger environmental space. If animals (or humans) have any genetic predisposition towards particular environmental experiences, and if variation in those environments is offered, then a covariation between genotype and environment is even more likely to occur.

In human studies this is recognised, but in animal studies controlled environments has been thought of as synonymous with $V_E \approx 0$ (Falconer & MacKay 1996; Plomin 2013). This study demonstrates that this is not the case, and that a single enriched environment can give rise to large-scale phenotypic variations. This means that potentially any organism housed within a sufficiently enriched environment is able to self-select a ‘micro-habitat’ of some form, which would shape their development, and may partially account for variation in any measured phenotypes. In quantitative genetic studies it is likely that any resulting phenotypic variance is counted as V_G , and not V_E or $2Cov_{GE}$. This brings us back to the debate (introduced in section 4.3) as to whether the selection of an influencing environment via active G-E covariance should be counted as a separate form of variance from genetic variance at all.

5.4.1 Estimation in Animal Models

Covariances of the kinds described above are problematic for heritability studies, and as such, some may argue that enriched environments could be detrimental for the validity of experimental designs. However, as shown in section 5.2, environments that are not enriched have their own drawbacks – they are ethically questionable – and do not produce natural behaviours and development in many laboratory animals.

An alternative, then, is to be able to estimate the magnitude and scope of G-E covariance as it occurs in a heritability study with an enriched environment, and then to subtract that from the originally estimated V_G term. No one to date has designed a study that is able to separate this source of variation from the initial genetic variation, or from the more direct effects of other initial sources of variation, such as epigenetics or early experience, which predisposes individuals to select an environment. Prominent quantitative geneticists believe that this phenomenon does not occur in animal studies, and as mentioned in section 5.2, the estimation of G-E covariance in human populations has been controversial (section

4.4). Present efforts to characterise this parameter are confined to the social sciences (Jaffee & Price 2007; Meek et al. 2013), however, the human context inhibits the estimation of active and reactive G-E covariance as environments cannot be manipulated. In order to address this, researchers could simply compare animals which have been allowed to choose their environment to those which have been assigned one. If those in the choice group selected their environments based on any genetic predispositions, then resulting discrepancies in the phenotypic variances would indicate whether, and how much, phenotypic variation could be accounted for by the covariance of genes and environment.

To understand this, let us return to the human examples. In chapters 1 and 4 I presented an example in which some children have a genetic predisposition to seek out extra stimulation, perhaps in the form of books; and that this environmental variable affects the phenotype of intelligence. In this case a covariance between the predisposing genes and the book-filled or otherwise stimulating environment is occurring. In order to principally separate the effects of genes, environment, and their covariation, you could assign some children to a highly stimulating environment, some to a less stimulating environment, and allow other children to choose their environment (assuming that this choice would be based on differences in genetics).

To examine the comparative effects of V_G , V_E and $2Cov_{GE}$, all that would be needed was a heritability analysis for the choice and non-choice groups. When comparing estimates attained from those who have chosen their environment (and thus G-E covariance is present) to those who have been assigned an environment (no G-E covariance present) one would be able to see if, and to what degree, a discrepancy in the estimates existed. Any difference between G-E covariance groups and groups where no G-E covariance were present would give an estimation of G-E covariance in this scenario.

Evidence for the genetic basis of habitat selection already exist for some species. For instance tendency to disperse has been demonstrated as heritable in birds (Pulido et al. 2001) and fish (Chapman et al. 2011), as well as exploratory behaviour in a range of species (Dingemanse et al. 2002; Drent et al. 2003). Heritable personality traits in animals such as boldness (Ariyomo, Carter & Watt 2013; Brown et al. 2007; Oswald, Singer & Robinson 2013) and sociality (Irving & Brown 2013) are also quite likely to impact upon the physical and social environments experienced. Once habitat selection choice can be shown independently to be at least somewhat heritable, then assuming that that heritability reflected a majority V_G component (although this could include other confounds, such as passive G-E covariance and parental effects), then this method could be used.

5.5 Summary and Conclusion

I have shown in this chapter that the phenomenon of G-E covariance is not confined to studies of human behaviour. As has been demonstrated, this phenomenon is likely to occur even in animal studies with well-controlled heritable variation, potentially skewing the heritability estimate attained. Animals may be able to actively seek out their own ‘micro-habitat’, experiencing a non-shared environment to others in the population, yet V_E could still be estimated as equal or close to zero.

This is particularly true for experiments with enriched environments, which are becoming increasingly prevalent due to ethical and developmental concerns. The more varied and enriched the environment, the greater the possibility for different environmental experiences that could be ‘non-shared’ between individuals. These experiences could be actively selected, encompassing the active- G-E covariance cases presented in human examples in section 4.2.2.

Reactive covariance could also occur in controlled experimental situations with animals if the animals are housed socially. Other individuals or groups within the population could react to individuals, and this reaction may be, at least in part, due to some genetic difference. If this were the case, then reactive G-E covariance would be occurring. In both the active and reactive cases, current heritability models would ascribe phenotypic variance to genetic variation, potentially skewing the h^2 or H^2 attained.

This chapter also highlighted the possibility of other sources of (co)variation. Although the scope of this thesis is limited to the examination of genetic and environmental variance, empirical data points to additional sources of phenotypic variance, such as maternal effects like intrauterine experience, and inherited epigenetic variation. If these are to affect phenotypic diversity, as has been conclusively shown in empirical studies, then they are likely to also affect environmental selection, in the same way the genetic variation may. If this is the case, there is the strong possibility of covariance between the environment, genotype, epigenotype, and maternal effects. Thus these factors need to be considered not only as additive sources of phenotypic variation, but in their interactions and covariances.

Active G-E covariance has to date proven difficult to quantify in human populations, largely due to the challenge of disentangling the effects of V_G from V_E due to microhabitat selection (Plomin et al. 2008, see chapter 4). However, animal models may shed light on some of these apparent anomalies, allowing researchers to compare populations which have been allowed to actively modify their environments to those which have not. Thus animal studies may be used to estimate the magnitude and scope of G-E covariance, and may shed light on its impact in human studies, although there are limits to the comparison.

Now that I have highlighted the potentially serious consequences of G-E covariance, and some potential future directions in estimation, I shall turn to issues of interpretation that were introduced at the end of chapter 4. If G-E covariance is shown to occur, what do we

make of it? Do we still ascribe the resulting variation as genetic, as environmental, or neither? This is the focus of chapters 6 to 8.

Chapter 6 Causal Structures

The previous chapter showed how G-E covariance might drive phenotypic variation in controlled animal studies. In this chapter I return to human behavioural genetics, and to some of the seemingly problematic scenarios introduced in chapter 4. G-E covariance challenges the assumption that traits with high H^2 (and thus a high V_G) have a large amount of their phenotypic variance attributable to genetic variance. This and the following two chapters examine why G-E covariance cases can sometimes conflict with what Sesardic (2003, p.1004) calls ‘common-sense etiological ascriptions’.

Recall that there are three different types of G-E covariance: passive, active, and reactive. Passive G-E covariance occurs because individuals inherit both their genes and environment from their parents, and as such there is an association between the two. Active G-E covariance occurs when individuals with certain genotypes actively seek out and modify their own environments. Reactive G-E covariance occurs when individuals with a particular genotype are treated differently by others, and as a result, experience a different environment.

At the end of chapter 4 I showed that interpretations of different types of G-E covariance varied. When reactive or passive G-E covariance is present in examples, the resulting V_P is undisputedly attributed to V_E (Plomin, DeFries, & Loehlin 1977; Price & Jaffee 2008; Scarr & McCartney, 1983; Sesardic 2003; 2005).⁷³ But for active G-E covariance there is disagreement regarding its interpretation. This was summarised in Table 4.1 (p.139).

⁷³ As noted in chapter 4, agreement exists as to how this form of G-E covariance should be treated, although it is not always controlled for in practise.

One approach to understanding this disagreement is to compare two different scenarios where a high H^2 is attained: one where V_P is thought to be largely caused by V_G , and one where this causal attribution seems to be inappropriate.

I have already said that both passive and reactive cases fit the latter scenario, and non-G-E-covariance cases usually appear to fit the former.⁷⁴ If one can determine the point of difference between these examples, this information can be applied to active G-E covariance, where interpretation is disputed. Are they more similar to the non-G-E covariance cases, or to the reactive and passive ones? Where do these similarities and differences lie? The absence or presence of features found in reactive, passive and non-G-E covariance examples may provide some clues for how to interpret active cases.

As the nature of the disagreement concerns causal attributions, a natural starting point for this investigation is to look at the underlying causal structures in each case. Sections 6.1 to 6.4 illustrate the causal relationships involved in passive, reactive, active, and non-G-E covariance cases. I show that non-G-E-covariance cases display a common cause structure, while active and reactive cases both share an indirect causal structure. Passive G-E covariance cases display a causal structure where V_G and V_E both cause V_P independently of one another. Section 6.5 outlines Block (1995) and Block and Dworkin's (1976) response to this problem, by appealing to a distinction between direct and indirect causes. I show that this account is limited, as the direct-indirect continuum is vague, their given definition is flawed, and it does not account for the differences in interpretation between active and reactive covariance.

To illustrate the differences between causal scenarios that may present for different types of G-E covariance, I will refer back to the results of the ANOVA example presented in section 2.4.1. In this example children were cloned in a laboratory to give three genotype

⁷⁴ Assuming no $V_{G \times E}$, significant maternal effects, or other confounds.

groups of 100 children each: G1, G2 and G3. Children were allocated to four different environments in a fully factorial design, so that 25 children of each genotype group experienced one each of the four possible environments (Table 2.1, p. 48). When given an IQ test later in life, G1 children scored significantly higher than G2 children, and G2 children significantly higher than G3 children. The IQ score differences are maintained across the varying environments, as summarised in Table 2.2 (p. 48) and Figure 2.4 (p.62).

To supplement this story, I will assume in this chapter that the different genotype groups also have different physical characteristics. This additional detail was introduced in section 4.1. Imagine that G1 children have higher IQs, and they also have brown hair. G2 children have lower IQs than G1s, and they all have auburn hair. G3 children have the lowest IQs, and are all red-haired. This information is summarised in Table 6.1 below.

Genotype Group	Hair Colour	Average IQ score of Group
G1	Brown	120
G2	Auburn	100
G3	Red	80

Table 6.1 Example Results

6.1 Non-G-E-Covariance Cases

In the absence of G-E covariance these kinds of results – where a physical characteristic (hair colour) and a psychological measure (IQ) are correlated – are best explained by a

common cause structure. In this instance genotype variation is responsible for both the variation in hair colour and differential performance in IQ scores. Recall that under an interventionist account causation occurs if an intervention on the causal variable produces a change in the effect variable. Given the three variables: variance in genes (V_G), variance in hair colour (V_{P1}) and variance in IQ scores (V_{P2}), the interventionist account can be used to distinguish causal and non-causal relationships between the three. In a common cause scenario, intervening on V_G would produce a change in the value of V_{P1} and V_{P2} . However, an intervention on V_{P1} or V_{P2} would produce no change in any of the other variables in this system.

This is presented in Figure 6.1. Here we can see that variation in genetics (V_G) is a common cause of variation in two phenotypes: variation in hair colour (V_{P1}) and variation in IQ scores (V_{P2}). There are no causal arrows coming out of V_{P1} or V_{P2} , but one leaving from V_G to both. This presents a basis to make the claim that IQ score differences are caused by genetic variance, so V_G can be thought to causally account for V_{P2} (IQ). In this kind of scenario a high H^2 for IQ does not appear to conflict with any common-sense causal intuitions about genetic causes of phenotypic variance. This is because V_G is responsible for variation in IQ scores *independently* of its causal relationship with variation in hair colour.

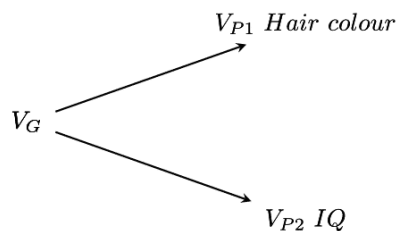


Figure 6.1 A Common Cause Scenario Variance in genetics is a common cause of both variance in hair colour (V_{P1}) and variance in IQ scores (V_{P2})

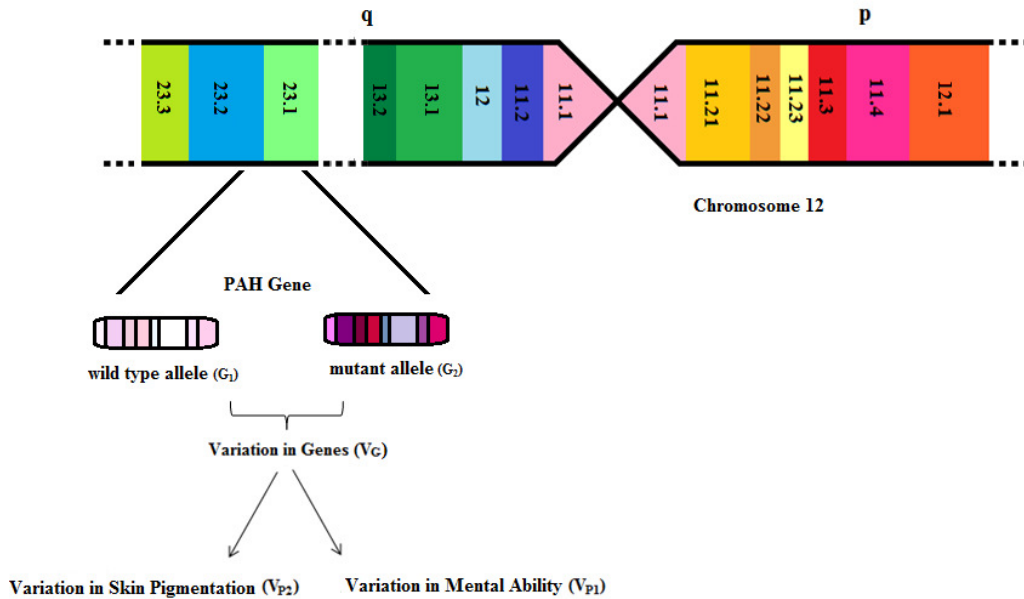
In this scenario, if one were to remove variation in hair colour (V_{P1}) from the picture, the causal relationship between genetic variation (V_G) and IQ differences (V_{P2}) would continue to hold, as indicated by the arrow directed from V_G to V_{P2} . Likewise, if variation in IQ (V_{P2}) were removed from the graph, a causal relationship would still be maintained between genetic variance (V_G) and variance in hair colour (V_{P1}).

Chapter 4 suggested some possible mechanisms for this kind of scenario. It could be that genes for hair colour differences and genes for cognitive ability differences are linked, meaning they are more likely to be inherited together. Another possibility is that there are epistatic interactions, where the effect of one allele (say for hair colour) impacts on another allele at a different locus (affecting cognitive development). Lastly, there could be pleiotropic genes which affect both hair colour and cognitive ability.

This kind of scenario is analogous to an empirical example, where individuals in one genotype group (G_1) have mutations on the distal end of the long arm of chromosome 12, and another (G_2) have no such mutations, instead possessing the ‘wild type’ gene in this region. In this case the mutant allele carried by G_1 individuals causes both mental retardation and hyperpigmentation of the skin. Individuals with the wild type allele do not have any impairment in mental functioning, and have normal skin pigmentation. Thus variation in genotype (V_G) (via the difference between G_1 and G_2 individuals), causes variation in both cognitive ability (V_{P1}), by virtue of one group having mental retardation and another not, as well as variation in skin pigmentation (V_{P2}).

This describes the difference between healthy individuals, and those carrying a mutation on *PAH*, the gene responsible for phenylketonuria. *PAH* is a pleiotropic gene, so differences in the allele at this locus cause multiple phenotypic differences between genotype groups. This is presented in Figure 6.2, but the effects could also be mapped onto

Figure 6.1 - where ‘variation in hair colour’ and ‘variation in IQ scores’ could be replaced with ‘variation in pigmentation’ and ‘variation in mental functioning’⁷⁵.



6.2 Chromosome 12 Variation as a Common Cause Phenylketonuria is caused by mutations in the *PAH* gene, coding for the enzyme phenylalanine hydroxylase (PAH), located on the long (q) arm of chromosome 12 between positions 22 and 24.2.

Phenylketonuria is an example that is often used to demonstrate $V_{G \times E}$ – as the effects of V_G at the *PAH* gene are only evident given certain environmental backgrounds. I shall return to this in chapter 7, where I demonstrate the relationship between G-E covariance and $V_{G \times E}$.

⁷⁵ Although retaining IQ scores as this variable would probably represent a good proxy.

6.2 Reactive G-E Covariance: An Indirect Causal Relationship

In reactive G-E covariance cases, the causal relationship is different to the one shown above. These examples embody the ‘nature-via-nurture’ causal scenario, where V_P is affected by V_G , *via* V_E , through an indirect causal relationship.

To go back to the story from the beginning of this chapter, one way to explain the association between hair colour and IQ scores is that G1, G2, and G3 children are all treated differently in society, and so they systematically experience different environments correlated with their genotype. Section 4.1.1 presented an example of how this may occur. G3 children are discriminated against based on their red-hair – a genetically determined phenotype. This discrimination affects the educational environment that they have access to, leading to lower IQ scores. G1 children have brown hair, and suffer no such discrimination. In fact they are encouraged educationally, and as a result, score highly on the IQ test. G2 children have auburn hair –so are also discriminated against in this red-hair-hating society, although not quite to the extent of the G3 children. Because of this treatment their educational environments are worse than the G1 children, but better than the G3s, and their IQ scores are in-between the two.

In this example genetic variation (V_G) causes variation in hair colour (V_{P1}), which causes variation in the educational environment experienced (V_E), which in turn causes differences in IQ test performance (V_{P2}). This is shown in Figure 6.3.

$$V_G \longrightarrow V_{P1} \text{ Hair colour} \longrightarrow V_E \text{ Educational resources} \longrightarrow V_{P2} \text{ IQ}$$

Figure 6.3 An Indirect Cause of IQ Variation V_G causes V_P (Variation in IQ) via variation in Hair Colour (V_{P1}) causing variation in educational resources (V_E)

The first step in Figure 6.3 shows that variation in genes (V_G) causes variation in hair colour – brown, auburn, and red (V_{P1}). The last step in this diagram shows that variation in educational resources and abuse (V_E) causes variation in IQ (V_{P2}). These steps are uncontroversial. In this and Jencks’ red-hair example there is no disagreement as to whether or not differences in hair colour are due to differences in a genetic background. Additionally, it is accepted that variation in IQ between the different genotype groups is due to variation in the environment; namely, the educational resources available, and the amount of abuse that the different groups are subjected to.

It is the middle step - where variation in hair colour (V_{P1}) causes systematic variation in educational resources and degrees of abuse (V_E) - that is the more controversial connection. Some may suggest that this kind of causal claim is akin to someone’s race causing the racism they receive. To say that V_G indirectly causes variation in IQ, one must show that the causal relationship $V_G \rightarrow V_{P1} \rightarrow V_E \rightarrow V_{P2}$ holds. In the remainder of this section I shall show that under an interventionist account of causation this is the case. This suggests the need for an additional explanation to account for the intuition that variation in IQ in reactive cases should not be interpreted as ‘caused by’ V_G .

Recall from chapter 3 that to determine if a variable E is indirectly caused by C - such that $C \rightarrow I \rightarrow E$ - we must first look at what value the intermediate variable I would have been

if C was intervened on, changing its value from c_1 to c_2 . If C had the value c_2 post intervention, then I would have the value i_2 , as C is a cause of I.

To take this back to our example, variation in genes (V_G) can be incontrovertibly said to cause variation in hair colour (V_{P1}). This means an intervention on V_G , setting it from vg_1 to vg_2 would result in a corresponding change to the value of V_{P1} (From $vp_{1(1)}$ to $vp_{1(2)}$). In this example, vg_1 could correspond to no variance in genetics ($V_G = 0$), and vg_2 some variance in genetics, or a non-zero value ($0 < V_G \leq 1$). Similarly, $vp_{1(1)}$ could be a value of V_{P1} where there is no variation in hair colour ($V_{P1} = 0$), and $V_{P1(2)}$ the value where some variation does obtain ($0 < V_{P1} \leq 1$). Changing V_G from no genetic variance to some genetic variance produces a change in the V_{P1} variable: from no variation in hair colour, to some variation in hair colour. Therefore $V_G \rightarrow V_{P1}$. This is the same as saying that $C \rightarrow I$, as an intervention on C changing c_1 to c_2 produces a change in I from i_1 to i_2 . A change in V_G from vg_1 to vg_2 produces a change in V_{P1} , from $vp_{1(1)}$ to $vp_{1(2)}$.

The next step to determining an indirect causal relationship is to hold I (V_{P1}) at the value that would have been attained if C was intervened upon (set to c_2). This is $I = i_2$, or in our example, $V_{P1} = vp_{1(2)}$, where there *is* variation in hair colour. Given the causal background conditions of a selectively prejudiced society in this example, when $V_{P1} = vp_{1(2)}$ the variable V_E will also change. In this case the value of V_E will change from ve_1 – in which the environments experienced by individuals do not vary, to ve_2 , in which environmental experiences vary between individuals. This is because (again given the background conditions of societal prejudice set by the example)⁷⁶ a change from no variation to some variation in hair colour (from vp_1 to vp_2) would produce a change in the environments experienced by the genotype group, from one where there are no differences in

⁷⁶ The relevance of background conditions is discussed in chapter 7.

environmental experience (e_1), to one where there are differences experienced, as described in the example (e_2). Thus under an interventionist account of causation, $V_{P1} \rightarrow V_E$.

According to Pearl (2001; 2009) V_G is an indirect cause of V_E if when V_G is held fixed at vg_1 , and V_{P1} is intervened upon to set the value of V_{P1} to what it would be had V_G been set to vg_2 (which is $vp_1(2)$), then V_E changes its value to ve_2 . As this is the same value that would have occurred had V_G been intervened upon and set to vg_2 , V_G is an indirect cause of V_E . Thus: $V_G \rightarrow V_{P1} \rightarrow V_E$.

So far I have shown that (given the causal background conditions of the example) variation in genes (V_G) indirectly causes variation in the environmental experience of the population (V_E), via variation in the phenotype of hair colour (V_{P1}). The last step, linking V_E to V_{P2} is uncontroversial, meaning that both V_G and V_{P1} are indirect causes of V_{P2} .

Thus I have shown, using Woodward (2003) and Pearl's (2001; 2009) interventionist accounts of causation, that variation in genes causes variation in hair colour, which causes variation in environmental experience, causing variation in IQ scores:

$$V_G \rightarrow V_{P1} \rightarrow V_E \rightarrow V_{P2}$$

In reactive G-E covariance cases V_G is an indirect cause of V_P , via the intermediate variable V_E .

The notion that V_G is an indirect cause of V_{P2} in reactive cases is exemplified further by Sesardic, who's paper 'Heritability and Indirect Causation' (2003) addresses cases of active and reactive G-E covariance. Sesardic also refers to G-E covariance as indirect causes of phenotypic variance in his (2005) book⁷⁷:

⁷⁷ Here Sesardic refers to G-E covariance generally, however, one can assume that passive cases are not included, as he states earlier that passive cases are not relevant to the debate, and are often excluded due to the possibility of controlling for them methodologically (p.93).

..model (1) with **no indirect causation (i.e. without G-E correlation)**... (p.118, emphasis mine)

...in the hereditarian case the danger is to mistake **an indirect cause for a direct one**. (p.121, emphasis mine)

And more particularly in reference to reactive G-E covariance cases:

I am unaware that any serious scholar ever defended the idea that the **indirect effects of Jencks-type scenarios** should be treated as heritable. (p. 95, emphasis mine)

Similarly, Block (1995) has treated reactive G-E covariance cases as situations where phenotypic variance is indirectly caused by V_G :

In the case of IQ, no one has any idea how to separate out **the direct from indirect genetic effects** because no one has much of an idea how genes and environments affect IQ. (Block 1995, p.117, emphasis mine)

Since we don't know much about how variation in environment differentially affects IQ, we can only guess about how **variation in genes differentially affects IQ indirectly, via the environment**. (Block 1995, p.119, emphasis mine)

Block and Dworkin (1976) also discuss the problem of reactive G-E covariance in relation to direct and indirect effects:

Imagine a population in which, for religious reasons, all red-haired children are given a near-starvation diet. Then, since such a diet can affect height, **differences in hair-color genes would indirectly cause differences in height**. (Block & Dworkin 1976, p.481, emphasis mine)

So as illustrated by the interventionist account and supported by the writings of Block (1995), Block and Dworkin (1976), and Sesardic (2003; 2005), reactive G-E covariance cases display an indirect causal structure, where V_G causes V_P via V_E .

6.3 Active G-E Covariance: Parallel Causal Structure

In the above section I demonstrated how reactive G-E covariance cases have an indirect causal structure: $V_G \rightarrow V_{P1} \rightarrow V_E \rightarrow V_{P2}$, where variation in a phenotype is indirectly caused by variation in genotype, via a systematically biased variation in the environment. I will now show that active G-E cases follow the same kind of causal structure.

To do this I return to the example summarised in Table 6.1, but with some supplementation. This time there is another gene that is linked to the hair-colour locus, meaning that the two genes are likely to be inherited together and associated within a population. Imagine that, due to linkage, the brown-haired G1 children are homozygous dominant (BB) at the BSP locus –which means they have genes which engender a love for the musty smell of books. Red-haired G3 children are homozygous recessive (bb), so they do not possess the variant that make books smell attractive. Instead the opposite occurs, and their olfactory response to book-smell is disgust, so they avoid books at all costs. Auburn-haired G2 children are heterozygotes (Bb) – meaning they have no preference or aversion to book-smells. Based on this, G1 children are compelled to seek out and surround themselves with books, G2 children are indifferent, and G3 children actively avoid them. As a result, the three genotype groups develop in different environments with respect to books (V_E). Thus V_G and V_E are correlated because of the active environmental modifications of the children: active G-E covariance.

Because of the correlated difference in environment (V_E), the book smelling children end up spending a larger amount of time reading books and learning their contents, which aids them in the skills needed to perform on the IQ test. G3 children avoid books at all costs and so fail the comprehension component of the IQ test, resulting in a below average

score.⁷⁸ As a result, G1 children are measured as having higher IQs than G2s, and G2s higher than G3s.

In this situation variation in genotype (V_G) causes variation in book smelling preference (V_{P1}) which causes variation in the number of books in the environment (V_E), in turn causing variation in IQ scores (V_{P2}). According to Pearl's criteria (given in section 3.2.3) and the transitivity of causation, V_G is an indirect cause of V_{P2} in this example, paralleling the causal structure in reactive G-E covariance cases. This was shown in Figure 6.3.

Like with reactive G-E covariance, the idea that V_G indirectly causes V_P in active cases is supported by the way that philosophers have treated these types of examples. For instance Sesardic's general claims about G-E covariance, given in section 6.1.2, also refer to active G-E covariance as being indirect, and his 2003 paper 'Heritability and Indirect Causation' refers to both active and reactive cases. Similarly, Block (1995) titles one of his subheadings 'Indirect Heritability' (p.115) and assesses both reactive and active G-E covariance examples. More specifically, when referring to active G-E covariance, Block (1995, p.119) asserts:

Without an understanding of how the environment affects IQ, we simply have no way of determining how much of the variance in IQ is **indirect genetic variance**' (emphasis mine)

Similarly, Block and Dworkin (1979, p.479) refer to active G-E covariance, where:

'Big **environmental differences, caused by genetic differences**, may have a large effect on intelligence.' (emphasis mine)

Lastly, Sesardic (2003, p.1006) recognises the causal similarity of reactive and active G-E covariance: 'I do not want to suggest that active and reactive covariance differ intrinsically from one another with respect to their causal status...'

⁷⁸ Most standardised IQ tests include both a verbal comprehension component, which focuses on language skills, as well as a 'culture fair' component which is devoid of language based tasks. I am assuming for this example that the test given included a language component which affected the final scores.

6.4 Passive G-E Covariance: Causal Differences

Unlike the active and reactive cases, passive G-E covariance appears to fit a different causal structure. Recall that when passive G-E covariance occurs an individual inherits both her genetics and part of her environment from her parents, meaning that both genes and environment are correlated (or covary).

For instance a child may inherit genes from their parents that help them to enjoy and excel at reading. Parents with this kind of genotype are likely to enjoy and excel at reading themselves, and are thus more likely to provide their child with books and spend time helping them to read. The child's environment is correlated with their genetics, both of which facilitate reading skills. As a result this child may have above average reading skills compared to other children (example from Scarr & McCartney 1983). This could work in the other direction also: a child may inherit genes which are not conducive to reading ability, and also inherit a parental environment lacking in books and reading time. If these two children (or groups of children like these) were compared in a heritability study, it would appear that reading ability is heritable, as V_G and the correlated V_E accounts for the V_G portion of at least some of V_P .

To translate this into the example from chapter 2, the details of the study would have to be amended slightly, so that the children are no longer laboratory clones adopted out to homes in a fully-factorial design. Instead children with a particular genotype would need to be raised by biological parents. G1 children may be raised by parents with a great interest in books, G2 children by parents who are less interested in reading, and G3 children by parents who ban books in the home. In this situation the home environment correlated with the children's genotype varies systematically in its access to books.

In this example the child's educational environment is not indirectly caused by their genotype, like in active and reactive G-E covariance. Instead it is an effect of her parent's phenotype, which we will assume is at least partly caused by their genotype. The correlation in this case does not occur because a child's genes (cG) cause their developmental environment (E), but because their parent's genes (pG) cause the child's developmental environment (E), via the parent's phenotype. As such, the parent's genotype (pG) is correlated with the genotype of the child (cG). Both cG and E are independent causes of the IQ phenotype (P_2), and of hair colour (P_1) in passive G-E covariance cases.

This causal underpinning is recognised by Sesardic (2003, p.1004): 'It is called "passive" because neither the children's behavior nor their genotype is a causal factor that could account for the correlation', and is represented in Figure 6.4a).

When translated into groups of children and measures of variance, we can see that variance in IQ (V_{P_2}) is an effect of two causally independent variables: the children's genetic variance (cV_G) and variance in their developmental environments (V_E). Variance in hair colour (V_{P_1}), being a genetically determined trait, is a result of only the children's genetic variance. As variance in the children's developmental environments (V_E), is caused in part by differences in their parents genotypes (pV_G), and differences in parental genotypes (pV_G) are correlated with the genotype of the child (cV_G), a correlation between cV_G (just V_G in heritability studies) and V_E occurs. This is shown in Figure 6.4b).

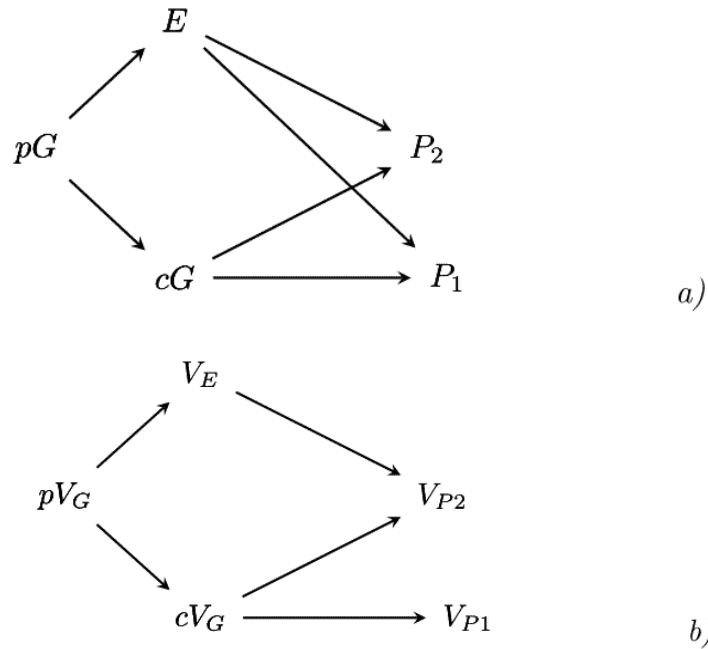


Figure 6.4 The Causal Structure of Passive G-E covariance a) shows the causal relationships in a token case of passive G-E covariance, where a parents genotype (pG) causes the child's genotype (cG) and their developmental environment (E). IQ (P_2) is affected by both the child's genotype and environment. Hair colour (P_1) is also affected by both the environment and the child's genotype, as in token cases both are considered as causes. Figure b) shows the causal relationships involved in producing phenotypic variance in a population. Variance in parental genotypes (pV_G) causes related variance in their children's genotypes (cV_G), as well as in the child's environment (V_E). Both variance in children's environment and in their genotypes causes variance in IQ (V_{P2}), but only variance in genotype causes variance in hair colour (V_{P1}).

Intervening on cV_G would change the value of V_{P2} , independently of V_E . Likewise an intervention on V_E would change the value of V_{P2} , independently of cV_G . An intervention on cV_G would also change the value of V_{P1} , while an intervention on V_E would not change the value of V_{P1} .

Because the V_G and V_E variables are causally independent, they are in principle separable through modification of experimental designs. Namely, adoption studies and/or cross-fostering methods would break the correlation between pV_G and V_E by raising children in

environments without their biological parents.⁷⁹ In these cases a correlation between cV_G and V_E would no longer occur, as there is no causal influence from pV_G to V_E .

6.5 Direct and Indirect Causes

I have shown in sections 6.1-6.4 that both reactive and active cases of G-E covariance display an indirect causal structure, where V_G causes V_E , causing V_P . Recall from the beginning of this chapter, and from chapter 4, that the current consensus on the interpretation of G-E covariance is that reactive cases with high H^2 should have any resulting V_P attributed to V_E (Table 4.1, p.139). But why is the phenotypic variance in reactive G-E covariance so obviously environmentally derived? And why are the non-covariance cases with high H^2 's so evidently genetic? One response is that because V_P in active and reactive G-E covariance cases is indirectly caused by V_G and more directly caused by V_E , the more proximal causes – V_E in this case - are the more 'important' causes of V_P .

Although causation is generally recognised as a transitive relation it appears that in cases where the causal influence of V_G is mediated by V_E , people are less likely to say that V_G is causally responsible for the differences in phenotype. This may point to some general intuitions about the directness or proximity of causes being more intuitively important for an effect.

6.5.1 Block and Dworkin on Indirectness

This kind of solution has been advocated by Block and Dworkin (1976) and later by Block (1995), who were motivated by both active and reactive G-E covariance cases⁸⁰. Block

⁷⁹ The practical problems with such studies have been discussed in section 4.2.1, however, the application of these ideas, and the translation of thought experiments to practicable empirical studies is not the focus of this chapter.

(1995) believes that reactive G-E covariance cases are in ‘violent conflict’ with ‘ordinary socially important ideas of causation’ (p.116), and that V_P resulting from any type of G-E covariance should be discounted from the V_G term (Block 1995, p.118).

To distinguish acceptable measures of heritability (where no G-E covariance is involved) from unacceptable measures of heritability (where G-E covariance is present), Block introduces the terms ‘direct heritability’ and ‘indirect heritability’. Direct heritability describes cases where active and reactive G-E covariance are absent and indirect heritability when they are present.

Similarly, Block and Dworkin (1976, pp.480-481) distinguish between direct genetic effects and indirect genetic effects:

We shall call the effect of a gene on a phenotypic characteristic a *direct* genetic effect just in case the gene affects the characteristic by means of an internal biochemical process initiated by its product. A gene affects a characteristic *indirectly* when it produces a direct effect which in turn produces or affects a feature of the environment (including the immediate environment) which itself affects the characteristic’. (Block & Dworkin 1976, pp.480-481)

Before getting into the details of this distinction, it must be noted that Block and Dworkin make the mistake of conflating the causal relationship between gene and phenotype with the causal relationship between genetic variation and phenotypic variation⁸¹. To be charitable, the above statement can be amended to read:

We shall call the effect of **genetic differences** on **differences in** a phenotypic characteristic a *direct* effect just in case the **differences in genes** affects the **variation in** a characteristic by means of an internal biochemical process initiated by its product. **Genetic variation** affects **variation in** a characteristic *indirectly* when it produces a direct effect which in turn produces or affects a feature of the environment (including the immediate environment) which itself affects **variation in** the characteristic. (emphasis mine, indicating changes to text)

⁸⁰ In text they refer to phenomena (1) which is an active case, and (2) which is a reactive case. See pp. 479-480 of Block and Dworkin (1976).

⁸¹ For more detail on this distinction refer back to chapters 2 and 3.

Now that I have characterised the problem in the language of heritability – causes and effects of *variation* – the argument can be examined more closely.

6.5.2 Why Privilege Direct Causes?

Missing from Block (1995) and Block and Dworkin's (1976) account is an explanation as to why direct causes should be privileged over indirect ones. More recent literature on causation in biology (Woodward 2010) has examined the relationship between proximity and causal explanation, and these ideas can be invoked to support Block and Dworkin's position. In chapter 3 I introduced some criteria that have been used to causally privilege, or at least to explain, the causal attribution of some variables over others. Section 3.5 described two causal dimensions that have been used in this way: stability and invariance. In this section I will illustrate the relationship between proximity and stability, which could be used as a motivation to causally prioritize proximate causes over distal ones.

Proximate causal relationships are those which concern relata that are closely causally connected in space and/or time. This is opposed to distal causal relationships where the relata occur further apart. The term proximate has also been used by Mayr (1961; 1988; 1993) who distinguishes between proximate and ultimate causes to describe different types of explanations within biology. This is not the meaning of the term proximity used here. Instead of a proximate-ultimate distinction, I am using a proximate-distal distinction. The causal relata in the proximate-distal distinction are variables within the same causal system, and are used at the same level of explanation. This differs from Mayr's use, in which proximate and distal causes of a given effect act at different levels of explanation and have different biological methods and disciplines associated with each.

One feature of proximity in causal systems is that the more proximal a cause is to its effect, the fewer 'steps' or 'links' there are in the causal process between the two. This is related to the stability concept, introduced in chapter 3, which concerns the degree to which a

causal relationship holds under changes to variables outside of that relationship. If the generalisation ‘C causes E’ continues to hold under a large amount of changes to the values of other variables which form part of the causal background of the relationship, then the generalisation is highly stable. Woodward (2010) notes that the degree of stability of a causal relationship is partially dependent on the number of links in its causal chain, that is, its proximity. This is because the more distal C and E are from one another, the more intermediate steps there are between them, and the more intermediate links between those steps. Each link can be assessed on its own for its degree of stability – depending on how it survives changes to the causal background. The more links put together, the more chances that the causal relationship could be disrupted by a background perturbation. Given this, the more distal a causal relationship, the less stable that relationship is likely to be.

As with other dimensions of causation, Woodward does not claim that more stable causal relationships are more ‘causal’ than less stable ones. However he does think that stability is a feature that may explain different attitudes about causal attribution and priority (Woodward 2006). Given that the more proximate a relationship is, the more likely it is to be stable, stability may give reason to privilege proximate causal relationships above distal ones. As Woodward asserts:

Thus to the extent that we value finding stable causal relationships, we will often be able to accomplish this goal by looking for more proximate causal relationships that mediate distal relationships. (Woodward 2010, pp. 294-295).

However, quantification of the number of causal links, which are integral to the assessment of proximity, and can affect stability, depends upon on the way in which variables in the causal system are described. Particularly, the proximity of a cause to its effect is relative to the fineness-of-grain of the variable descriptions.

To illustrate, take the causal process: UV radiation causes skin to darken. In this case UV radiation causes skin to darken by causing the body to produce dark pigment (melanin) in the basal layer of the skin. The causal process in this example is represented in Figure 6.5.

This process has only 3 steps, or 3 variables in the causal relation, but a more fine grained explanation of these variables is also possible. UV radiation causes the activation of melanocyte-stimulating hormone (MSH) which increases the activity of tyrosinase, an enzyme responsible for melanin synthesis (Hadley & Levine 1993). UV radiation also causes damage to DNA fragments, which in turn activates DNA repair enzymes such as photolyase, which are shown to enhance the melanogenic response (Eller et al. 1996). These factors cause the production of melanin in the basal layer of the epidermis, causing skin to darken. This is illustrated in Figure 6.6.

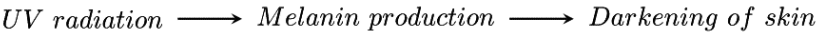


Figure 6.5 Skin Darkening with Coarse-Grained Description

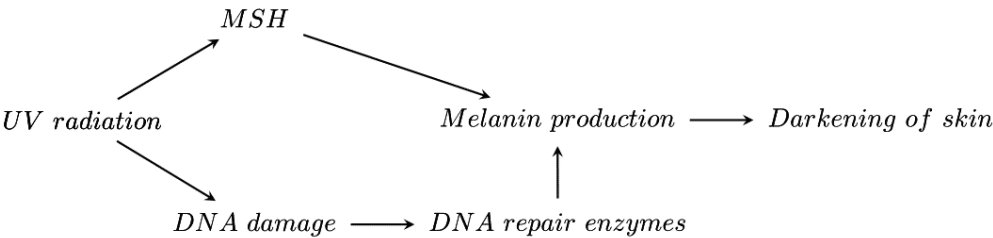


Figure 6.6 Skin Darkening with Fine-Grained Description

The latter account is still a grossly simplified version of the molecular causal process, which in turn will be less fine grained than say, an atomic level representation. However, it illustrates that both the number of steps and the causal structure of a process depends upon how fine grained ones account is.

6.5.3 How Indirect is Indirect?

The divide between proximate and distal causal relationships has a somewhat blurry boundary. There is no set distance at which a causal relationship crosses the border from proximate to distal: proximity occurs as a matter of degree. Further, the problem arises of how to categorise causal relationships that occur at small physical distances, yet the relata occur distally across time: for example the tides slowly causing the erosion of rocks. Conversely, there is the issue of how to deal with causal relationships that occur proximately in time but distally in space⁸².

Block and Dworkin recognise that the distinction between direct and indirect causes is a 'somewhat pragmatic one' (1976, p. 480). They illustrate the utility of these criteria with reference to height, first giving an example of height differences being 'directly' caused, and thus when H^2 is high, V_G can be reasonably considered to account for V_P :

Differences in genes produce polypeptides or proteins which in turn control secretion of pituitary hormone-which, in conjunction with diet and other factors, affects height – this would be direct causation. (Block & Dworkin 1976, p. 480)

They then go on to show an example of indirect causation which would also yield a high heritability measure for height. In keeping with tradition, the example involves the abuse of red-haired children:

⁸² There may be limits imposed upon this kind of causal relationship which do not apply to its converse. This is because of the physical limitations on the time that must lapse between causal relata at a given distance, given the fixed speed of light. These issues, however, shall not impact upon the discussion in this chapter, nor this thesis as a whole.

The following is an (imaginary) example of indirect causation. Imagine a population in which, for religious reasons, all red-haired children (but not other children) are given a near-starvation diet. Then, since such a diet can affect height, differences in hair-color genes would indirectly cause differences in height. (Block and Dworkin 1976, p. 481)

As this example does not fit the criteria for direct genetic causation, the effects stemming from V_G should not, according to Block and Dworkin, be counted in the heritability estimate. The criteria also apply to active G-E covariance cases, as they acknowledge (p. 481). In a case where a child modifies their environment to intellectually stimulate themselves, resulting in a higher IQ, the initial genetic basis for intellectual stimulation is counted as an indirect cause of the resulting IQ phenotype (example from Block & Dworkin 1976, p. 481). They thus conclude that in cases where a high H^2 estimate is attained, and either reactive or active G-E covariance is present, the covarying V_G should not be counted towards H^2 . Whereas when no G-E covariance is present, the resulting V_P can be attributed to V_G .

Similarly, Block (1995, p. 116) refers to Jenck's red-haired children example, where he states that:

The effect of a red-hair gene on red hair is a "direct" genetic effect because the gene affects the color via an internal biochemical process. By contrast, a gene affects a characteristic indirectly by producing a direct effect which interacts with the environment so as to affect the characteristic.

This is represented in Figure 6.7.

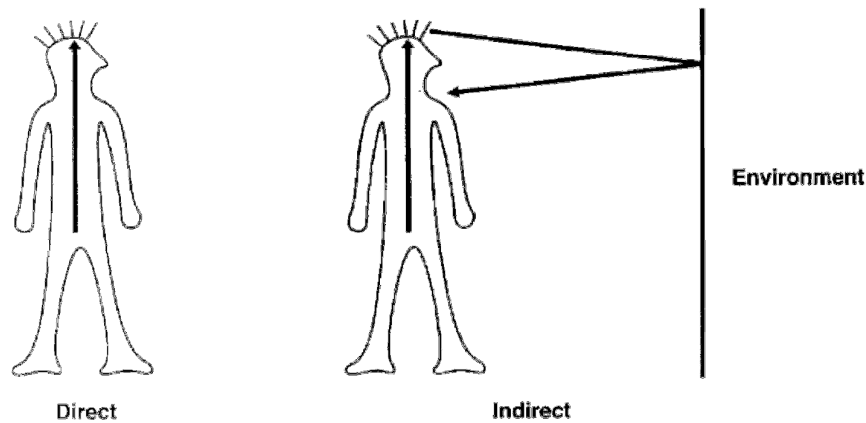


Figure 6.7 Direct and Indirect Genetic Causes (Image from Block 1995, p.116)

However, Block and Dworkins' examples seem to show a lack of biological understanding. According to their definition, for genes to be direct causes of phenotypes they must initiate a product which drives some internal biochemical process without an interaction with the environment. In a token causal relationship this is not possible, as shown by the interactionist consensus. In the language of genetic variance, it means that variation in genes must directly produce variation in some internal biochemical process in order to be a direct cause of phenotypic differences.

However, very few phenotypes arise out of these kinds of causally closed and internally limited biochemical processes. For example blood type might fit this definition, as the determinants of antigens found on the surface of red blood cells are endogenous, and can be traced to the DNA completely through internal biochemical pathways. Variation in genetics can cause variation in blood type without any related variation in the environment.

Yet we do want to make some claims about the heritability of traits other than blood and enzyme differences, and it is a widely held belief that there are many phenotypes that can be measured using heritability analyses which do not fit this definition, nor include G-E

covariance. Height is one of these, and the actual causal processes involved do not conform to the internal-biochemical definition given by Block and Dworkin.

Block and Dworkin themselves mention that in the case of height being directly genetically caused, this occurs in conjunction with diet and other causal factors. But factors like diet are not thought to influence height independently of the internal biochemical processes that result from gene expression. In Block and Dworkin's account of height, differences in genes (V_G) cause different proteins (V_{P1}) which cause differences in the secretion of a pituitary hormone (V_{P2}) which affect height (V_{P3}). All of the steps from V_G to V_{P3} are internal biochemical processes, and it is presumed that variation in diet and other factors (V_E) influence height independently from this process (Figure 6.8).

While V_G does affect height (V_{P3}) in some 'direct internal sense' through pituitary hormones (V_{P2}), it also affects things outside the organism – such as the nutrition that is received into the body. The *GHRL* gene located on the short arm of chromosome 3 produces ghrelin, a molecule that is secreted in the gastrointestinal tract. This molecule affects the hypothalamus, resulting in an appetite response, which in turn affects how much nutrition the body receives via human action in their own environment (Burger & Burner 2014). Ghrelin also affects pituitary hormone secretions which regulate growth (Howard et al. 1996; Schwartz et al. 2000). The expression of ghrelin is also mediated by environmental cues, such as over or under nutrition. These cues are themselves affected by ghrelin expression via appetite, feeding back into the causal pathway involved (Burger & Burner 2014). Further, the *GHRL* gene is variable at a population level, with multiple different SNPs at this region, and variation in this gene is thought to account for variation in height (Baessler et al. 2005; Gueorguiev et al. 2007). This means that a more accurate

picture of the causes of height variation is given in Figure 6.9

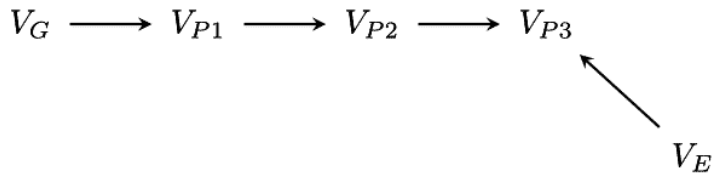


Figure 6.8 Block and Dworkin’s Direct Causes of Height Differences Variation in genes (V_G) causes variation in hair proteins (V_{P1}) which causes differences in the secretion of a pituitary hormone (V_{P2}) which causes differences in height (V_{P3}). Variation in the environment (V_E) also affects height differences, but this is an independent cause

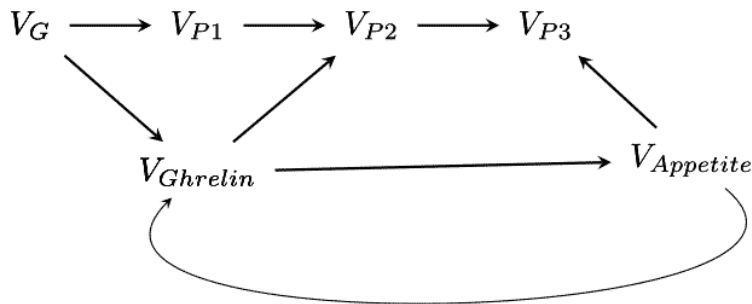


Figure 6.9 Actual Causes of Height Differences Variation in genes (V_G) causes variation in hair proteins (V_{P1}) which causes differences in the secretion of a pituitary hormone (V_{P2}) which causes differences in height (V_{P3}). V_G also causes variation in Ghrelin ($V_{Ghrelin}$), which causes variation appetite ($V_{Appetite}$) as well as variation in pituitary hormone secretions (V_{P2}). $V_{Appetite}$ feeds back on $V_{Ghrelin}$, exerting further causal influence on V_{P2} and $V_{Appetite}$

The development of height and height differences are complex processes which involve many pathways within the body, as well as constant environmental feedback from outside of it. It does not fit the internal biochemical picture that Block and Dworkin wish to propose in order to count as direct and thus heritable. Gilbert Gottlieb (1991; 1992; 1997; 1998) was one of the early proponents of the movement to recognise the complexity of

gene expression in development. He played a key role in emphasising the interactions and bi-directionality of causal factors, which he called ‘probabilistic epigenesis’. These ideas have been extended and refined by some Developmental Systems Theorists, who analysed the roles of other causal factors in development, particularly their interactions with genetic causes in the system (Griffiths & Stotz 2013; Stotz 2006; 2008).

The proposed thesis of ‘m probabilistic epigenesis’ reinterprets the central dogma (Crick 1970): that ‘genetic information’ flows in one direction, from DNA, to RNA, to the polypeptide chains of protein, resulting in a phenotype. DST authors show that other developmental factors, notably splicing and editing factors and the environmental signals that activate them, share the functional role of genetic coding sequences in determining the final sequence of gene products.

Block and Dworkin seem to have implicitly relied upon the central dogma for their direct/indirect distinction, as they appeal to a process where genes cause a polypeptide which causes a phenotype via some internal biochemical pathway. When described in the language of heritability, variation in genes causes variation in RNA, causing variation in a polypeptide, causing variation in phenotype, while environmental variation acts independently to effect V_P also (Figure 6.8).

It is now known that the environment, via splicing and editing factors and other epigenetic processes, is important in the regulation of gene expression and their phenotypic effects. All of these factors can vary in a population, producing variation in phenotypes. So the direct/indirect distinction proposed by Block and Dworkin is out-dated, given advances in molecular and developmental biology.

6.6 Summary and Conclusion

This chapter illustrated the causal differences between reactive, active, passive, and non-G-E covariance cases of heritability. Comparing the causal structures of different G-E covariance and non-covariance cases managed to distinguish passive cases from the others, and to show how reactive and active cases differed from both passive and non-G-E covariance cases. But it did not illuminate any salient factor(s) that could account for the interpretive differences between active and reactive G-E covariance, as both fit an identical causal structure.

Block (1995) and Block and Dworkin (1976) suggested that the direct and indirect criteria be used to distinguish different types of heritability. Direct heritability encompasses phenotypic variation that has been caused by genetic variation when no G-E covariance is present, and indirect heritability when active or reactive G-E covariance is present. They argue that any V_P resulting from indirect genetic causes should not be ascribed to V_G , but to V_E instead.

I showed that the criteria used in these accounts for direct and indirect causes was outdated, and is unlikely to be present for many heritable traits, including the height example they themselves used. Further, missing from Block (1995) and Block and Dworkin's (1976) accounts was an explanation of why reactive and active cases differ in their interpretation. While reactive cases are uniformly acknowledged to be problematic for H^2 , and it is thought that any resulting V_P should be attributed to V_G , the response for active G-E covariance is not consistent in this way. As described in section 4.3.3, some believe that the resulting V_P should be encompassed as V_G , and some that it should be considered an additional source of variance. This means that there is something different about active G-E covariance cases compared to reactive G-E covariance cases. By lumping them together

as indirect causes that should be excluded from heritability, Block and Dworkin have overlooked this difference in interpretation.

This chapter has made the first step in identifying the factors that contribute to the way that different G-E covariance cases are interpreted. The underlying causal structures seem to play some role, as they distinguish passive and non-G-E covariance cases from active and reactive ones. However, an explanation is still needed to account for the differences in interpretation between reactive and active cases, and to account for the differences in interpretation within active cases alone.

The next chapter (7) gives an account of why active and reactive cases appear different in regards to causal attributions. The following chapter (8) then explains why some people have interpreted active G-E covariance as problematic for H^2 , and some have not.

Chapter 7 Background Conditions

In chapter 6 I contrasted the causal structures of different types of G-E covariance cases: active, reactive, and passive, as well as a situation where no G-E covariance was present. Active and reactive cases displayed an indirect causal relationship, while passive and non-G-E covariance cases did not. This helps to explain why reactive and active G-E covariance are treated differently to passive and non- G-E covariance situations, but fails to explain the interpretative differences between active and reactive G-E covariance, which were described in section 4.3.

One approach which may elucidate these differences is to consider the causal structures present within the examples themselves. In this section I will present what initially appears to be a point of difference between reactive and active G-E covariance: the way that the causal background is structured between genotype groups. Section 7.1.1 shows that for reactive G-E covariance, the causal background between genotype groups differs. Section 7.1.2 shows that for active G-E covariance, the causal background between genotype groups is the same. This illustrates a point of difference between the two: the absence or presence of variability in the causal background.

However, in section 7.2 I show how this comparative difference is eliminated by a re-definition of the causal background variables. Section 7.3 shows how, under a coarse-grained description of environmental variables, G-E covariance cases relate to $V_{G \times E}$. Thus by looking at the causal structure (under this particular level of description), the relationship between the two major limitations of heritability estimates, $V_{G \times E}$ and G-E covariance, is illuminated. This is useful as it shows that most G-E covariance examples are limited to a single environment, minimizing V_E , which was argued in section 3.5 to be a limiting factor for heritability in terms of explanatory depth. When multiple environments are introduced (conceptualised at this level of description), active and

reactive G-E covariance can be reformulated as an instance V_{GxE} , which may be more easily detected than G-E covariance.

Although this is a useful discovery, the original question concerning the differentiation of active and reactive G-E covariance cases is not answered by an appeal to causal background conditions when they are described in such a way. I argue in section 7.4 that the coarser-grained description used in section 7.2 is not an appropriate level of explanation for G-E covariance cases, as it does not satisfy Woodward's (2010) proportionality principle. The variable description in section 7.1 does fulfil the conditions for proportionality, and as such it can be argued that it is the most appropriate description of the causal system. Given this, a difference between active and reactive G-E covariance cases can be found by looking at differences in the causal structures within active and reactive examples.

An alternative approach to clarifying these differences is given in section 7.5, where I return to some of the psychological factors introduced in chapter 3 that have been shown to influence causal attribution. I argue that an additional difference between active and reactive cases lies with the presence of another blame-worthy agent in the system, where active G-E covariance cases have no other blameworthy agent, whereas reactive cases do. As such, this chapter illuminates the factors that account for interpretative differences between active and reactive G-E covariance.

7.1 Differences in Background Conditions

In the Jencks-style reactive G-E covariance examples (at least) two genotype groups are compared: red-haired children and non-red-haired children. In the example used in the last chapter I extended this to three genotype groups (G1, G2, and G3), which corresponded to

red, auburn, and brown-haired children. For ease of explanation in this chapter I will revert back to a comparison between just two genotype groups: red-haired and blonde-haired children. Here genotype G1 represents red-haired children, who have low IQ scores, and G2 represents blonde-haired children, who have average IQ scores. For later reference, this is displayed in Table 7.1.

Genotype Group	Hair Colour	IQ scores
G1	Red	Low
G2	Blonde	Average

Table 7.1 Example Results

7.1.1 Reactive G-E Covariance

In the reactive version of this scenario, red-haired children perform poorly on the IQ test because of the prejudice they receive in reaction to their hair colour. This prejudice results in abuse and a denial of educational resources in their environment, which affects their scores. Blonde-haired children are not subject to this kind of prejudice or lack of resources, and so out-perform the red-haired children on the IQ test.

In this example of reactive G-E covariance, common sense causal attributions conflict with the high H^2 result – where V_G largely accounts for variation in IQ. A ‘common sense’ or more agreed-upon heritability estimate in this case would be achieved if the effect of V_G on

IQ was studied in a population of children, *none* of whom had been abused and subject to educational neglect. That is, the IQ scores of red-haired and blonde-haired children should be compared making sure that both genotype groups have equal access to social and educational resources. This more ideal situation involves a change to the background conditions between groups, as for one group prejudice is apparent, and in the other it is not. Controlling for educational limitation and prejudice, which are causal background variables, would allow the ‘real’ causal relationship between genotype and IQ score variance to become apparent. Conditionalising on environmental confounds in this way is common practice in experimental and epidemiological situations. For instance Tielsch et al. (1990) observed significant differences in the prevalence of blindness between black and white racial groups in Baltimore (USA), with blindness in ‘blacks’ doubling that of ‘whites’⁸³. However, Sommer et al. (1991) found a second significant difference between these two groups - the history of cataract surgery. Cataract surgery was 43% more common among white individuals than blacks of the same age. White people were much more likely to have their eye conditions operated on than those from the black group, leaving a larger proportion of black people with conditions leading to blindness. To accurately determine whether racial differences make a difference to blindness, irrespective of confounds, researchers would need to keep fixed or account for differences in the availability (due to differences in access to health insurance or other socioeconomic factors) or cultural propensity to undertake cataract surgery between the two groups.

In the reactive G-E covariance example presented at the beginning of this chapter, background variables are not the same between the two groups, and this leads to a difference in causal structure between genotype groups – shown in Figure 7.1. In this

⁸³ Although I feel uncomfortable using the terms ‘blacks’ and ‘whites’ to designate racial groups, these are the terms used by Tielsch et al. in their study, and without knowledge of the particular ethnic groups involved, I feel I cannot change these terms, for instance to ‘African American’ or ‘Caucasian’ as this may misinterpret their results.

figure G_1 and G_2 represent the two genotype groups, and P_1 represents the phenotype of hair colour, which has two values: red (r) and blonde (b). P_2 represents the phenotype of IQ, which also has two values: average (a) and poor (p). E_1 represents the educational environment of the individual, and again takes two possible values: limited (l) and not limited (-l). Lastly, the background variable E_2 represents the societal environment, which has two values: prejudiced (p) and not prejudiced (-p).

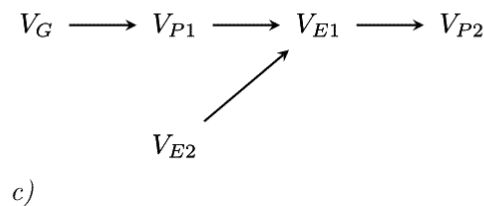
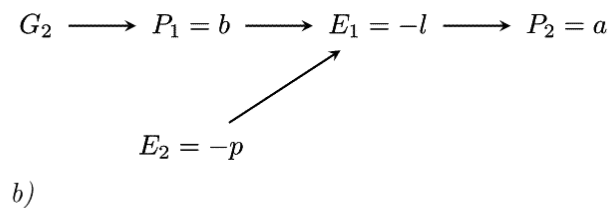
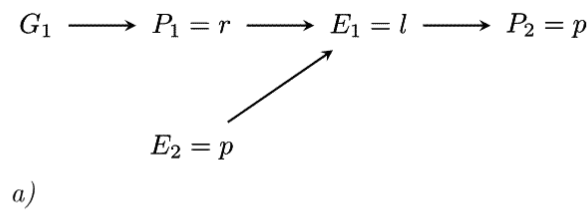


Figure 7.1. Causal Background Conditions Differ Between Groups in Reactive G-E Covariance a) illustrates the causal process in the red-haired children group, where genotype 1 (G_1) causes red hair ($P_1 = r$) which, along with a societal prejudice ($E_2 = p$) causes limited educational access ($E_1 = l$), which causes poor IQ scores ($P_2 = p$). b) shows the causal process for blonde haired children, which have a different genotype (G_2), causing blonde hair ($P_1 = b$), and as they are not subjected to prejudices ($E_2 = -p$) have no educational limitations ($E_1 = -l$) and produce average IQ scores ($P_2 = a$). c) shows how this translates into variance: variance in genotype (V_G) produces variance in hair colour (V_{P1}), which, when combined with variance in societal prejudices (V_{E2}), produces variance in IQ scores (V_{P2}).

Figures 7.1a) and b) illustrate the differences between the two genotype groups. In a) the red-haired children (G_1) are raised in a society with prejudice ($E_2 = p$), which when combined with the variable of having red hair ($P_1 = r$), limits their educational environment ($E_1 = l$). This results in poor scores on the IQ test ($P_2 = p$). In b) G_2 children have blonde hair ($P_1 = b$), are subjected to no prejudices ($E_2 = -p$) and thus have no educational limitations ($E_1 = -l$), leading to average IQ scores ($P_2 = a$).

Between these groups, there is variation in genotypes (V_G), which produces variation in the hair colour phenotype (V_{P1}). Additionally there is variation in the societal environment (V_{E2}) which, along with variation in hair colour, produces a varying educational environment (V_{E1}), producing variation in test scores (V_{P2}). This is shown in Figure 7.1c).

When causal background conditions systematically differ between two compared groups, they confound the outcome of the causal relationship between the variables of interest (V_G and V_P). In this reactive G-E covariance example it seems that the red-haired and blonde-haired children have systematically different environments imposed upon them – some are subjected to prejudice and some are not (V_{E1}). This difference in the environment could be interpreted as a difference in causal background conditions, which confounds the investigation of the causal relationship between V_G and V_P , much like the way cataract surgery confounded the causal relationship between race and blindness. This may account for the intuition that reactive G-E covariance cases are problematic - as the causal relationship under investigation is confounded, and as such any resulting causal claims about the effects of V_G on V_P are undermined.

In the cataract case the causal relationship between race and blindness was arrived at by controlling for differences in the causal background – cataract surgery. The presence of a systematically varying variable was clearly problematic for the results in the original study by Tielsch et al. (1990). This explanatory structure is paralleled in the interventionist

account of causation, where C causes E when a change in C produces a change in E, *when all other variables are held fixed* (Woodward 2003). In the reactive G-E covariance case, fixing other causal background variables such as societal prejudices should allow the causal relationship between the variables of interest (in this case V_G and V_P) to become clear. This raises the question: what to fix these other variables to? What should be controlled or eliminated, and what should be left as part of the normal causal background? Is some concept of ‘normal’ development or ‘normal’ environment required for this process?

Some philosophers (Hitchcock & Knobe 2009; Menzies 2009; Schaffer 2005) believe that invoking norms is useful for determining a causal background, and thus elucidating a causal structure. This can be problematic, given the difficulty of defining concepts like ‘normal development’ or ‘normal causal background’. Norms can be statistical, moral, social, or norms of proper functioning (Hitchcock & Knobe 2009), and these norm types do not always overlap for a particular variable. For example, in some parts of the world it is statistically normal for people to be obese or overweight, however, this is not normal in terms of the ‘norms of proper functioning’ of the human body. Given these limitations, it is unclear if variables like ‘access to cataract surgery’ should be considered part of a normal causal background for the assessment of causes of differences in blindness.

These difficulties however, should not concern us here. As long as the environment selected is not systematically biased between treatment groups it does not matter whether the background conditions are considered ‘normal’ or not. In the example above we may think it would be normal if both groups had similar access and volition to use cataract surgical facilities. If this was held fixed between both groups, the true causal relationship (or lack of one) between race and blindness could be determined. This relationship could be similarly discovered if the normal background for both groups was to not partake in

cataract surgeries. As long as the causal background between genotype groups does not systematically differ, so that there are no confounding variables, the causal relationship between V_G and V_P can be ascertained, and norms are not needed.

Similarly, in the thought experiment from the beginning of this chapter, some may think that it is normal for all children to have access to educational resources. If both red-haired and blonde-haired children were given the same access, then a relationship between V_G and IQ differences could be ascertained. It is expected in these examples that when this educational access is equal, the variation in IQ between the two groups disappears (assuming that genotype has no differential effect on IQ independently of its indirect effects via hair colour). Even though the conditions may seem less 'normal', if all children experienced abuse and had poor access to educational resources, a similar result would be reached. There would be no difference between red-haired and blonde-haired children for IQ, although the overall mean for both groups would be lower. The variation between groups in this case should be the same as if all children had ample access, meaning that the H^2 of IQ would be the same. It does not matter what kind of educational access is considered 'normal' in this situation – as long as it remains identical between groups.

To properly conduct a study on the genetic basis of IQ differences, any systematic variation (between genotype groups) in the societal environment (E_2) needs to be eliminated⁸⁴. Realistically, variation within groups would still occur. This is not problematic so long as the differences are recognised, and are not systematic between genotype groups (producing a covariation with the environment and genotype). In heritability studies the impact of different environments is often studied along with differences in genotype – as was demonstrated in the ANOVA example in chapter 2. The simplest way to eliminate the covariance between genotype and this environmental factor

⁸⁴ This would be almost impossible to control empirically, but for the thought experiment we will assume that this is possible.

though, is to imagine that in this thought experiment variation in this variable is eradicated. Either all children go to school, and are not subjected to abuse, or no children go to school, and all are subjected to abuse. Both of these situations are presented in Figure 7.2. Here, Figures a) and b) represent both groups (G1 and G2 respectively) in the first of these two scenarios, where there is no societal prejudice imparted on either group ($E_2 = -p$). As a result, both groups attain average IQ scores ($P_2 = a$), despite their differences in genetics (V_G) and hair colour (V_{P1}).

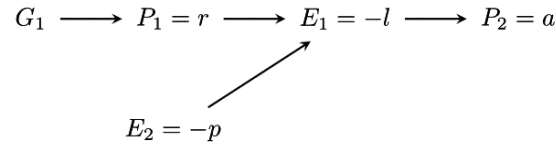
In c) and d) both groups are subjected to societal prejudices ($E_2 = p$), meaning that both groups attain the same low score average on the IQ test ($P_2 = p$). If the underlying causal structure between groups of red-haired and blonde-haired children is the same, then the causal background (E_2) is the same for G1 and G2s. This means that either both groups are subjected to societal prejudices (Figure 7.2c) and 7.2d)), or neither group are subjected to societal prejudices (Figure 7.2a) and 7.2b)).

In both cases, there is variation in genetics (V_G), and therefore variation in hair colour (V_{P1}), however, no systematic variation in societal prejudices (E_2) between groups, and thus no variation in the educational resources available to each (E_1). As a result there is no variation in IQ scores (P_2); they are either average or low across both groups. This is no longer a reactive G-E covariance scenario, and is shown in Figure 7.2e).

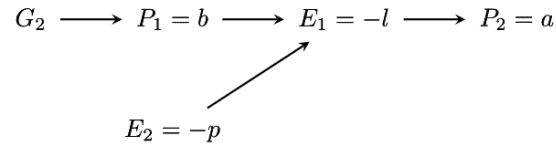
This illustrates why reactive G-E covariance seems to be so problematic for heritability studies – the examples present an implicit confound to the causal relationship under investigation. Mentioned in chapter 4, reactive G-E covariance cases are unequivocally interpreted as problematic for H^2 , with the resulting V_P being attributed to V_E rather than V_G . It appears that when reactive G-E covariance occurs there is systematic variation between genotype groups in some form of environmental variation (E_2 in this example)

which impacts the causal relationship between V_G and V_P . So it is not surprising that H^2 's for cases of this kind are rejected and deemed inappropriate or invalid.

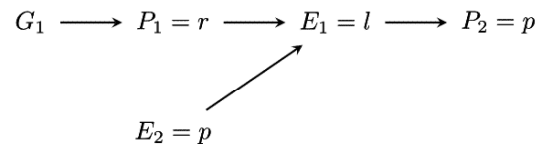
The interpretation for active G-E covariance cases are less clear, despite showing the same underlying causal structure as reactive cases (chapter 6). An examination of the differences in background conditions for active cases may help to explain this interpretation difference. This is outlined in the section below.



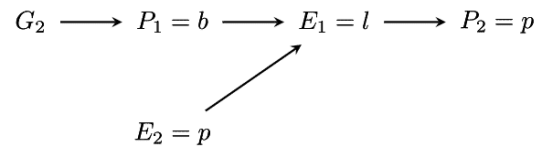
a)



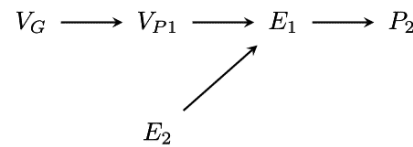
b)



c)



d)



e)

Figure 7.2 Conditionalising on the Causal Background in Reactive G-E Covariance

Educational environment (E_2) is kept the same between genotype groups G_1 and G_2 : either fixed at no prejudice ($-p$) (Figures a and b) or prejudice (p) (Figures c and d). As a result either both groups have no educational limitation ($E_1 = -l$), leading to average IQ scores ($P_2 = a$) (Figures a and b), or both groups have suffer from educational limitation ($E_1 = l$), leading to poor IQ scores ($P_2 = p$). This means that there is no difference in IQ between genotype groups, as though genotypes vary (V_G), leading to variation in hair colour (V_{P1}), the societal environment does not vary (E_2), meaning that the educational environment does not vary (E_1), and there is no variation in IQ (P_2) (Figure e).

7.1.2 Active G-E Covariance

Chapter 6 showed that active cases of G-E covariance have the same underlying causal structure as reactive ones, but do they display this same systematic difference in background variables between genotype groups? In this section I will show that at first sight it appears not, which may be the differentiating factor between active and reactive G-E covariance cases, accounting for the differences in their interpretations.

To illustrate the active G-E covariance case I will be using the example introduced at the beginning of this chapter, the results of which are displayed in Table 7.1. This time the genetic differences between G1 and G2 children not only affect hair colour, but their odour receptors. G2 children enjoy the smell of books, whereas G1 children are revolted by the smell. This leads G2 children to spend more time reading books than G1 children, and as a result they outperform G1s on the IQ test. In this example genetic variation between groups (V_G) causes variation in the level of books in the environment (V_{E1}), meaning that V_G and V_E are correlated due to the active environmental modifications of the children.

This situation is represented in Figures 7.3a) and b), where a preference for the smell of books ($P_1 = p$) in G2 children leads (through their own volition) to development in a more book-filled environment ($E1 = b$), than the G1 children. G1 children dislike the smell of books ($P_1 = -p$) and so instead develop in an environment lacking them ($E1 = -b$). G2 children perform averagely on the IQ test ($P_2 = a$), which is better than those with the non-book preferring genes (G1), who perform poorly ($P_2 = p$).

Figure 7.3c) shows this situation in terms of variance, where variance in genotype (V_G) causes variance in book smelling preference (V_{P1}) causing variance in the number of books in the environment (V_{E1}), in turn causing variation in IQ scores (V_{P2}). V_G is an indirect cause of V_{P2} in this example, paralleling the causal structure in reactive G-E covariance

cases. However, unlike the reactive scenario presented in 7.1.1, there is no variance in the causal background between the two genotype groups. In this example the background conditions (E_2) are assumed to be the same, or at least not to systematically differ between the two genotype groups. The background conditions in this example have the value n , for normal, which can be assumed in this case to mean no prejudice. Thus the causal structure between groups does not display the same differences as the structure between the two groups in reactive G-E covariance cases.

This shows how active G-E covariance differs from reactive G-E covariance. In reactive cases there are systematic environmental differences between genotype groups (Figure 7.1), which need to be held fixed (Figure 7.2) in order to see the causal relationship between V_G and V_P . However, in active G-E covariance cases these differences in the causal background are not present (Figure 7.3).

This suggests that the differences in intuition and interpretation between active and reactive cases is due to differences in how the causal background conditions systematically vary between genotype groups. In reactive G-E covariance there are other, non-genetic variables which explain variation phenotype, which differ as V_G differs. In the example used in section 7.1 this variable was the presence or absence of societal prejudice, which systematically varied between genotype groups. Variables of this kind are causal background conditions, forming part of the environment (measured as V_E in heritability estimates) which differ systematically between treatment groups. In active G-E covariance these systematic differences are not present. In the example shown in this section, both G1 and G2 children were exposed to a normal causal background, where neither were subject to societal prejudices, and both groups had equal educational access. Therefore, it seems that a point of difference between active and reactive G-E covariance is the presence (in

reactive cases) or absence (in active cases) of systematic variation in a causal background variable between genotype groups.

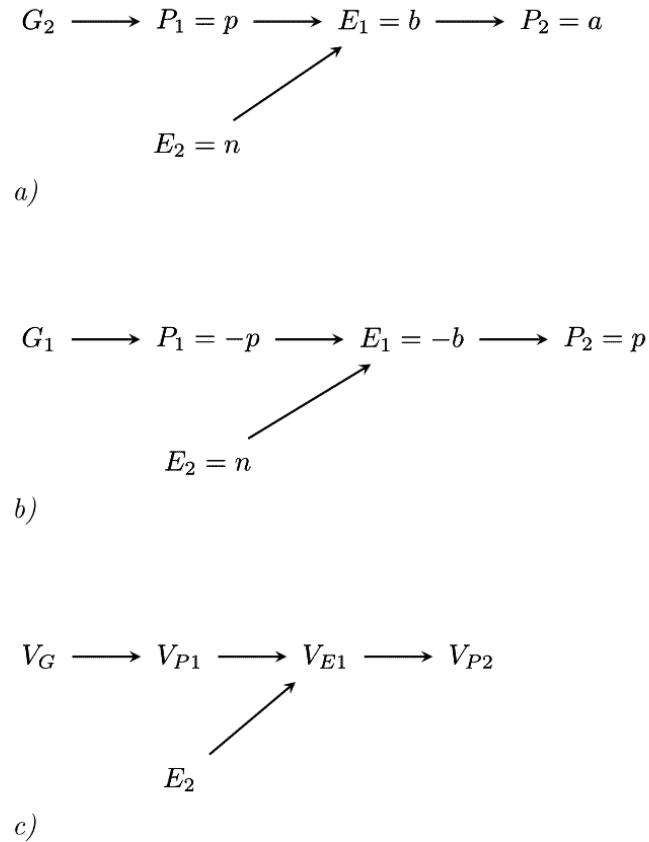


Figure 7.3 Causal Background Conditions Fixed Between Groups in Active G-E

Covariance Different genotypes (V_G : G_1, G_2) cause differences in the phenotype of book smelling preference (V_{P1} : P_1); with the values of preference (p) or no preference ($-p$). This in turn causes variation in the number of books present in the developmental environment (V_{E1} : E_1); with the values of many books (b) or not many books ($-b$). As a result there is a variation in IQ test scores (V_{P2} : P_2), with the values average (a) in the G_1 group, and poor (p) in the G_2 group. The causal background conditions (E_2) are the same between groups, with the value normal, or no prejudice (n).

7.2 A Variable Re-description

Although the section above demonstrated a difference in causal background structures between active and reactive G-E covariance cases, this point of difference can be dissipated by a re-description of the causal variables in the system. In section 7.1 there was a difference in causal background conditions (V_{E2}) between active and reactive G-E covariance cases, where V_E differed between groups in reactive but not active situations. Thus the causal structure between these two different types of G-E covariance differed. However, this is not the only way of representing the causal systems involved. I will show in this section how a re-description of these variables eradicates the distinction between active and reactive G-E covariance cases that was established in section 7.1.

A different representation of the same scenarios is shown in Figure 7.4. Here, the background variable in the system has been re-named as Norm 1. Norm 1 is the societal norm to be prejudiced against red-haired children and to abstain from granting them educational access. Societies in which Norm 1 is part of the causal background abuse and limit the educational resources of red-haired children, yet do not treat blonde-haired children in the same way. In this scenario the environment is determined at a population level, where the values of the variable are determined by how they apply to the whole population, not to particular individuals or groups within that population.

As shown in Figure 7.4a), when Norm 1 is combined with the presence of a red-haired phenotype it causes educational limitation ($E_1 = 1$), resulting in a decrease in IQ scores ($P_2 = p$) for G1 children. If a blonde-haired child was to be raised with identical background conditions then in this sense they would live in same society as the red-haired child, the society which has Norm1 (Figure 7.4b)). Thus to control for causal background conditions between groups when variables are described at the societal-norm level of explanation, both groups should live in a Norm 1 society. However, Norm 1 specifies only the abuse

and educational limitation of red-haired children, and when combined with the phenotype of blonde hair no educational limitation occurs ($E_1 = -1$), meaning that an average IQ is attained ($P = a$) for G2 children. We have now managed to represent a Jencks-style reactive G-E covariance scenario in which the causal background conditions (societal norms) between groups are fixed, and the only varying causes of P_2 are G (genotype) and P_1 (hair colour).

This is illustrated in Figure 7.4c). Variation in genotype (V_G) causes variation in hair colour (V_{P1}) which, when combined with a uniform environment (E_2 , which equals Norm 1 across both conditions, so $V_E = 0$), produces systematic variation in the educational environment of the groups (V_{E1}), resulting in variation in IQ scores (V_{P2}).

The causal structure of reactive G-E covariance displayed in Figure 7.4c) is identical to the one that was shown in Figure 7.3c), which illustrated active G-E covariance. Thus a variable re-description of the causal background using these more coarse-grained environmental variables representing societal norms illustrates that there is no difference in causal structure between active and reactive G-E covariance cases.

Therefore, under this description it seems that a difference in causal background conditions does not as a rule demonstrate a difference in the underlying causal structures between active and reactive cases, as it first appeared to in section 7.1 This is because the environmental conditions specified depend on exactly how the background conditions are defined. Under this re-description of variables, active and reactive G-E covariance cases are identical.

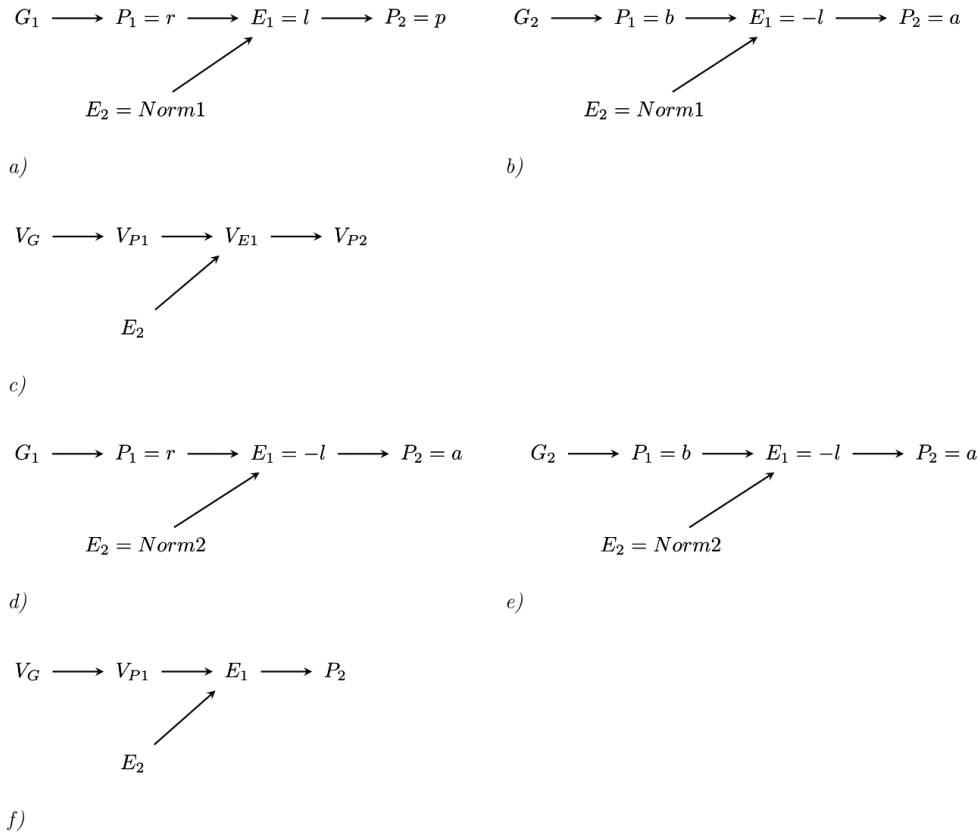


Figure 7.4 A Re-description of the Variables in Reactive G-E Covariance Cases

Different genotypes (V_G : G_1, G_2) cause differences in the phenotype of hair colour (V_{P1} : P_1); with the values of red (r) or blonde (b). Both genotype groups are subjected to the same societal norms (E_2), either Norm1 (figures a-c): where there is prejudice against red-haired children, or Norm 2 (figures d-f): where there is no prejudice against any children. In a) G_1 children develop in a Norm 1 environment, so their educational is limited ($E_2 = l$) (as they are red-haired), and they attain poor IQ scores ($P_2 = p$). In b) blonde haired children develop in a Norm 1 environment and their education is not limited ($E_2 = -l$), and they attain average IQ scores ($P_2 = a$). In d) and e) G_1 and G_2 children develop in a Norm 2 environment, where no prejudice is subjected to any children. As a result both groups have no educational limitation ($E_1 = -l$) and both attain average IQ scores ($P_2 = a$). Figures c) and f) show the differences between these two groups in terms of variance, where V_G represents variation in genotypes, E_2 represents a non-varying environment of Norm 1 or Norm2, V_{P1} represents variation in hair colour, V_E variation in environment, E_1 no variation in environment, V_{P2} variation in IQ and P_2 no variation in IQ.

7.3 A Return to Gene-Environment Interaction

We have just seen what happens when Norm 1 is maintained across the two groups, what happens if the background conditions are changed to a different societal norm? Let us say that Norm 2 is the norm for no prejudice against any children, leading to the supply of ample educational resources for both genotype groups. In this case both groups have no limits placed on the educational resources available ($E_1 = -1$), as the availability of educational resources is independent of hair colour. This scenario is shown in Figures 7.4d, e) and f). Here, V_G causes variation in hair colour (V_{P1}), however, variation in hair colour, when combined with Norm 2 (which is fixed between groups), produces no differential effects on E_1 (educational access) or P_2 (IQ). Both of these variables have the same value between the two genotype groups: $E_1 = -1$ (education is not limited) and $P_2 = a$ (IQ scores are average).

Just like in 7.4c) there is variation in genotype (V_G) and hair colour (V_{P1}), and no variation in E_1 (societal norm). However, 7.4c) (where both groups are subject to Norm 1) results in variation in E_1 and P_2 , while 7.4f) (where both groups are subject to Norm 2) results in no variation in either variable.

Figure 7.4 shows two different scenarios: in a), b) and c) the causal background conditions are both fixed between groups to Norm 1 –the norm for prejudice towards red-haired children. This results in differences in IQ between the two genotype groups as one is red-haired, and the other is not. In Figures 7.4 d), e) and f) the causal background conditions are also fixed, this time to Norm 2 –where no children are prejudiced against. This results in no differences in IQ between the two groups, as neither have their education limited. What appears to be happening when we compare cases like this is that the variation in phenotype (IQ) depends upon a combination of genotype (G_1 or G_2) and the kind of environment is present for that genotype to develop in (Norm 1 or Norm 2). Thus G-E

covariance, when considered over a range of possible background conditions (characterised at this level of description), appears to describe $V_{G \times E}$. When $V_{G \times E}$ is present variation in either genes or environments does not produce a consistent change in phenotype, as the change depends upon the given genetic and environmental background conditions. This is just what has been illustrated in Figure 7.4. An alteration to the background conditions in the form of the environmental variable E_2 , produces a change in the IQ phenotype (P_2) for some children, but not for others. A change from Norm 1 to Norm 2 produces no change in IQ for blonde-haired children, as these norms do not specify prejudice towards them either way. However, a change from Norm 1 to Norm 2 (or vice versa) will affect the IQ of red-haired children, as under Norm 1 they will receive limited educational access, while under Norm 2 this will not be the case.

In chapter 6 I described the case of PKU, where some children can digest phenylalanine, and others - with the mutation causing PKU - cannot, resulting in mental retardation. PKU is a textbook example of gene-environment interaction. This example can be superimposed onto the results shown in Figure 7.4. Instead of $E_2 = \text{norm 1}$ (shown in Figures 7.4a) and b)), imagine that $E_2 = p$ (for phenylalanine). Children with PKU (G_1) versus those without the genetic mutation (G_2) could be all subject to the same diet containing phenylalanine ($E_2 = p$). This would result in variation in IQ between the groups (G_1 children having mental retardation, as this is an effect of PKU sufferers digesting phenylalanine). In this case variation in the causal background (at the diet description) is eliminated, and a high heritability estimate is attained as the genotype groups differ in intelligence. However, there are several scenarios which would change the heritability measures in this population. If the causal background were to systematically differ between groups so that G_1 children had a low phenylalanine diet ($E_2 = -p$) and G_2 children had a higher phenylalanine diet ($E_2 = p$), then the differences between genotype groups would disappear, and the heritability estimate for IQ would decrease –such as shown in Figure 7.4c) and d).

This scenario describes a typical medical intervention. A typical heritability study would expose PKU and non-PKU carriers respectively to high, and low (or no) phenylalanine, showing a high interaction effect between PKU and phenylalanine.

Another $V_{G \times E}$ case was described in chapter 2, where environmental exposure to benzene is significantly associated with shorter gestation periods in pregnant women, depending on their genetic background. Those with the homozygous dominant (AA) genotypes for the *CYP1A1* locus had shorter gestation periods under a benzene environment than one without benzene present. However, women with the homozygous recessive (aa) or heterozygous (Aa) genotypes had no difference in gestation period times. This result is shown in the norm of reaction graph in Figure 7.5.

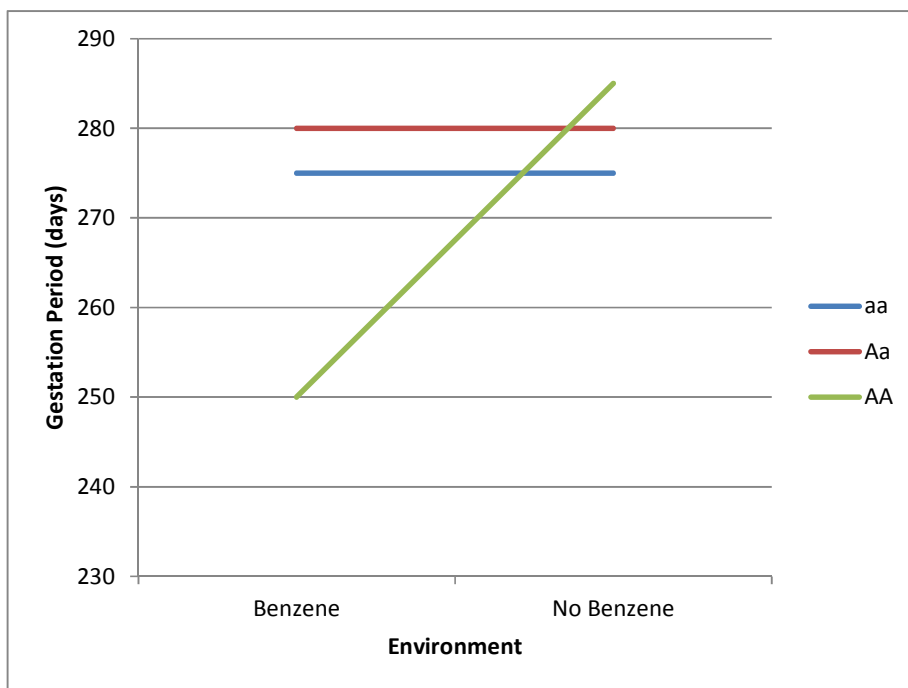


Figure 7.5 Norm of Reaction for Benzene Exposure on Three Genotypes

In this figure we can see that the reaction norms for each genotype follow different patterns, indicative of a gene-environment interaction. This is because the response to environment (benzene or no benzene) depends upon the genetic background of the individual.

Now look to Figure 7.6, which graphs the norm of reaction for the cases described in this and the last section, and illustrated in Figure 7.4.

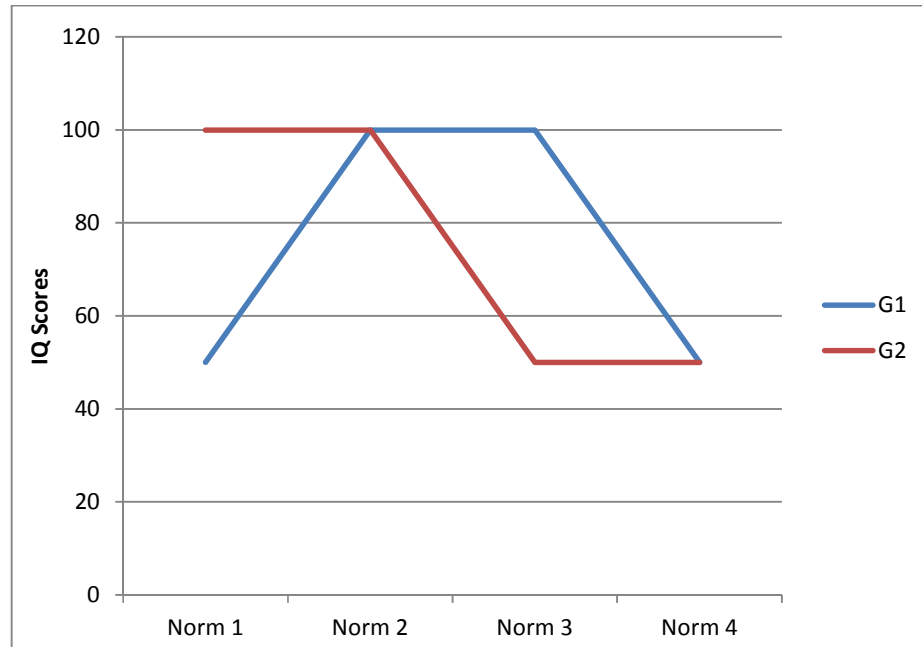


Figure 7.6 Norm of Reaction for Societal Norms on IQ scores in Two genotypes G1 represents red-haired and G2 represents blonde-haired children. The y-axis represents average IQ scores for each group, and the x-axis represents environments that differ in their societal norms. Norm 1 is a society which discriminates against red-haired children, Norm 2 is a society that does not discriminate to any children, Norm 3 is a society which discriminates against blonde-haired children, and Norm 4 is a society which discriminates against both blonde-haired and red-haired children.

Figure 7.6 shows that the examples used in this chapter also illustrate $V_{G \times E}$. G1 represents children with red hair, and G2 represents children with blonde hair. Points on the graph indicate the average IQ of the genotype groups. For the purpose of this graph we will assume that 100 is an average IQ score, and that scores below 100 indicate a poor performance.

Norm 1 shows the situation in which society discriminates against red-haired children. As a result, the red-haired (G1) children have lower IQ test scores than blonde-haired children (G2). Norm 2 shows the situation in which society does not discriminate against any children on the basis of hair colour. In this situation both genotype groups have good access to educational resources, and so both have similar IQ scores, with a mean of 100. Norm 3, although not described in section 7.3, could be a case in which society discriminates against blonde-haired children, and not red-haired ones. This is the converse of Norm 1, and results in the opposite effect on IQ scores: blonde-haired children score more poorly than red-haired children do. Lastly, Norm 4, again not described in this section, illustrates a society in which both red-haired and blonde-haired (G1 and G2) children are discriminated against, and denied educational resources. As a result, both perform poorly on IQ tests.

The same relationship with $V_{G \times E}$ can also be observed for active G-E covariance cases. In the book-smelling example, G1 children actively avoid books due to their smell, and so perform worse than G2 children who seek them out. But this phenotypic difference between genotype groups disappears if the environment is changed so that no books are present. This effect would also disappear if the materials used to make books changed, such that they had a different smell, or if paper books were replaced by electronic devices – an example that is not too abstracted from the potential future of some children. Thus if multiple environments were studied, some in which books were present and some not, then an interaction of these genotypes and the environment could be discovered.

I have shown that by using a different description of environmental background variables, the differences in causal background structure disappear between genotype groups, meaning that both active and reactive cases of G-E covariance conform to the same type of causal structures. This also demonstrated that reactive and active G-E covariance cases

illustrate part of the $V_{G \times E}$ phenomenon, as different environments produce variation in phenotypic effects which are also dependent upon variation in genotype. By trying to understand the causal structure underlying reactive G-E covariance cases I have shown that reactive G-E covariance cases can be redescribed to represent part of the causal scenario involved in a case of gene-environment interaction.

The difference between $V_{G \times E}$ and G-E covariance is that $V_{G \times E}$ looks at the effects of multiple environments (or values of an environmental variable) in interaction with genetic differences on phenotypic outcomes, whereas G-E covariance describes a situation where just one environment (or one value of an environmental variable) is studied. In Jenck's example only one society was examined – the one where red-haired children were abused, so the interaction of the red-hair genes and this societal variable were not apparent. In chapter 3 I examined the relationship between heritability and explanatory depth, and concluded that the depth of a heritability claim depended (at least partially) upon its invariance. This could be assessed by studying different genotypes and environments, and seeing if they had similar relationships to phenotypic differences. The larger extent that a phenotype has been studied - in terms of different genotypes and environments factoring into heritability estimates - the more reasonable it will be to take causal claims about the heritability of this trait as type or general. $V_{G \times E}$ is problematic for general heritability claims, as the causal relationships depend upon differences in the values of genetic and environmental variables.

When described using this kind of environmental variable (societal norms) active and reactive G-E covariance provides a snapshot of $V_{G \times E}$, illustrating the reaction of different genotypes in just one environmental value (e.g. either Norm 1 or Norm 2). These cases have been thought to be problematic for the causal attributions made in heritability estimates, and this chapter may provide a clue as to why. $V_{G \times E}$ affects the stability of the

causal relationship in H^2 , meaning that claims about the relative effects of genetic and environmental variation are not stable over different environments and genotypes. If G-E covariance is a subset of this problem, then it makes sense that it is also problematic for causal claims about the heritability of a trait – as that H^2 estimate cannot be extrapolated across other environments. Thus like $V_{G \times E}$, active and reactive G-E covariance cases are problematic for heritability because of the extrapolation potential and explanatory depth of the causal relationship involved.

7.4 Which Description is Best?

At the beginning of section 7.3 I mentioned that the causal background conditions could be re-described, which I have shown in the section above eliminated the differences between genotype groups. This means that under one level of description (section 7.1) the genotype groups do differ in environmental background conditions, whereas under another level of description (sections 7.2 and 7.3) they do not. So which description should be used? How can one determine the more appropriate or best way of representing the variables in the causal background conditions of the system?

It could be argued that variables like societal prejudice are too broad for the assessment of the causal relationships involved in G-E covariance, and should instead be assessed at a more individual-specific level, such as those suggested in section 7.1. Since values like Norm 1 are defined by their biased treatment towards different groups, and the effect studied is phenotype differences between groups, it seems problematic to ascribe variation of this kind to a single value – like Norm 1 or Norm 3.

To further illustrate this point, imagine a heritability study in plants, in which two different plant genotypes (G1 and G2) were grown under different nutrient conditions. Imagine now

that in this situation the environmental variable was not defined as degrees of nutrient supply, but described as norms. Norm 1 could be that G1 plants receive high nutrient supplies, while G2 plants received low nutrition. In this case Norm 1 fixed across both groups would lead to differences in nutrition to the different plant genotypes, resulting in phenotypic differences in growth. In this case, differences in height could not be attributed to differences in an environmental condition – as Norm 1 is fixed between treatment groups. Instead, height differences would be attributed to differences in genotype.

Yet it does not seem right to ascribe height differences to differences in genotype, when differences in nutrient supply appear to have made a difference between groups. Common-sense intuitions in this case indicate that the background conditions of nutrient level make a difference to plant height. Similarly, in the reactive G-E covariance scenario, the difference maker seems to be societal prejudice. G1 children are subject to prejudice, whilst G2 children are not, leading to differences in IQ scores. Section 7.2 attempted to re-describe these differences as norms, eliminating differences between groups, but this does not seem to be the right level of description for environmental background variables.

In an attempt to provide a more sound basis for appropriate levels of explanation, Woodward (2010) has outlined a proportionality condition (P), which defines a cause that is neither inappropriately broad or general, nor overly narrow:

(P) There is a pattern of systematic counterfactual dependence (with the dependence understood along interventionist lines) between different possible states of the cause and the different possible states of the effect, where this pattern of dependence at least approximates to the following ideal: the dependence (and the associated characterization of the cause) should be such that (a) it explicitly or implicitly conveys accurate information about the conditions under which alternative states of the effect will be realized *and* (b) it conveys *only* such information – that is, the cause is not characterized in such a way that alternative states of it *fail* to be associated with changes in the effect. (p.298)

Woodward refers to an example taken from Yablo (1992) where a pigeon is trained to peck at a target when presented with any shade of red. Given this, Woodward presents two possible causal explanations:

(3.1) The presentation of a scarlet target caused the pigeon to peck.

(3.2) The presentation of a red target caused the pigeon to peck. (Woodward 2010, p.297)

Claim (3.2) in this case is the most appropriate causal explanation, as (3.1) fails to convey the relevant detail that any shade of red will cause the pigeon to peck. Under (P), (3.1) fails condition (a), as it fails to specify alternative states of affairs where the effect will be realised (like the presence of other shades of red), and it also fails (b), as (under what Woodward calls the “natural interpretation”) it suggests that changes from scarlet to non-scarlet may affect the occurrence of pecking.

To apply this to the reactive G-E covariance case the two options are:

(1) An environmental value of no prejudice causes average IQ scores in G2 children.

(2) An environmental value of Norm 1 (where red-haired children are prejudiced against) causes average IQ scores in G2 children.

Claim (1) seems in this case to fulfil the criteria given in (P), as it conveys (a) the conditions under which alternative states of the effect will be realised – if prejudice is present then the G2 children will have low IQ scores rather than average ones. In this example it seems natural that the contrast class for (1) is prejudice, and a change to this value will produce a change in the effect. This claim also fulfils condition (b), as it does not contain any other irrelevant information.

Claim (2) on the other hand fails (P) under condition (a), as it does not convey how G2 children will have low IQ scores – the contrast class for Norm 1 it is not clear. If contrasted with Norm 2, in which no children are subjected to prejudice, then the effect will still not

change. Norms 3 and 4 will change the value of the effect (IQ scores for G2 children), but it is not obvious that these are the contrasts for this causal claim. Additionally, claim (2) fails condition (b) of the P criteria, as irrelevant information is included in the claim. Claim (2) relates to IQ scores of G2 (blonde-haired) children, yet the explanation of these scores (Norm 1) encompasses information about the treatment of red-haired children.

Thus the most appropriate description of background variables is those given in section 7.1, where E_2 was defined as the presence of prejudice or no prejudice, and differed between genotype groups. This description of E_2 includes the relevant amount of detail to explain differences in educational environments (E_1), which was not given by a re-description to norms (sections 7.2 and 7.3). This shows that a proportionality consideration is needed for distinguishing appropriate environmental descriptions, and clarifying what kind of environmental variables are included in the causal model.

7.5 An Alternative Account: Agency and Blame

Looking at the causal background conditions under a coarse-grained, population level description provided an insight concerning the relationship between G-E covariance and $V_{G \times E}$. However, it did not solve the original problem of distinguishing active and reactive G-E covariance cases. Under the more narrow, and as shown above, more proportional, environment description of the causal background given in section 7.1, these two types of G-E covariance appear different.

In support of the findings from 7.1, an alternative approach for distinguishing active and reactive cases is to turn to the psychological factors influencing causal attributions. In chapter 3 I described three factors that influenced the selection of causes for a given effect: agency, blame and norms. In order to see whether these impact on the causal assessment in

active and reactive G-E covariance cases, it will be useful to examine whether or not any of these factors differ between active and reactive G-E covariance examples.

To recap from chapter 3, the interpretation of causal scenarios that include an agent (such as John having car crash) are influenced by the addition of another agent into the causal system. In this example respondents were more likely to say that John caused the crash when inanimate objects like an oil spill or a tree branch contributed to the crash, rather than if another driver was involved (Alicke 1992). This work has been extended to show that it is not just agency but a *blameworthy* agent that is important for causal attribution. This was demonstrated in a vignette where John was speeding home to hide an object and was involved in a crash. Respondents were more likely to say that he caused the crash when his speeding was to hide cocaine, rather than a present for his parents (Alicke 1992). Lastly, Knobe (2006) and Knobe and Fraser (2007) demonstrated the relationship between blameworthiness and normality. They believe that blameworthiness is important for causal attributions as it illustrates a deviation from the norm – in this case a moral norm.

To return to active and reactive cases of G-E covariance, it appears that a salient difference between the two is the presence of another agent. In active G-E covariance cases an individual seeks out and modifies their own environment, in reactive G-E covariance cases another individual imposes an environment on them. Block and Dworkin (1976) have hinted at the importance of agency in their distinction of direct and indirect effects, where:

...the causal path from gene to characteristic passes through the behaviour of *other* persons (as in the example of discrimination against red-haired children)... (pp.481-482)

This seems evident from the examples used in this and the last chapter. In the active scenario individuals seek out different educational environments depending on their allelic form of the *BSP* (book smelling preference) locus. G2 children enjoy the smell of books and so end up in a more book filled environment, leading to a better IQ score than G1s

who actively avoid books. In this case no other blameworthy agents are involved in the assignment of environmental differences between groups. In the reactive example society reacts differently to G1 and G2 children based on their hair colour, withholding or providing educational environments accordingly. In this situation there is another blameworthy agent involved, maybe many of them – the individuals in the environment making these environmental decisions for the children.

To illustrate this further, take the following two scenarios:

1. G1 children have pale skin, and because of the reaction that society has to pale-skinned children, they are attacked with hot rods and their skin is burnt whenever they go out in public. As a result, these children spend more time indoors away from their peers and develop poor social skills. G2 children, who have darker skin, are not subjected to burning attacks from outsiders, and so spend more time outside with other children, developing better social skills.

This is a case of reactive G-E covariance. Differences in genotype result in differences in skin colour, which are reacted to differently in the environment (one genotype group is burnt while the other is not). As a result their environments differ, and this impacts on other phenotypic differences between the groups – social skills. Now consider the following alteration:

2. G1 children have pale skin, and because of the way that the sun reacts to pale-skinned children, their skin is burnt whenever they go out in public. As a result, these children spend more time indoors away from their peers and develop poor social skills. G2 children, who have darker skin, are not subjected to burning from the sun, and so spend more time outside with other children, developing better social skills.

This is a case of active G-E covariance. Differences in genotype result in physiological differences in the children in terms of how their skin burns. As a result they make active modifications to their environments, which differ, as G1 children must avoid the outside while G2 children do not. These environmental differences impact on other phenotypic

differences between the groups –social skills. The point of difference between cases 1 and 2 is the presence of a blameworthy agent. In the reactive example (1) other individuals are responsible for the burning of the pale-skinned children. In the active example (2) it is the sun, which is not an agent, and is responsible but cannot be assigned blame in any meaningful way.

Agency and blameworthiness may be related in these instances to the invariance of the causal relationships involved. The relationship between the sun and skin burning is highly invariant: few interventions on the sun would be able to prevent skin burns (although interventions on the skin such as sun-screen might). As a contrast, people in society may be manipulated or intervened upon to change their attitudes and behaviours towards pale-skinned children.

7.6 Summary and Conclusion

As shown in chapters 4 and 6, there are differences in causal intuitions and interpretations of different types of G-E covariance. Thus it seemed natural to examine G-E covariance at the causal level. Chapter 6 showed how passive G-E covariance differed from active and reactive types in its underlying causal structure. This did not account for why differences in interpretations still exist for active and reactive cases. This chapter aimed to find a difference between the two. I began by showing that the causal structures between genotype groups differed in each type of example (section 7.1), but in sections 7.2 and 7.3 I showed that this difference depends upon the way in which the environmental variables are defined. Section 7.2 re-described these cases at a broader societal-norm level of description, which showed no difference between active and reactive cases. It also illuminated the relationship between G-E covariance and $V_{G \times E}$ (section 7.3). Active and reactive G-E covariance cases appear to be part of $V_{G \times E}$, only with a single environment

under investigation. As G-E covariance is difficult to detect, the relationship between the two may help to identify these sources of variance.

Section 7.4 argued that the finer-grained description from section 7.1 was more appropriate for the study of G-E covariance, as it fulfilled the proportionality criteria, described by Woodward (2010). In support of this difference, section 7.5 turned to an alternative account for the differences between active and reactive G-E covariance. Here I appealed to psychological factors that have been shown to influence causal attributions. I argued that while active and reactive G-E covariance cases have the same causal structures, reactive cases include the presence of another blame-worthy agent, and this accounts for a difference in interpretation and causal intuition. So far I have shown in this thesis the differences between active, reactive, passive, and non-G-E covariance cases. The information given in chapters 6 and 7 can be used to explain why interpretations and causal intuitions differ between the different G-E covariance types. However, there is a final piece of the puzzle missing for the interpretation of G-E covariance. This regards active cases. Not only can the interpretation of active G-E covariance differ when compared to other G-E covariance types, but active G-E covariance itself is subject to differences in interpretation. The reasons for these differences shall be explored in the next chapter.

Chapter 8 Phenotypic Considerations: Why Motivation Matters

The previous two chapters examined the underlying causal structures of G-E covariance cases. In chapter 6 it was found that the causal structure between passive G-E covariance cases on the one hand, and active and reactive cases on other, differed. Examining the differences in causal background conditions illustrated the incongruity between reactive and active cases, when read using a proportional level of explanation. In support of this, an appeal to a psychological factor - the presence of a blame-worthy agent - also accounts for the differences between the two. Thus chapters 6 and 7 outlined the differences between passive, reactive, and active G-E covariance. These factors combined explain why different types of G-E covariance are treated differently, but this does not account for all of the divergences in interpretation for G-E covariance. As outlined in chapter 4, there is no consensus on how to interpret active G-E covariance cases. Some believe that active G-E covariance is not problematic for H^2 , and that resulting V_P can be encompassed under the V_G term. Others believe that the resulting V_P should be partitioned differently. Additionally, some cases of active G-E covariance appear to be more problematic than others. Despite this, there has been little work investigating the reasons for these differences in interpretation.

In this chapter I give an explanation as to why some but not all active G-E covariance cases conflict with ‘common sense’ causal ascriptions. This explanation reframes the debate surrounding active G-E covariance by considering a phenotype-specific approach to these cases. I show how causal intuitions for active G-E covariance are intimately tied with the conceptual understanding of the phenotype under investigation. In particular, phenotypes like intelligence, which relate to a relatively ill-defined and ill-measured set of

cognitive capacities, are more likely to spark disagreement for the interpretation of active G-E covariance. This observation is especially pertinent as a large amount of quantitative genetic research has focussed on intelligence and related traits. This is likely to have biased the interpretation of active G-E covariance in behavioural genetics, and may be the cause of disagreement over the interpretation of active cases.

As such, when attempting to interpret heritability estimates which include active G-E covariance, one must consider conceptual aspects of the phenotypic effect being measured. I contend that philosophical disagreement about causal attributions in active G-E covariance cases are in essence disagreements regarding how a phenotype should be defined. This moves the debate from one which concerns causal attributions and appropriate heritability models, to one concerning the conceptual definition of ambiguous phenotypes like intelligence.

8.1 The Heritability of Intelligence

Intelligence is the most widely studied phenotype in behavioural genetic research (Plomin & Spinath 2004). It is firmly established that intelligence plays an important role in human development and individual differences. Intelligence has been correlated with job performance (Schmidt & Hunter 1998), education (Lynn 2010), income (Lynn 2010), health (Gottfredson & Deary 2004), lifespan (Deary 2005; Gottfredson & Deary 2004), and happiness (Ali et al. 2013; Wilson 1967). Some claim that this is because differences in intelligence underlie the variation of numerous other phenotypes, claiming that:

...no matter the cognitive task being undertaken, much of the human variation in any cognitive task will be caused by people's differences in general intelligence (Davies et al. 2011, p. 997)

Some researchers have argued that an understanding of the heritability of intelligence will lead to better understanding of the efficacy of interventions, such as education (Herrnstein & Murray 1994; Jensen 1969). If intelligence has a low heritability, then environmental differences have a greater influence on intelligence differences than genetic variation. As such, environmental interventions such as education programs directed at those on the lower end of the scale may be able to ‘bridge the gap’, reducing overall intelligence differences.

This was the motivation of Alfred Binet (1903; 1905; 1908, all cited in Gould 1996), who devised the intelligence quotient (IQ), the first standardised measure of intelligence. He did so by taking the mean scores of children of different age groups on tests of mental ability. Then, based on the assumption that older children would outperform younger ones, he assigned a mental age to each score. Children ten years of age with the mean score for a ten year old would have a mental age of 10. Ten year old children with a score below average, say a score corresponding to the mean result among eight year olds, would have a mental age of 8. Although Binet believed intelligence could be quantified, he also believed that it was a plastic trait. He intended for its quantification to be used to selectively focus on children who were below the mean mental age, in order to try to improve their scores and cognitive abilities. Binet warned against a hereditarian interpretation of IQ, and believed that IQ scores did not reflect fixed limitations in an individual’s capacity.

Despite Binet’s ambitions the hereditarian attitude that intelligence is a fixed and heritable capacity predominated throughout the 19th Century, and this attitude was applied to the interpretation of IQ. This was largely due to the work of American psychologists Goddard, Terman and Yerkes (Gould 1996). While Binet believed that IQ scores could, and should, be used to help identify and improve the abilities of low scorers, Goddard, Terman and

Yerkes maintained that IQ was 'inborn', inevitable, and stable, and that the tests should instead be used to support eugenic practises (Gould 1996, pp. 190, 209 & 228).

Goddard was responsible for introducing the IQ scale to the USA, where he translated Binet's articles into English and advocated the use of IQ testing. Goddard was also responsible for introducing the term 'moron' in to the American vernacular, which described individuals who scored below their age mean on IQ tests. Terman revised Binet's scale, creating the Stanford-Binet, which remains widely used and is now in its 5th edition. He also altered the scale so that average children were assigned an IQ of 100, and differences between age groups had a standard deviation of 15 points. Terman was responsible for marketing his IQ test to schools, workplaces, and along with Yerkes, the US Army.

Yerkes was responsible for distributing intelligence tests to the US Army, with 1.75 million men tested during World War 1. This population attained, on average, the IQ score corresponding to the 13 year old mean. The army contained a large number of Jewish immigrants and African Americans - who achieved the lowest scores in the group. This result was used to support eugenicist attitudes and to restrict immigration into America. Goddard, Terman and Yerkes were all staunch eugenicists who believed in immigration restrictions and proposed that breeding should be segregated based on IQ scores (Gould 1996).

These approaches are not surprising, as all three psychologists drew upon eugenic and hereditarian views stemming from Galton and Burt. Galton's 1869 'Hereditary Genius' examined the heritability of intelligence⁸⁵ by comparing the relatives of successful men across more than 300 families. He found that the further away on a family tree relatives

⁸⁵ At this time the currently used statistical heritability measures were not in place, Galton simply looked at similarities across family groups.

were from the successful ancestor (and thus less closely related), the less likely they were to be eminent themselves. He took this as evidence for the heritability of abilities such as intelligence and artistic talent (music, poetry, painting) as well as physical strength (derived from a study of oarsmen and wrestlers). Burt published studies similar to Galton, but used a standardised measure of intelligence: Binet's intelligence quotient. He compared the IQ test scores of children of Oxford academics to ordinary townspeople, with results⁸⁶ showing that children from the group of Oxford parents had higher IQ scores than ordinary children (Burt 1909 as cited in Hearnshaw 1979). Burt concluded on the basis of this experiment that intelligence is heritable and that people have limited capacities for learning and intelligence.

Galton and Burt did not use the formal statistical measures now in place to make claims about heritability, but many succeeding them have, using behavioural genetic designs such as twin studies, described in chapter 2. A host of reviews (Bartels et al. 2002; Bouchard & McGue 1981; Deary, Spinath & Bates 2006; Devlin, Daniels & Roeder 1997; Erlenmeyer-Kimling & Jarvik 1963; Feldman & Otto 1997; Plomin et al. 2008) have confirmed significant heritability estimates for intelligence, ranging between 0.5 - 0.8 (Plomin & Spinath 2004). These estimates are slightly lower for young children (Bartels et al. 2002), and increased in the elderly (McClearn et al. 1997). Estimates in this range have also been replicated across various environments worldwide (Plomin et al. 2008).

Given these results, some hereditarians have argued that the heritability of intelligence indicates that environmental interventions are of little use, as variation in the environment has limited power to produce differences in an inherited and 'fixed' trait (for example Herrnstein & Murray 1994; Jensen 1969). This is contra to environmental interventions

⁸⁶ See footnote 6.

that could be made if the estimate was low, reducing V_P by homogenizing environments.

The argument has been made even more controversial by the conjecture that genetic variation may map to racial variation⁸⁷, and as such racial differences in intelligence could be thought of as 'genetic' or predisposed (Herrnstein & Murray 1994; Jensen 1968; 1969). Jensen (1969) has further inferred that educational programs aimed at bridging the gap between racial groups in the USA, such as the Head Start program which targeted children of low socio-economic backgrounds - often of African American heritage, would be of no use.

These kinds of extreme positions have led to a closer examination of the methods used within behavioural genetics. Some (including, but not limited to, Block & Dworkin 1976; Eysenck & Kamin 1981; Kamin 1974; Lewontin 1974; Wahlsten 1990) have concluded that the H^2 's for intelligence do not translate to V_P being caused by V_G , with some going so far as to say that intelligence has little or no heritable basis (e.g. Kamin 1974).

One of these criticisms concerns the prevalence of $V_{G \times E}$. This has been used as a conceptual criticism against heritability generally (Lewontin 1974), as well as specifically for intelligence (Wahlsten 1990), and was discussed in sections 2.6, 3.5 and 7.4. More recently, it has been empirically demonstrated that $V_{G \times E}$ affects heritability measures of intelligence (Harden, Turkheimer & Loehlin 2007; Tucker-Drob et al. 2011; Turkheimer et al. 2003). For example, Turkheimer et al. (2003) studied the interaction of socioeconomic status and genotype for IQ, finding that V_G accounted for a large amount of V_P in children raised in high-socioeconomic homes, but less so for those in low-socioeconomic situations. Another criticism of heritability measures of intelligence is G-E covariance (Block 1995; Block & Dworkin 1976; Gibbard 2001; Jencks et al. 1972; Scarr & McCartney 1983; Sober 2000; 2001). As described in chapters 4, 6 and 7, it is possible that G-E covariance

⁸⁷ See footnote 53.

accounts for phenotypic differences between groups which are attributed to V_G . The reactive G-E covariance examples illustrated how prejudice towards red-haired but not brown-haired children could lead to an interpretation that intelligence differences were largely due to genetic differences, and thus the trait is highly heritable. This logic can be applied to more realistic situations where differential treatment of different races or genders⁸⁸ could lead to differences in environments (socio-economics, educational access) as well as other phenotypes (self-esteem and motivation) that would influence differences in intelligence.

Less discussed than the reactive cases is active G-E covariance. Recall that in the active form, an alteration of an individual's environment is due to the motivation of the individual possessing the covarying genotype. Individuals differ in their genetics, resulting in different environmental selection or construction behaviours between genotype groups. While it is recognised that environmental selection is likely to be influenced by both genotype and the environment, any genetic cause of environmental selection results in a covariation between genes and environment. As such, active G-E covariance leads to different genotypes systematically experiencing differences in the selection of environments, resulting in phenotypic differences between genotype groups, contributing to H^2 . In the following section I shall examine how active G-E covariance may contribute to the heritability estimated for intelligence.

8.2 Active G-E Covariance and Intelligence

Dickens and Flynn (2001; 2002) propose an explanation of intelligence differences by appealing to active G-E covariance. Additionally, they claim that this explanation solves

⁸⁸ Strongly correlated with genetic sex.

the ‘paradox of intelligence’ that is the Flynn effect. The Flynn effect (Flynn 1984), which had been discovered by earlier researchers (see Lynn 2013), accounts for the rise in average IQ scores over time. Thanks to Binet and Terman, IQ is standardised by a representative population, where the median score of test-takers sets the benchmark for a score of 100; and each standard deviation above or below the median represents a score difference of 15 points on the test. The scores of a population reliably trend towards a normal distribution, or bell curve. However, the median raw scores of later generations are higher than those of earlier ones, resulting in a continual re-adjustment of the raw scores corresponding to the median score of 100. This phenomenon of rising IQ test score performance averages a 3 point per decade adjustment (Flynn 1984; 1987; Herrnstein & Murray 1994).

Dickens and Flynn (2001; 2002) propose that this increase is due to G-E covariance. Although the types are not made explicit by Dickens and Flynn, they use passive, active and reactive examples in their work. They believe that firstly there is a covariance between genotype and the selection or imposition of an enriched environment. This results in V_P for IQ being measured as heritable, even though V_E may be more directly exerting its causal influence. Secondly, this kind of causal relationship produces a ‘social multiplying effect’. An individual’s IQ is not only raised by modifying their own environment, but from encountering others with inflated IQs and their modified environments. This raises IQ at a population level. Raised IQs contribute to more environmental scaffolding in the population, which are inherited. Thus over multiple generations, the median IQ score of a population increases due to multiple overlapping generations experiencing a scaffolded environment during development, which mirrors downstream or developmental niche construction (see section 4.1.4). Rowe and Rodgers (2002), in their critique of Dickens and Flynn (2001), extrapolate an example of this:

Heavy readers gain larger vocabularies than light readers, but they also may possess gene variants favourable to higher IQ. (p.760)

They also expanded upon Dickens and Flynn's premise, stating that present-day environments are more conducive to G-E covariance's occurring:

For example, in 1900 many people worked on farms; today most individuals work in more or less intellectually demanding jobs. The extent to which modern occupations are more evocative of genetic tendencies would raise the genotype–environment correlation for IQ. (Rowe & Rodgers 2002, p.760)

However, what Dickens and Flynn lack in their analysis is an *interpretation* of this theory in light of the nature-nurture debate. Does this kind of causal story cohere with intelligence differences that are genetically caused? Should we still be calling intelligence a highly heritable trait, if G-E covariance is present?

As stated at the outset, there is considerable disagreement amongst biologists and philosophers as to how to interpret active G-E covariance cases. Some believe that actively sought environmental influences can be considered as part of the 'self-realization' of the genetic basis of the phenotype (Eaves et al. 1977; Jensen 1969; Jinks & Fulker 1970).

Under this interpretation, active G-E covariance is not problematic for heritability estimation, and any resulting phenotypic variance should be considered as accounted for by V_G . Others believe that these cases present a separate source of variation, and that the resulting phenotypic variation should not be encompassed under the V_G term (see below). Thus even if active G-E covariance can be empirically shown to underlie some of the genetically ascribed phenotypic variation for intelligence; disagreement as to how to interpret this result remains.

Given Dickens and Flynn's hypothesis, some researchers would interpret the active G-E covariance in the model as 'self-realizations' of the phenotype and thus conclude that current heritability estimates for intelligence are accurate. For example Jinks and Fulker

(1970, p.323) indicate that active G-E covariance simply reflects a type of genetic causation:

An innately intelligent person may well select his environment so as to produce positive *r_{whwe}*, [G-E covariance] and likewise a dull person may produce the same correlation by selecting less stimulating features of his environment. But is not this a more or less inevitable result of genotype? To what extent could we ever get a dull person to select for himself an intellectually stimulating environment to the same extent as a bright person might?

Eaves et al. (1977), Jencks (1980), Jensen (1969), Jinks and Fulker (1970), Roberts (1967), and Rowe (1994; 1997) similarly conclude that these cases are simply a reflection of the expression of genetic variation, and that the environmental causes are a natural extension or expression of the phenotype under study, which ‘...present no more of a dilemma than the observation that fast growing genotypes eat more’ (Eaves et al. 1977, p.19). These scholars presumably believe that the heritability models summarised in equations (1) or (7), where no $2Cov_{GE}$ variable is present, are all that are needed for a suitable H^2 estimate.

However, not everybody agrees with this interpretation. As noted above, some believe that, along with the reactive cases, active G-E covariance cases should be treated as having a separate source of variation, and thus estimates should include a $2Cov_{GE}$ component as a separate variable (equations 8 and 9) (Block 1995; Block & Dworkin 1976; DeFries & Loehlin 1977; Feldman & Lewontin 1975; Gibbard 2001; Layzer 1974; 1976; Loehlin, Lindzey & Spuhler 1975; Plomin 1987; Plomin, Loehlin & DeFries 1987; Sober 2001).

Counter to both positions, Sesardic (2003, p.1012) believes that decisions guiding causal attributions in active covariance cases are ‘...a practical decision primarily guided by an attempt to follow the common-sense way of apportioning causal responsibility’, and as such can differ on a case by case basis. This interpretation has also been advocated by Emigh (1977).

Given the disagreement surrounding how to interpret active G-E covariance cases, it is likely that what is ‘common sense’ to one philosopher or geneticist may not have the same intuitive appeal to another. Sesardic concludes that:

This is all admittedly pretty vague, and I am not sure how intuitions underlying our different approach to these two kinds of cases should be refined further and made more precise. Fortunately this doesn’t really matter, for I only want to claim that in dealing with G-E correlations, behaviour geneticists are by and large guided by the common-sense considerations about causality, with all their characteristic vagueness and ambiguities. (Sesardic 2003, pp.1012-1013)

I contend that this does matter, as common-sense considerations about causality in active G-E covariance are a source of disagreement amongst scholars, and this disagreement has profound impacts as to how people think about the heritability of a trait. This chapter aims to give an account of the underlying assumptions which guide these common-sense considerations for active G-E covariance. I will show that these assumptions give rise to the vagueness, ambiguities, and as such, disagreements, over how to interpret active G-E covariance.

I propose that part of the current uncertainty in the debate is due to the historical framework in which the study of active G-E covariance arose. The majority of critiques which concerned active G-E covariance have focused upon the heritability of a small and specific set of human phenotypes, namely, complex cognitive traits such as intelligence (see, for example: Block 1995; Block & Dworkin 1976; Eaves et al. 1977; Jencks 1980; Jensen 1969; Jinks & Fulker 1970; Layzer 1974; 1976; Loehlin & DeFries 1987; Loehlin, Lindzey & Spuhler 1975; Plomin 1987; Plomin, DeFries & Loehlin 1977). I will show that by considering a more diverse array of phenotypes, a predictable pattern to causal intuitions emerges. In the succeeding sections I will present a series of examples that illustrate a continuum of intuitions about how to interpret active G-E covariance cases. By studying these examples I show that there are phenotype-specific considerations which

influence one's assessment of 'genetic causation' in active cases, and as such those considerations can be used to decide which model is most appropriate when deriving a heritability estimate.

8.3 Active G-E Covariance and Other Phenotypes

To illustrate these features I will be using examples which compare two populations. In one population active G-E covariance is present, and intuitions about causal attributions may be unclear. In the second, no G-E covariance is present, and causal attributions to V_G , and the appropriateness of the H^2 attained are generally thought to be acceptable.⁸⁹ Some of these examples may seem far-fetched at first appearance, but are necessary to illustrate the continuum of intuitions that arise by considering different phenotypes, so I ask the reader to bear with me on these points

8.3.1 IQ

First imagine population A, in which a high H^2 for IQ is estimated and no G-E covariance is present. In this population, individuals with particular genes have higher IQ scores than others, as their genes affect their intelligence⁹⁰ 'directly', perhaps through protein expression that influences neural development. This coheres with Block (1995) and Block and Dworkin's (1976) 'direct' heritability concept, and according to Jencks (1980, p.730), is the assumed or received interpretation of the heritability of intelligence:

⁸⁹ In both populations I am assuming that there is no $V_{G \times E}$ or other complications which may undermine the validity of the H^2 estimate.

⁹⁰ See footnote 55.

Both hereditarians and environmentalists have simply assumed that if genes do, in fact, affect IQ, they do so by affecting the development of the central nervous system - particularly the brain.

Now consider population B, where individuals who score highly on the IQ test had a genetic propensity to modify their environments towards intellectual stimulation. They sought out books, took extra classes, and worked on problems which resulted in better literacy skills, and so scored better on the IQ test. In this population the high heritability estimate is (at least partially) a result of active G-E covariance. Variation in genotypes causes systematic variation in environments between the two genotype groups, producing variation between the groups for phenotype (IQ). This is illustrated in Figure 8.1c).

When considering ‘common-sense’ causal attributions, there is no concern about the heritability of IQ in population A. A large amount of V_P is attributed to V_G , leading to a high H^2 . In population B, however, there is contention. Section 8.2 above illustrated the division in interpretations for these kinds of cases. Some believe that cases like this should be interpreted in the same way as population A – where the resulting V_P is thought to be due to V_G . Others believe that the covariance should be partitioned separately (as $2Cov_{GE}$), lowering the H^2 .

8.3.2 Entrepreneurship

Putting IQ aside for a moment, I would now like to focus on a different phenotype.

Suppose a study set out to measure the heritability of entrepreneurship, and assuming the accuracy of some quantifiable entrepreneurial scale, a high H^2 estimate is reached.

Although this may seem implausible, a number of studies have estimated the genetic influence on entrepreneurship. For instance, Nicolaou et al. (2008a; 2008b) compared MZ and DZ twins on a 13-item questionnaire designed to measure entrepreneurship as a quantitative trait. They found that V_G accounted for between 37 - 48% of the phenotypic

variance. This result was repeated by Zhang et al. (2009), who found that heritability was higher for females, indicating a possible $V_{G \times E}$. These studies were extended even further by Nicolaou et al. (2011), who found a significant association with entrepreneurialism and a SNP of the dopamine receptor gene *DRD3*, which has been previously associated with novelty and sensation seeking.

Given that this trait is thought to be heritable, again imagine two populations in which a similar H^2 is attained. In population A high scorers on the entrepreneurial scale developed their phenotype in a similar way to that illustrated by Jenck's quote above. Their genes affected their nervous system, which led to entrepreneurial behaviours and attributes in a direct, neurologically-mediated way. This is contrasted with population B, in which individuals who scored highly on the entrepreneurial scale were (at least partially) genetically influenced to actively seek out particular environments. These environments helped them to acquire the knowledge and skills that would aid in their entrepreneurial endeavours. This is a case of active G-E covariance, where an individual's genotype causes them to seek out a particular environment, causing a correlation between V_G and V_E in a population. Nicolau and Shane (2009) have suggested that an active G-E covariance component is likely to explain their H^2 estimates, for instance through a genetic influence on educational and occupational preferences.

By mapping out the causal pathways that occur in population B for both the IQ and entrepreneurship examples one can see that they are causally congruous (Figures 8.1c and d). In terms of phenotypic variation, both map onto the indirect causal pathways shown in chapter 6, where V_G indirectly causes V_P (IQ or entrepreneurship), via V_E (seeking out a more stimulating environment or set of skills). As such, the entrepreneurship phenotype and mediating environment in population B for this example could be superimposed onto the causal diagram representing population B for IQ in Figure 8.1c.

In the above (and related) examples of active G-E covariance and IQ, interpretation for the active G-E covariance case is split between those who believe that the seeking out of intellectual stimulation reflects V_G , and those who believe that this environmentally mediated cause should be considered as a separate source of variance ($2Cov_{GE}$). But it does not look like there would be a similar division in causal intuitions for the entrepreneurial case. The presence of active G-E covariance in this example does not seem problematic for the heritability of entrepreneurship. A scenario in which high scorers on the entrepreneurial scale had actively sought out skills and knowledge seems compatible with V_P being caused by V_G , resulting in a high H^2 . This is because seeking out the skills and knowledge needed to be a successful entrepreneur seem to be part of *what it is* to be an entrepreneur. So when thinking about the heritability of entrepreneurship, implicit in the assessment of genetic and environmental causation is the assumption that individuals who display entrepreneurial traits would have reached them through some sort of active G-E covariance processes.

Despite the active G-E covariance present, claiming in this case that the phenotype is heritable appears to be acceptable, because part of the phenotype in question involves the seeking of knowledge and skills necessary for success. For this example, the H^2 's attained in populations A and B both seem to accord with 'common sense' causal attributions. That is, it is acceptable that the H^2 for both of these populations accurately reflect the genetic causes of variation in entrepreneurship -with or without active G-E covariance.

8.3.3 Obesity

Now to a different example: the heritability of obesity. Obesity has been empirically shown to be highly heritable, with twin-study estimates of H^2 around 0.8 (Stunkard, Foch & Hrubec 1986), although GWAS's have only been able to recover about 5% of this estimate (O'Malley & Stotz 2011). The causal dynamics involved in the development of obesity,

and the development of obesity differences, are still largely unknown⁹¹. One theory is that genetic differences affect ‘nutrient partitioning’ where some individuals lay down extra energy as fat or tissue based on genetic differences (O’Rahilly & Farooqi 2008). Other explanations involve a genetic influence on the regulation of appetite and energy balance, for example via the production of leptin – a hormone involved in relaying the fat status in the body to the brain (O’Malley & Stotz 2011). This is supported by molecular genetic research, as some of the common variants associated in GWAS appear to affect appetite and energy balance control (O’Rahilly & Farooqi 2008). Additionally, psychological influences have been suggested to account for V_P . Depression is correlated with obesity, but it is unclear whether this is a cause or an effect of the condition (Stunkard, Faith & Allison 2003). A genetic basis of food preferences has also been suggested as part of the genetic cause for obesity differences, as genetic associations with a preference for fat consumption, and resulting obesity, have been found in twin and family studies (Reed et al. 1997).

To return to our two hypothetical populations, the heritability of obesity in Population A is due to the ‘direct effects’ of nutrient partitioning – where heavier individuals lay down more energy as fat than less obese individuals. In population B, individuals are obese because they actively sought out environments that would contribute to weight gain. Perhaps, as suggested by Reed et al. (1997), they had a preference for fattier foods, and so sought jobs in candy stores, for instance, or pursued careers as taste testers, competitive eaters, or pastry chefs. Or perhaps they suffered from depression (which I assume here has some genetic basis), which led to over-eating as a psychological coping mechanism. The inclination to behave in these ways is at least partially genetically caused, and as such this

⁹¹ Along with genetic factors, there is also good evidence to suggest that epigenetic factors play a major role in the regulation of hormonal systems, appetite and metabolism. So as not to complicate these examples this shall not be discussed here. For more information see O’Malley and Stotz (2011).

is an instance of active G-E covariance: initial variation in genotype causes individuals to develop in a particular environment, and differences in that environment contributes to the variation in the measured phenotypic effect. This is shown in Figure 8.1b, where Population A shows a direct relationship between V_G and V_P , and Population B an indirect active G-E covariant relationship.

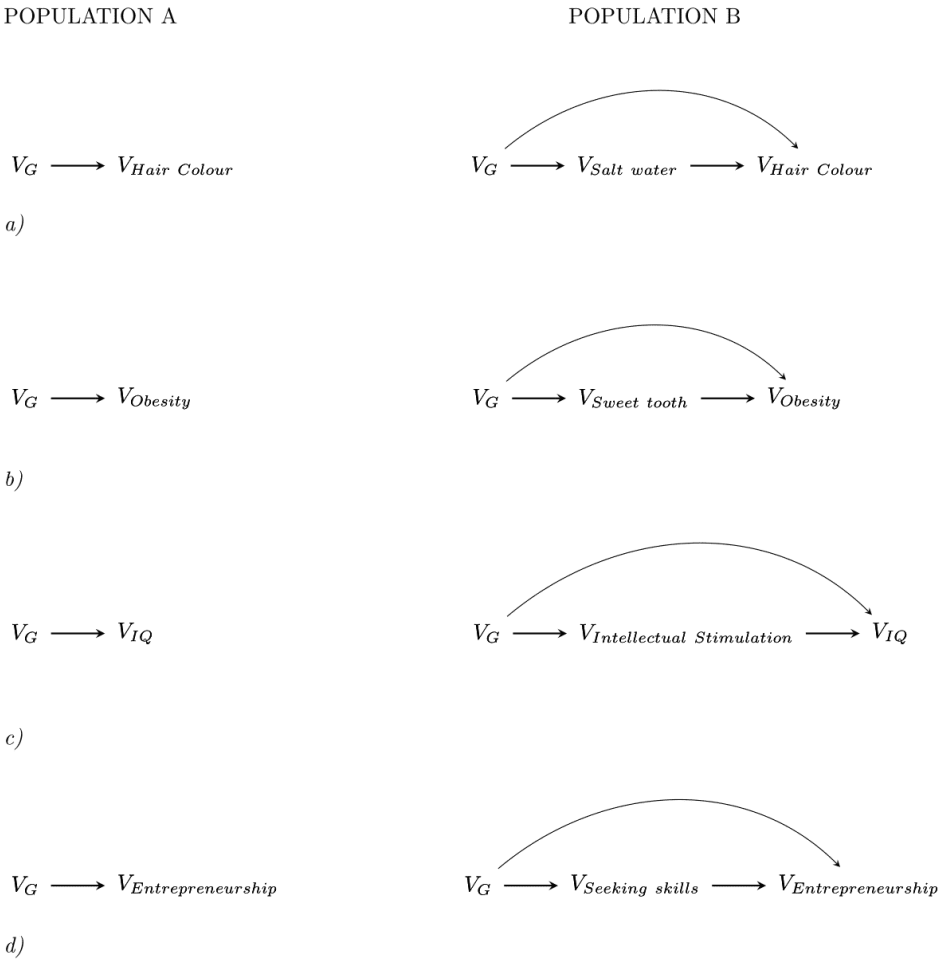


Figure 8.1 A Gradation of Intuitions In Population A no G-E covariance is present, Population B includes active G-E covariance. Intuitions about how to interpret the heritability estimates in Population B differ between different phenotypes (a-d)

Now think about how the heritability estimates for these two populations would be interpreted. In population A obese individuals make no active adjustments to their environments: there is no active G-E covariance. In population B, there is active G-E covariance, as obese individuals actively modify their environments by way of surrounding themselves with large amounts of high calorie foods –and this modifying behaviour has a genetic correlate. In this situation it seems intuitive to say that obesity is heritable in population A, in which no G-E covariance is present. In this population genetic differences lead to differences in nutrient portioning –so that some individuals lay more energy down as fat than others, even when consuming the same caloric input.

In population B (in which G-E covariance is present) the interpretation is less straightforward. In this population obesity may be more likely attributed to environmental variance, as it is the more direct cause of phenotypic variation.⁹² If this is the case then variation in obesity would be attributed to differences in diet (V_E), rather than genetic differences between individuals in a population (V_G), which means that the H^2 would be rejected as causally inaccurate.

8.3.4 Hair Colour

Lastly, consider the heritability of hair colour. Early studies of the genetic basis of hair-colour considered it as a quantitative trait, with an estimated H^2 of 0.61 (Brauer & Chopra 1980). Recent GWAS's have also found significant associations for pigmentation variation with a number of SNPs (Han et al. 2008; Sulem et al. 2007). This may seem odd, as hair colour is generally conceptualised as varying across multiple continuums, such as hue (brown, black, red, blonde) and tone (how light or dark a hue is, also sometimes called

⁹² Interpretations of this example may also be biased due to prejudices that exist against obese and overweight individuals in that people tend to blame them for their plight, rather than viewing obesity as an illness (as suggested by K. Stotz, personal communication).

‘value’ in colour theory). To overcome this problem of multi-dimensionality hair colour in these studies was measured quantitatively as ‘degree of pigmentation’, allowing for a heritability estimate to be attained.

As with IQ, entrepreneurship, and obesity, there are different ways in which hair colour could be heritable. To return to our two populations, let us say that both Population A and B attain a high H^2 for hair colour, but in population B active G-E covariance is present. In this population some individuals have a genetic predisposition to disproportionately seek out time in the sun and in the ocean. Perhaps these individuals are excellent surfers - due to genetic variants which aid them in strength and balance. This means that some individuals actively modify their environment so as to spend more time in the sun and saltwater – resulting in lighter hair. This activity contributes to the V_P of hair pigmentation in population B. In population A, no such environmental modifications were made on the basis of genetic differences. This is presented in Figure 8.1a.

This may seem the most far-fetched of the four examples, however, heritability for recreational interests such as ‘wilderness activities’ and ‘physical fitness’ have been found, with V_G accounting for approximately 50% of the variance of ‘interests’ more generally (Lykken et al. 1993). In another study 37% of V_P for ‘hunting and outdoor activities’ was attributed to V_G (Hur, McGue & Iacono 1996), so it is within the bounds of possibility that V_G could correlate with V_E because of genetic influences on environmental preference. Additionally, this preference could influence hair colour (in coast-dwelling populations), meaning that an active G-E covariance of this kind could bias the H^2 result.

In this example, the H^2 in Population B is likely to be rejected, as time spent in the sun and saltwater – although covariant with V_G , appear to confound the results. In Population B it seems that variation in hair colour would be more intuitively attributed as being caused by

differences in environmental factors (such as the sun and saltwater), which is not representative of V_G . Instead Population A represents the kind of scenario that would generally be considered in a study of the heritability of hair colour – where variation in hair pigmentation is assessed without a genetic covariance with these kinds of environmental influences.

The active G-E covariance debate has not generally considered physiological phenotypes such as hair colour or obesity, but has instead centred on cases like IQ. This is because the discussion has largely taken place in the field of behavioural genetics, and not quantitative genetics more generally. In these cases, as stated earlier, the intuitions about how to interpret active G-E covariance are divided. Some have the intuition that resulting V_P in the active G-E covariance case is due to V_G , as they are ‘... a more or less inevitable result of the genotype’ (Jinks & Fulker 1970, p. 323). In contrast, others believe that these are cases which ‘... illustrate obscurities in what is to count as genetically caused variance, and thus show corresponding obscurities in the notion of heritability’ (Block & Dworkin 1976, p. 480).

I have presented four cases of active G-E covariance featuring four different phenotypes. Despite the equivalence in causal structure between the cases (Figure 8.1), I have shown how each case can elicit a different intuition about the validity of its heritability estimate. Variation in hair colour in Population B seems common-sensically to be environmentally caused. It seems clear that the active G-E covariance in this example does not correspond to an accepted account of H^2 . Variation in entrepreneurship in Population B appears to be legitimately due to genetic differences, as part of what it is to be an entrepreneur entails the kinds of environmental modifications made in active G-E covariance situations. The active G-E covariance cases for IQ and obesity are more ambiguous. Some may be inclined to

view the environmental modifications in these examples as expressions of the genotype, others may class them as separate sources of variance.

8.4 A Gradation of Intuitions

Of the four actively covariant phenotypes from population B (Figure 8.1), the underlying causal structures are the same, yet the ‘common sense’ causal attributions differ. A high H^2 for hair colour seems to clash with common sense causal intuitions when active G-E covariance is present. This is because in this example it seems more intuitive to attribute the variation in hair pigmentation to an environmental factor: sun and/or saltwater exposure. Active G-E covariance cases of obesity also appear to be problematic for a heritability claim, although perhaps to a lesser degree than hair colour. In Population B, where individuals actively sought out particular environmental influences leading to weight gain, the corresponding high H^2 seemed to be a more contentious heritability estimate than in Population A – where heritable obesity differences were not due to environmental modifications. Intuitions about intelligence are even less clear. This is evident from the existing debate surrounding active G-E covariance, where philosophers and biologists differ in their account of causal attributions for active G-E covariance cases concerning intelligence. At the other end of the spectrum, entrepreneurship is a phenotype for which both G-E covariant and non-G-E covariant cases would accurately reflect genetic variance given a high heritability estimate. Active G-E covariance in this example does not seem problematic for heritability.

These four phenotypes can be ordered along a continuum, with ‘hair colour’ at one extreme – where active G-E covariance cases are obviously problematic for the estimation of V_G (and thus H^2), and ‘entrepreneurship’ at the other, where the active G-E covariance cases can be considered equal to non-G-E covariance cases in terms of their estimation of

V_G . Thus the more ‘acceptable’ active G-E covariance cases are represented at the bottom of Figure 8.1, and the less acceptable cases at the top. This can also be represented as:

‘hair colour’ < ‘obesity’ < ‘intelligence’ < ‘entrepreneurship’

Where ‘<’ denotes a more or less likelihood for the environment to be considered as an accurate reflection of V_G .

This raises the question: what accounts for the difference in intuition between the four examples? Identifying the difference making factor(s) may shed light on how to interpret cases of active G-E covariance. Thus the question of how to handle cases of active covariance changes from a general dichotomous question about what to do with cases generally, to one which may be assessed on a case-by-case basis, by considering a continuum of interpretations, which can also depend upon how the phenotype is defined.

8.4.1 Relevance and Norms

One feature has been hinted at in the literature. Phenotypes in which the co-varying environmental causes are generally considered as part of the ‘self-realization’ of the phenotype are those which are the least problematic for heritability analyses (Eaves et al. 1977; Jensen 1969; Jinks & Fulker 1970). This accords with the four examples presented above. Sun-seeking is not a relevant behaviour to the phenotype of hair colour. We think of hair colour as a physiological phenotype, separate from the behaviours which may alter its expression. The ‘normal’ development of hair colour does not include excess time spent in the sun and saltwater, leading to bleaching of hair follicles. However, seeking out resources and opportunities is highly relevant to the phenotype of entrepreneurship. Further, these activities make sense as an expression of the development of the trait itself, or as embodying its ‘normal genetic development’. One could term them a ‘natural

manifestation' (Sesardic 2005, p.94) of the genotype for entrepreneurship, and thus an expression of V_G .

Norms have already been shown to play a role in causal attributions (section 3.6.3), and this might be relevant to the active G-E covariance cases. For phenotypes like intelligence and obesity, the causal attributions for active G-E covariance cases are debated or unclear. This may be because the concept of 'normal development' for these phenotypes is also unclear, debated, or underspecified. What is the normal development of obesity, or of intelligence? What environmental modifications are relevant to the trait? Because these questions are hard to answer without some controversy or debate, an interpretation of active G-E covariance is similarly difficult.

The relevance of environmental modifying activity to a trait may be the defining feature for the interpretation of active G-E covariance, explaining the differences in 'common-sense' causal attributions. If relevance and normal development are the key factors between cases, this leads to the question; what is it for something to be relevant to or normal for the realization of a phenotype? And what makes some phenotypes relate to active modifications of the environment and others not? To answer this question, one must now turn to the phenotype under investigation. The question has now become: What kind of phenotypes include self-modification of the environment as part of their 'normal' realisation?

8.4.2 Motivation

It appears that there is something important about the 'seeking out' of stimulation or other environmental features which distinguishes some active G-E covariance cases from others. Based on this, the important feature which determines if the environmental covariance is relevant to a phenotype's realization is whether or not there is some active, *motivational*

component to the phenotype itself. If there is some motivational component to the phenotype under study, then the activity of modifying one's environment can be thought of as a relevant expression of that phenotype, and thus incorporated into it as the phenotype being measured. When this is the case, we may be happy to include active G-E covariance as part of genetic variance (V_G). Conversely, if phenotypes do not include some sort of motivational feature, we may be less inclined to include active G-E covariance in a H^2 estimate, and instead want to partition this influence as a separate source of variance in the heritability model ($2Cov_{GE}$).

This is evident across all the examples I have used. Entrepreneurship is a behavioural or personality-related phenotype in which the motivation to modify one's environment is paramount. Part of what it is to be an entrepreneur is to have the motivation to seek out resources and modify one's environment in a way that aids in economic success. On the other hand, physiological phenotypes such as hair colour do not seem to have any necessary motivational component as part of their concepts. So when motivational behaviour impacts upon the expression of the trait – even when such *motivations* are genetically caused, we tend to regard the resulting environmental variation as a separate source of variance.

Obesity is a slightly trickier case than hair colour. While it is pretty clear that individuals who modify their environment to change their hair colour are not reflecting genetic causes of variation, some may be more inclined to grant an accurate heritability estimate in the obesity case – where obese individuals actively seek out the resources which contribute to their weight gain. I believe that this sense of ambiguity is due to an inherent ambiguity in the obesity concept (see O'Malley & Stotz 2011). Those who believe that the concept of obesity is purely a physiological one may not attribute the H^2 estimate as accurately reflecting V_G . However, those who include psychological, motivational and behavioural

factors like appetite and food preferences as part of what it is to be obese may accept active G-E covariance to represent a part of genetic variance.

Similarly, intelligence is a phenotype in which intuitions are at odds. I believe that this is because intelligence is an ambiguous concept. Does actively seeking out educational resources and intellectual stimulation constitute part of what it means to be intelligent? Jinks and Fulker (1970, p. 323) seem to think so:

To what extent could we ever get a dull person to select for himself an intellectually stimulating environment to the same extent as a bright person might?

Those, like Jinks and Fulker, who believe that the seeking out of intellectual stimulation is a natural component of the intelligence phenotype would be inclined to accept the heritability measures given in active G-E covariance cases. They would agree that the H^2 estimates attained in both Population A and Population B in the IQ example were accurate reflections of the influence of V_G on V_P .

However, if one believed that the concept of intelligence was something separate from the motivational impulse that compels individuals to seek stimulation, then active G-E covariance becomes problematic for estimating its heritability. The disagreement for this case may, therefore, come down to whether we think that part of what we are measuring when we look at intelligence is an interest in learning and practicing cognitive capacities, or whether it is simply an ability to perform the tasks.

Thus to determine if active G-E covariance is problematic for heritability estimates, one must look at the *phenotype* under study. If the phenotype includes some kind of motivational component, then active G-E covariance is much less problematic for H^2 , as it can be subsumed under V_G . However, if the phenotype does not have any sort of motivational component to it, and an individual's (genetically influenced) motivation to

alter their environment could not be considered as an extension of that phenotype, then the variable 2Cov_{GE} must be added to the heritability equation (equations 8 and 9).

8.5 Summary and Conclusion

Given that the interpretation of active G-E covariance cases are dependent upon the kind of phenotype studied, it is not surprising that phenotypes for which we have vague or inexact definitions are the most problematic when assessing what to do with active G-E covariance. This is because it is unclear if the phenotype has some form of motivational component, and how inherent to the concept this feature is. If one believed that the motivation to seek out resources and learn about the world were included as part of the intelligence concept, then active G-E covariance should not be a problem for heritability analyses. However, if one believes that motivation is a small or non-existent part of what it means to be intelligent, active G-E covariance is problematic and may need to be regarded as a separate source of variance.

The reason that this final component of our intuition – the motivational component of the phenotype - is so important is that discussion of active G-E covariance in heritability studies has focussed heavily on a single phenotype – intelligence. I suggest that the ambiguity of the intelligence concept is responsible for the disparity in interpretation for active cases, as it is unclear whether motivated, environmental modifying behaviours are part of what is considered a ‘normal realisation’ of this phenotype.

Some may regard intelligence as a trait which includes an interest in learning and the practice of cognitive capacities, not simply an ability to perform tasks with them. Thus the seeking out of stimulating environments which contribute to the development of the phenotype becomes part of the phenotype itself. Under this view, cases of active G-E

covariance would be permissible as being treated as heritable to the same extent as non-G-E covariance cases. This is the interpretation that Eaves et al. (1977), Jencks (1980), Jensen (1969), Jinks and Fulker (1970), Roberts (1967) and Rowe (1994; 1997) take.

However, those who think that intelligence does not have anything to do with the motivation to learn and improve reasoning skills would maintain that any G-E covariance skews the heritability estimate by artificially inflating it, and that the resulting phenotypic variance should be considered as caused by something other than V_G . This is the view of Block (1995), Block and Dworkin (1976), Feldman and Lewontin (1975), Gibbard (2001), Layzer (1974; 1976), Loehlin and DeFries (1987), Loehlin, Lindzey and Spuhler (1975), Plomin (1987), Plomin, DeFries & Loehlin (1977), and Sober (2001).

Since intelligence has been the case study for discussion of active G-E covariance, intuitions elicited over this case study have differed between theorists. Further, the interpretive intuitions evoked in this case have been applied more generally by philosophers and geneticists when trying to devise a rule of how to interpret active G-E covariance cases, leading to a more general disagreement about the interpretation of active G-E covariance.

What I have hoped to have shown with these examples is that active G-E covariance may or may not be intuitively considered as part of a ‘commonsensical’ heritability estimate based on the kind of phenotype which is being measured. If the phenotype is one which has a large motivational dimension, as presented in cognitive and behavioural phenotypes such as the entrepreneurial example, and to a lesser extent IQ, then active G-E covariance will be less problematic than in examples where the phenotype has a low motivational component, such as obesity or hair colour.

This may account for why the debate surrounding active G-E covariance is still unresolved. So far the debate about what to do with active G-E covariance cases has largely focused on

behavioural and cognitive traits, particularly intelligence (see, for example: Block 1995; Block & Dworkin 1976; Eaves et al. 1977; Jencks 1980; Jensen 1969; Jinks & Fulker 1970; Layzer 1974; 1976; Loehlin & DeFries 1987; Loehlin, Lindzey & Spuhler 1975; Plomin 1987; Plomin, DeFries & Loehlin 1977). I believe that this focus has obscured some of the key features of active G-E covariance, and as such has left the debate at a standstill. By considering other phenotypes, and identifying the role motivation plays in interpreting active G-E covariance, the debate has been shifted to one concerning the specification of phenotypes. In order to decide how to interpret active G-E covariance one must simply decide how to define intelligence (or whichever phenotype is under study) and whether this includes a motivational component, which may be expressed in the active alteration of the environment.

This chapter has put into place the final piece of the puzzle for G-E covariance. Chapter 6 illustrated the differences between passive G-E covariance cases and active and reactive ones by looking at their underlying causal structures. Chapter 7 explained why active and reactive cases differed, despite their similarity in causal structure. This chapter has illustrated why different interpretations exist for active G-E covariance, and why some cases seem more problematic than others. Combined, a consideration of causal structures, causal background conditions, notions of agency and blame, and the phenotype under study, can be used to account for interpretations of G-E covariance.

Chapter 9 Conclusion

The nature-nurture debate is not likely to dissipate any time soon. The debate itself concerns a range of topics and questions spanning different investigative fields, some of which were described in chapters 1 and 3. It is also laden with ideological and political biases, for example the eugenic motivations described in chapter 1, and racial prejudices described in chapter 4. Because of the breadth and depth of the debate, it is unclear what a ‘resolution’ would look like, but a deeper understanding will require a combination of empirical and theoretical advances. One step towards an increased understanding is to clarify the existing sources of disagreement, so that stagnant dialectic can make progress.

This thesis has articulated some of the sources of disagreement surrounding the interpretation of G-E covariance by illustrating the underlying reasons and assumptions that perpetuate disagreement about interpretation. G-E covariance appears problematic for heritability studies because it gives heritability estimates that do not cohere with common-sense causal ascriptions – even when these ascriptions concern the correct kind of causal relationship (described in chapter 3). The variety of factors that account for differences in interpretation include: the underlying causal structures of the cases, the specification of environmental variables, appeals to human agency and blame, and a consideration of the concepts inherent in the phenotype under study, particularly motivation.

9.1 Heritability and Causation

In chapter 3 I described the different kinds of causal claims that can relate to genes and environment, and chapters 1 and 2 outlined how these contribute to, and are often confused in, the heritability debate. Chapter 3 argued that heritability estimates can represent a type-

causal claim, where the causal relata are variation in genotype (V_G), variation in environment (V_E) and variation in phenotype (V_P). Although the relationships involved are type-causes, they generally have low invariance and stability, due to the limited numbers of variables and their values which are used within heritability studies, and are a factor of experimental design. This feature may account for the existing dispute surrounding the explanatory import and extrapolative potential of heritability estimates, relating to Richard Lewontin's (1974) 'locality problem'. Once phenotypic variance is thought to be at least in part caused by V_G in estimates where the phenotype is heritable, the causal processes underlying G-E covariance can be assessed. This was the subject of chapters 6 and 7. Chapters 2 and 3 laid the foundation for later chapters, by providing the details of heritability and its estimation, and the theoretical underpinnings required for an investigation of causation and explanatory dimensions of causal relationships.

9.2 Gene-Environment Covariance

Gene-environment covariance was described in chapter 4. It has been recognised as a potential confound in the field of behavioural genetics, and a potential cause for behavioural phenotypes such as autism, psychiatric disorders, and intelligence (chapters 4 and 5). Philosophers have taken note of this problem because the reactive cases provide an analogy for how racial and sexual discrimination may influence heritability estimates. Active cases bring into question wider issues concerning the nature of causation, although this topic has been underexplored in the philosophical literature. As the phenomena are difficult to estimate, it is possible that they are a large problem for heritability.

I showed in chapter 6 that some forms of G-E covariance reflect a pattern of direct causation whereby particular genomes could bias the choice of developmental environment,

reflecting ‘nature-via-nurture’. Others conform to a common-cause type structure, when both genotype and some environmental factors are inherited from one’s parents. The identification of causal differences between cases provides some clues regarding differences in interpretation. However, I showed that identification of these structures is not sufficient to explain the discord between common-sense ascriptions of genetic causation and the results obtained in G-E covariant heritability estimates. Both the scientific and philosophical community treat active and reactive G-E covariance cases differently. However, both active and reactive cases display the nature-via-nurture causal structure.

Chapter 7 demonstrated that the difference between active and reactive cases could be attributed to differences in causal background conditions, however, this is dependent on how those conditions are defined. An appeal to background conditions only works using an appropriate level of description of the environment concept that is not inappropriately coarse-grained and hence failing to include relevant details, which can be problematic. An alternative account then is to appeal to the influences of agency and blame for shaping causal intuitions. These are factors that have been demonstrated to have an effect on causal decision making, as described in chapter 3.

Chapter 8 looked at the intuition discord present for active G-E covariance cases, which is the main source of the dispute, despite receiving less attention than the reactive cases in the philosophical literature. I showed that in order to understand differences in interpretation it is useful to look at different phenotypic scenarios, in which causal intuitions are likely to vary. By doing this I demonstrated that the associated difference with these examples is the degree of motivation that is inherent in the phenotypic concepts under study. I argued that the key factor to interpretative differences in active G-E covariance cases is differences in the way the phenotype has been conceptualised. Those which encompass a motivational

component may consider active G-E covariance as an extension of the phenotype. Studies of phenotypes without this component will find the existence of active G-E covariance problematic. Taken together these factors can account for the dispute between philosophers, and shed light on how identified cases of G-E covariance should be treated.

9.3 Directions for Future Work

Gene-environment covariance is an empirical and conceptual problem that needs to be accounted for in both human and animal quantitative genetic research. Currently, quantitative geneticists using animal models do not account for the possibility of G-E covariance as a confounding variable, and it is noticeably recognised as an irrelevant factor when estimating heritability in laboratory research. As a challenge to this oversight, Chapter 5 showed how recent findings from a neuroethological study could cohere with the phenomenon of all three kinds of G-E covariance. One of the reasons for this oversight may be due to a lack of empirical work and experimental quantification. Chapter 5 concluded with further ways in which G-E covariance may be identified and estimated in animal populations, providing fruitful ground for future work.

This chapter also suggested other possible variables that could covary during individual development, biasing heritability estimates and shaping unique developmental trajectories. This suggests that along with an oversight of G-E covariance, other non-additive variables may be unaccounted for in current heritability estimates. This may account for the problem of ‘missing heritability’, described in chapter 3. These cofactors include epigenetics and early experience. An inclusion of these variables and their covariances into the heritability model is something that requires consideration and further work. Epigenetics in particular has been shown to account for phenotypic variation, and is a rapidly developing field of

biology. There is much scope for future research concerning the non-additivity of epigenetic variation. When genes and environment are factored into the additive heritability model, G-E covariance, and gene-environment interaction ($V_{G \times E}$) arise as non-additive possibilities. Should epigenetics enter the heritability mix, it is possible that non-additive epigenetic variables also be taken into account. There is already good evidence to suggest that there are interactive epigenetic effects, with either environment, genotype, or between all three⁹³ (Bossdorf et al. 2010). Chapter 5 suggests that this may also apply to covariances.

To date, there has been no evidence or theoretical suggestion that epigenetic variations covary with environments or genotype in the manner of G-E covariance. This should come as little surprise given the sparse attention that G-E covariance has received in existing genetic research. Epigenetic variation may provide an analogous basis for the ‘nature-via-nurture’ problem of G-E covariance, although an epigenetically mediated causal pathway is likely to be more complex given the differences in transmission and stability between genetic and epigenetic variation. As such, the study of non-additivity in epigenetics is a burgeoning area for future research that may provide novel insights into the complexity of the causes of phenotypic variation. Empirical advances in this area will no doubt require corresponding conceptual work. As I have demonstrated in this thesis, G-E covariance has been subject to considerable theoretical dispute, and multiple conceptual considerations are needed in order to understand the basis of these interpretative differences. Adding epigenetic variation to the heritability model will add further complexity and is likely to require a considerable amount of philosophical treatment.

⁹³ If factored in to heritability models these interactions would encompass the non-additive variables $V_{G \times Ep}$, V_{ExEp} and $V_{G \times ExEp}$

Additionally, there are avenues for future work regarding the interpretation of active G-E covariance cases. Chapter 8 presented four examples of active G-E covariance which elicited intuitions that varied along a continuum of H^2 acceptability. These were entrepreneurship, IQ, obesity, and hair colour. A limitation to the argument presented in chapter 8 was a reliance on the intuitions of the author⁹⁴. To strengthen the case argued in chapter 8, methods from experimental philosophy could be employed, where examples of this kind are randomly presented to a large group of participants from varying educational and occupational backgrounds (including philosophers of biology and geneticists). This would help to paint a clearer picture of the interpretative differences between active G-E covariance cases, which may lead to further insights regarding the current interpretive dispute.

Thus while this thesis has provided a solid foundation on the topic by highlighting the importance of, magnitude, and scope of G-E covariance in experimental research, and provided tools to explain interpretative differences within the fields of philosophy and behavioural genetics, this is an important field of study that warrants future research.

⁹⁴ And those of colleagues to whom these examples had been presented.

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