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The nature of nurture: the role of gene-environment interplay in the development of intelligence

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CHAPTER 2

NONLINEAR EPIGENETIC VARIANCE: LITERATURE REVIEW AND ILLUSTRATIVE SIMULATION STUDY

Abstract

We present a review of empirical evidence that suggests that a substantial portion of phenotypic variance is due to non-linear (epigenetic) processes during ontogenesis. The role of such processes as a source of phenotypic variance in human behavior genetic studies is not fully appreciated. In addition to our review, we present simulation studies of nonlinear epigenetic variance using a computational model of neuronal network development. In each simulation study, time series for monozygotic (MZ) and dizygotic (DZ) twins were generated and analyzed using conventional behavior genetic modeling. In the results of these analyses, the nonlinear epigenetic variance was subsumed under the nonshared environmental component. As is commonly found in behavior genetic studies, observed heritabilities and unique environmentabilities increased with time, whereas common environmentabilities decreased. The fact that the phenotypic effects of nonlinear epigenetic processes appear as unsystematic variance in conventional twin analyses complicates the identification and quantification of the ultimate genetic and environmental causes of individual differences. We believe nonlinear dynamical system theories provide a challenging perspective on the development of individual differences, which may enrich behavior genetic studies.

2.1 Nonlinear Epigenetic Variance: Literature Review and Illustrative Simulation Study

The nature-nurture question, as addressed in (behavior) genetic studies, concerns the decomposition in a linear statistical model of phenotypic (observed) variance into components attributable to latent factors. In humans, this decomposition is carried out in genetically informative designs, such as the twin design (e.g. Plomin, DeFries, McClearn, and McGuffin, 2008). Generally two general latent sources of variance are distinguished, namely the genetic and the environmental. Phenotypic variance attributable to the former may be decomposed into additive, dominance, and epistatic genetic variance, whereas phenotypic variance attributable to the latter can be further decomposed into shared environmental variance, and nonshared environmental variance, where shared influences are attributable to the environment cohabiting individuals (both human and infra-human) share.

Regardless of the (genetically informative) design employed, it is assumed that genotypic and environmental factors reflect the underlying mechanisms causing phenotypic individual differences (e.g. Plomin et al., 2008).¹ An important characteristic of the behavior genetic methodology is that the partitioning of variance and the attendant causal interpretation pertains to phenotypic individual differences, and not to phenotypes themselves (Dolan & Molenaar, 1995; Lewontin, 1974; Oyama, 1985).² However, if we remain strictly within the domain of individual differences, a causal interpretation still requires caution. First, the validity of the interpretation may be undermined by the limitations of the statistical model employed to carry out the decomposition of phenotypic variance. These may concern the failure to take into account genotype-environment interaction, genotypic-environment covariance, assortative mating, etc. However, it should be noted that in principle, i.e., given a suitable design or given sufficient information, these effects can be modeled (e.g. Plomin et al.).

Indeed, there is an increasing effort to devise statistical models that can accommodate these complicating effects (Dick & Rose, 2002; Purcell, 2002; Eaves & Erkanli, 2003). At present, the issue

¹ It is in this sense that we take the term “explained” seriously, i.e., genetic and environmental differences cause phenotypic differences.

² What causes (say) cognitive functioning, and what causes individual differences in cognitive functioning are different questions (Oyama, 1985).

of genotype-environment interaction is the focus of much attention (Turkheimer, D'Onofrio, Maes, & Eaves, 2005; Moffitt, Caspi & Rutter, 2005). Increasingly, specific - measured - genetic and environmental variables are incorporated in the model, thus replacing in part the latent factors (Plomin, et. al, 2008), and creating important opportunities for studying genotype-environment interaction. Error in the measurement of the phenotype remains hard to pin down, as it is due, by definition, to transitory effects (e.g. Molenaar, Boomsma, & Dolan, 1993; Turkheimer & Waldron, 2000).

The achievements within behavior genetics have transformed present day psychology and the standard behavior genetic model, including the interpretation of the roles of genetic and environmental variables as causes of individual differences, has been successful enough to convince most psychologists that genetic and environmental factors do indeed contribute to phenotypic variance, and to encourage further research into the role of specific environmental agents and actual genes (i.e., possible ranging in effect from major loci to quantitative trait loci). This research is based on the premise that the phenotypic variance is ultimately traceable to identifiable variables. However, as we will argue, the search for such specific genetic and environmental variables may be complicated in that a substantial portion of phenotypic variance may be due to non-linear (epigenetic) processes (Molenaar et al., 1993). As explained below, these effects will appear unsystematic, and are therefore difficult to distinguish from specific environmental effects or measurement error.

The aim of this chapter is to study the role of non-linear epigenetic processes as a source of phenotypic variance. To this end, we review the relevant literature and demonstrate that there is ample evidence in support of these processes. In addition, we present the results of computer simulations. The implications and consequences of the presence of nonlinear epigenetic variance are particularly interesting in the light of the attempts to identify specific nonshared, environmental influences (e.g. see Turkheimer & Waldron, 2000; Plomin et al., 2008).

The chapter is organized as follows. We first consider non-linear epigenetic processes in more detail. Second, we present a review of relevant studies involving inbred and isogenic animals, animal and human studies of developmental instability in several biological traits, and behavior genetic studies of human behavior. Third, we present a computational model of neuronal developmental processes, i.e., the two-cell model of neurite outgrowth of van Oss and van Ooyen (1997). This non-linear model displays the characteristics that are hypothesized to underlie nonlinear epigenetic variance. We present the results of computer simulation studies based on this model. In these studies we simulated phenotypic twin data, which allowed us to study the effects of nonlinear epigenetic variance in the standard twin design (e.g. Plomin et al. 2008). We end this chapter with a discussion concerning the role of such processes in development, the implications for behavior genetic studies, and possible limitations of our simulations.

2.2 Nonlinear Epigenetic Processes During Development

In the present section we discuss the hypothesis, that nonlinear epigenetic processes may constitute a source of phenotypic variance. In the subsequent section, we review empirical support for this hypothesis, stemming from both animal and human studies, and we discuss nonlinear epigenetic processes as a source of nonshared environmental variance in human psychological traits.

All developmental processes can be conceived of as the outcome of some dynamical system (Guckenheimer & Holmes, 2002; van der Maas & Molenaar, 1992). Viewing the development of an organism as the outcome of a nonlinear dynamical system, we accept the following characteristics. In contrast to linear systems, nonlinear systems are characterized by a disproportional relationship between cause and effect (Arnold, Afrajmovich, Il'yashenko, & Shil'nikov, 1994). This implies that large influences may have small or limited effects, whereas small causes, e.g. initial changes or differences, may have large effects. Hence, near-indistinguishable sets of initial conditions in the same system may produce different outcomes. In addition, if the system in question is sensitive to initial conditions, the outcome of the system may be hard to predict even if it is deterministic, i.e., any form of randomness is absent. This unpredictability arises from the lack of precise knowledge concerning the initial conditions. Hence, the outcome will appear stochastic despite the fact that the

system is fully deterministic. We refer to such unpredictable (either real stochastic or seemingly stochastic) relationships between cause and effect as *unsystematic*.

Sensitivity to initial conditions can refer to two related, but distinct, forms of unpredictability (Arnold et al., 1994). In some nonlinear systems the result is *seemingly random behavior*. Such behavior is referred to as chaotic. In other nonlinear systems the result is a *sudden qualitative change in behavior* when a small smooth change is made to a parameter. In mathematics, such a change is termed a bifurcation. Bifurcations are a general characteristic of nonlinear systems in physics (Prigogine, 1980), biology (Meinhardt, 1980), and psychology (e.g. van der Maas & Molenaar, 1992; Kelso, 1995; Ploeger, van der Maas, & Raijmakers, 2008). In physics they are called phase transitions; in biology and psychology they are often called stage transitions. Henceforth, we use the term bifurcation as a general term to refer to these transitions.

Non-linear systems can attain certain levels of order, structure, and stability by a process known as self-organization, i.e., an autonomous and self-regulating process (e.g. Camazine, 2001; Meinhardt, 1982). Numerous instances of self-organization have been found in both non-living and living systems. These include the formation of stripes in sand dunes and patterns on skins, coats, and shells (Camazine; Meinhardt). Self-organization has also been established in the process of morphogenesis that underlies the structured branching in organs, such as lungs, the cardiac muscle network, and the blood circulatory system. In addition, the brain may be viewed as a highly structured neural network. The notion that the formation of these structures involves self-organization is supported by the fact that the total amount of information stored in the genome is too small to prescribe these structures in any detail (Benno, 1990; Molenaar et al, 1993; Stent, 1978). In other words, self-organizing processes are required to explain the process of ontogenesis.

In this context, epigenetics and epigenesis are important concepts. In general terms, there is a close correspondence between self-organization and epigenesis, as Molenaar & Raijmakers (2000) emphasized: "[E]pigenesis constitutes an instance of a self-organizing developmental process" (p. 45). Or in the words of Belousov (2006): "Epigenesis may be regarded as the theory of self-organization as applied to ontogenetic phenomena" (p.1165). Traditionally, epigenetics refers to the study of such processes, i.e., "the way genes and their products bring the phenotype into being" (Jablonka & Lamb, 2002, p.82; Waddington, 1957). Nowadays, with the greater understanding of the molecular mechanisms that control gene activity during embryonic development and cell differentiation, epigenetics is defined as "the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence" (Jablonka & Lamb, p.87).

Despite differences in meaning and explanation, both traditional and molecular biological epigenetics focus on alternative developmental pathways, and on the influence of environmental conditions and its consequences for the organism. After fertilization, non-linear mechanisms³ initiate autonomous growth processes that give rise to structure and pattern (e.g. brain structure). However, the environment, the epigenetic process itself, and their interactions with both each other and with the genetic effects tend to perturb development, possibly resulting in variations in developmental pathway. That is, at critical points (i.e., bifurcation points, Arnold et al., 1995; Guckenheimer & Holmes, 2002), these perturbations may cause development to follow a different trajectory, resulting in variations in structure or pattern (Waddington, 1957). Given reciprocal influences between the development of neuronal form and function, on the one hand, and neural activity, on the other (e.g. van Oss & van Ooyen, 1997), differences in neuronal structure can result in differences in activity and, thus, can become manifest at the behavioral level (See also Benno, 1990). In the next sections we consider the plausibility of sensitivity to initial conditions and the related non-linear (epigenetic) processes as a source of unsystematic phenotypic variance.

³ Rather than needing to code each detail of an organism explicitly, the genes only require a minimal amount of genetic encoding specifying the rules that constitute these mechanisms.

2.3 Empirical Evidence Of Sources of Unsystematic Phenotypic Variance

Empirical evidence, from both animal and human studies, suggests that phenotypic variance cannot be explained completely by genetic and (external) environmental factors. For example, Gärtner (1990) reviewed the decades-long efforts in his own laboratory to minimize the variance of biological traits in laboratory animals by standardization of environmental and genetic conditions. The variance in a number of traits of highly inbred rats held under strict environmental control was compared with the variance in the same traits of rats living in a natural wild setting. These traits included morphological, biochemical, and other quantitative traits, such as blood parameters and kidney weight. The variance in inbred rats was not appreciably lower than the variance in wild rats. Hence, according to Gärtner, neither the postnatal environment nor genes appeared to constitute a major source of phenotypic variance in the inbred strains.

Subsequent research was performed to assess environmental variance directly. To this end, eight-cell stage mice embryos were divided, thereby creating monozygotic twin pairs. Each twin pair was transplanted into the uterus of the same foster mother, which raised both twins. Several physical characteristics, comparable to those described above, were measured after birth and compared with those of control mice. In genetically identical individuals, genetic variation is assumed to be eliminated, leaving only environmental stimuli to account for phenotypic differences, whereas in control (outbred) mice, phenotypic differences are due to both genetic and environmental differences. Hence, if both groups are held under identical conditions, the total variance within the group of control mice is expected to be greater than the variance within the group of genetically identical mice. However, the coefficients of variation appeared to be similar in both groups. Furthermore, measured environmental influences explained only 3 to 30% of the phenotypic variance.

In a similar experiment with Friesian cattle, an additional comparison was made with a group of divided embryos, which were transferred into, and raised by different uterine foster mothers. A large amount (70 to 97%) of the phenotypic variance remained unexplained. From these studies, Gärtner (1990) concluded that the remaining variance was due to influences other than genetic and (external) environmental influences.

Results obtained with cloned animals are consistent with the results of Gärtner (1990). For example, Archer, Dindot et al. (2003) compared cloned pigs with naturally bred controls on several phenotypic bodily traits as well as blood parameters. Controls were matched for age, breed, and sex, and were kept under identical conditions. Analysis of the phenotypic variance indicated that, compared to the controls, the cloned animals displayed as much or even increased variance in several traits. Although environmental conditions cannot be controlled fully, Archer, Dindot et al. argued that it is highly unlikely that (external) environmental effects could account for physical traits, such as hair growth pattern or skin type. They suggested that these differences in traits are caused by micro-environmental influences, minimal initial differences in uterine conditions, or small deviations that are introduced during cloning.

Besides phenotypic variation in genetically identical animals, studies of symmetry also reveal unexpected variation. Bilateral organisms often show intra-individual variation, which is known as fluctuating asymmetry. For example, Stige, Slagsvold, and Vøllestad (2005) repeatedly measured feather length and color patterns of wings and tail of the pied flycatcher. The degree of feather asymmetry persisted from nestling stage to adulthood, and even across moults. Genetic analyses revealed that the heritability of the asymmetry was almost zero, and that shared environmental factors had little influence. Moreover, differences in within-nest conditions did not explain the random variance in fluctuating asymmetry. The researchers concluded that asymmetry is possibly determined by (stochastic) events during early stages of development, permanently affecting the features of the feathers.

In humans, researchers have established small morphological asymmetries in various bilateral traits, such as bodily and facial features (Fink et al., 2004; Kowner, 2001). These variations emerge at a very young age and remain present throughout the lifespan. Furthermore, the direction of these asymmetries is not under genetic control. Fink et al. argued that facial asymmetries might be the results of perturbations in uterine conditions (e.g. hormone levels) in the first stages of embryonic development.

A related phenomenon, which counts as another indication of developmental instability, is the development of minor physical anomalies. Townsend et al. (2005), examining the dental records and radiographs of 278 monozygotic twin pairs, illustrated the contribution of developmental instability to phenotypic variability. They found that 24 twin pairs had developed missing or extra teeth. However, 21 of these pairs showed within-pair differences in patterns of expression (for instance, a mirrored effect). These researchers suggested that the observed differences in dental features of monozygotic twins stem from molecular interactions, leading to the initiation and, ultimately, the differentiation in the development of teeth.

Physical anomalies are also found in human brain organization and structure. Several studies have demonstrated the existence of atypical, non-genetically determined, asymmetries in human brain anatomy. For example, Eckert et al. (2002) examined the heritability of asymmetry in the planum temporale in 27 monozygotic and 13 dizygotic male twins. Magnetic Resonance Imaging (MRI) measurements revealed significant dissimilarities in gyral and sulcal features between monozygotic twins. The authors suggested that intra-uterine effects may lead to such variation in morphological development. Several other studies have replicated these results (e.g. Steinmetz, 1996; Thoma et al., 2002; Wright et al., 2002).

The unresolved variance originating in the process of development is not limited to biological or structural traits. Archer, Friend et al. (2003) compared the variance in several behavioral traits within litters of cloned swines and control (outbred) swines that were held under similar conditions. The traits included food preference, temperament, and time budgets such as feeding, standing, lying on concrete, lying in bedded area, and playing or fighting. The variance within the cloned group was as great as, or even greater than, the variance in naturally bred group. As we discuss in the next section, such unresolved variance may well characterize human psychological traits as well.

2.4 The Role of Nonshared Environment in Behavior Genetic Psychological Research

Researchers often distinguish five major domains of individual differences in psychological traits: cognitive abilities, personality, social attitudes, psychological interests, and psychopathology (McGue & Bouchard, 1998). Behavior genetic research within these domains has revealed a number of consistent, common findings (e.g. Turkheimer, 2000): First, a substantial amount of phenotypic variance can be attributed to genetic differences. Second, shared environmental variance is substantially smaller than the genetic variance. Third, a large portion of the phenotypic variance is attributed to nonshared environment. Moreover, over time heritabilities commonly increase, whereas environmentabilities decrease. However, the relative contributions of the shared component and nonshared component commonly change: If present, the contribution of the shared component decreases, often down to values close to zero. Hence, ultimately, most of the environmental variance is attributed to nonshared environment. Thus once genetic influences have been taken into consideration, siblings are ultimately hardly more similar than unrelated individuals drawn randomly from the population. Finally, MZ twins are often more than twice as similar as DZ twins, which often is explained by invoking dominance or epistasis (Turkheimer & Gottesman, 1996; Bouchard & McGue, 2003).

The amount of nonshared environmental variance ranges from about 20% in cognitive abilities in adults to about 60% in personality, phobias, and some social attitudes (Bouchard, 2004; Bouchard & McGue, 2003; McGue & Bouchard, 1998; Plomin et al., 2008). A meta-analysis of specific effects of objectively defined nonshared environmental variables (e.g. differences in sibling, teacher, and peer relationships) indicated that in behavioral genetic studies a considerable portion of nonshared environmental variance remains unexplained (Turkheimer & Waldron, 2000). The median percentage nonshared variance accounted for by these influences was no more than 2%. However, these effects are largely independent. So, “incorporating all of these measures of differential environment accounts for about 13 percent of the total variance of the outcome measures.” (Plomin et al, p.312). Thus, for personality, for example, a large portion of nonshared environmental variance remains unresolved.

How can these findings be explained? Firstly, estimates of nonshared environmental variance often include error variance. However, if we take into account reliabilities of many psychological tests (i.e., 0.80 or better), nonshared environmental variance still is relatively large. Secondly, a distinction should be made between environmental *events* and environmental *effects* (e.g. Turkheimer & Waldron, 2000; Rutter et al, 1997; Turkheimer, 2000; Plomin et al. 2008; Harris, 1995). Shared environmental events may affect children differently for the simple reason that individual children may react to a shared experience in different ways. Thirdly, it has been argued that specific nonshared environmental factors become increasingly important during development. Harris, for example, theorizes that over time the influences of children's peers become relatively more important than parental influences in shaping personality. However, as systematic studies have met with only limited success (Turkheimer & Waldron; Plomin et al., 2008), such specific nonshared effects are difficult to identify (Plomin, Asbury, & Dunn, 2001).

Why it is so difficult to identify nonshared influences? According to Turkheimer and Waldron (2000) both the underlying process and its effects appear unsystematic. Hence, one source of such environmental effects may be (molecular) chance processes (Finch & Kirkwood, 2000). Another possible explanation is that a significant part of unsystematic variance may result from deterministic non-linear epigenetic processes (Molenaar et al., 1993). Third, a possible class of nonshared environmental influences on psychological differences may be pre- and perinatal microenvironmental influences (McGue & Bouchard, 1998), which include, *inter alia*, molecular and cellular processes. Clearly, any combination between these sources of variance should be possible. For example, Smith (1993) argues that the intrinsic dynamics of the brain, e.g. indirect influences of spontaneous synaptic changes in activity, partially explain developmental variability.

In sum, experiments with both inbred and isogenic animals and studies of developmental instability in both humans and animals have produced converging evidence of unsystematic sources of phenotypic variance and dependency on initial conditions. In part, the ubiquitous nonshared environmental variance in psychological traits may in fact be due to nonlinear influences. Since the outcome of such processes is unsystematic (i.e., appears stochastic), these influences are hard to detect. This may explain why attempts to identify such influences have met with limited success (Turkheimer & Waldron, 2000). As suggested by Molenaar et al (1993), a part of the unsystematic phenotypic variance may actually be the result of nonlinear self-organizing epigenetic processes. Simulation studies of nonlinear epigenetic processes have been used to study the role and effects of such processes on behavior genetic analyses (Eaves et al., 1999; Molenaar & Raijmakers, 1999. The implications of these studies are discussed in the next section.

2.5 Computer Simulations of Non-linear Epigenetic variance

Both Eaves et al. (1999) and Molenaar and Raijmakers (1999) simulated nonlinear epigenetic variance in development using the discrete logistic equation as a simple model of development. This model can give rise to chaotic behavior, hence, these researchers were able to study the effects of sensitivity to initial conditions on twin correlations. In short, the main effect was a lowering of initial twin correlations. Specifically, intermediate or low (i.e., DZ) within pair correlations decreased at higher rates and to lower levels than high (i.e., MZ) within pair correlations (Eaves et al.). Genetic analyses revealed that, with time, the genetically induced correlations between the parameters had been concealed in the observed output: Observed heritabilities decreased to zero (Molenaar & Raijmakers).

From a theoretical and practical biological point of view, the model considered by Molenaar and Raijmakers (1999) and by Eaves et al. (1999) is limited. First, the discrete logistic equation prescribes that the current state depends on the previous state, but what biological or psychological state it denoted, was not specified. Second, the real time interval between the subsequent time steps was undefined. More importantly, in reality development does not unfold in discrete time. Third, the model displays chaotic behavior. According to Eaves et al., traits affected by chaotic processes should display DZ correlations close to zero while MZ correlations are high; a finding that is not frequently observed in human developmental research. In addition, over time chaotic processes will yield

observed heritabilities of 0 (Molenaar & Raijmakers), which is not observed in behavior genetic research. Hence, as Eaves et al. argued, the role of chaotic epigenetic processes in development may be quite limited. The possibility remains, however, that other types of non-linear processes, e.g. bifurcating systems, give rise to a different picture.

In this light, the computer simulations of Turkheimer and Gottesman (1996) are of interest. To study the dynamics of genes and environment in development, they considered a non-linear model that does not give rise to chaotic behavior, but that does display bifurcating behavior. Genotype, environment, and phenotype were conceived of as locations (dots) in two-dimensional space. Whereas genotype was simulated as a fixed location, environment and phenotype changed dynamically according to a set of simple rules, such as *phenotype is dynamically attracted to genotype*, *phenotype is dynamically attracted to environment*, and *environment is dynamically attracted to phenotype*. The relationship between locations of genotype and environment on the one hand, and of phenotype on the other hand, appeared highly unsystematic while the ultimate locations depended heavily on starting conditions.

Turkheimer (2000) conducted a twin simulation on the basis of this model. A significant part of phenotypic variance could be accounted for by genotypic variance, but none of it could be explained by the variance in environmentally determined starting locations. Furthermore, phenotypic DZ within-pair correlations were substantially smaller than MZ within-pair correlations. However, the DZ correlations were not close to zero as in the studies of Eaves et al (1999), and Molenaar and Raijmakers (1999). Although Turkheimer did not present his model explicitly as a model of nonlinear epigenetic variance, one may interpret it as such, especially in the light of his conclusion:

“[P]henotype at any moment in development is the cumulative result of an organism’s developmental history, encompassing genotype, environment, and all the complexities of their epigenetic interactions” (Turkheimer, 2000, p. 184).

Our present aim is to study the role of nonlinear epigenetic processes using a model of neurite outgrowth. The model shows bifurcating, but not chaotic, behavior and is biologically realistic: Time is modeled as continuous, the time-scale is defined, and the system’s output (the state of an organism) represents concrete characteristics (e.g. membrane potentials). Furthermore, previous computer simulations employing this model have demonstrated results that are consistent with empirically observed phenomena, such as a temporarily overproduction of synapses (see van Oss & van Ooyen, 1997). With our simulation study, we reconsider the plausibility of nonlinear epigenetic processes as a source of unsystematic phenotypic variance. Furthermore, by linear behavior genetic modeling, we estimate the contributions of genetic and environmental components, as well as their interactions. Below, we discuss the consequences of epigenetic processes for behavior genetic analyses, and the search for specific genes and environmental influences.

2.6 Modeling Network Development

The brain may be viewed as a highly organized neural network, comprising numerous structures and connections. As mentioned, the organization of the brain represents more information than is encoded in the genes, so this suggests that brain development involves self-organizing processes. As argued above, such processes may constitute a potential important source of individual differences.

During development neurons are assembled into functional network structures (for a review see, e.g. van Ooyen, 1994). One important factor determining neuronal morphology and network formation is intrinsic electrical activity; a mutual influence exists between network activity on the one hand, and neuronal form, connectivity, and function, on the other. That is, a network is able to generate patterns of activity, thereby changing the organization of the network, which in turn leads to an alteration of activity patterns. These can further modify the network’s structure or function, and so on. One example of a model of such activity dependent neural network development is the two-cell model of van Oss and van Ooyen (1997) that models neurite outgrowth.

Neurite outgrowth concerns the development of axons and dendrites, i.e., the development of connections between neuronal cells through which electrical activity is transmitted from one cell to

another. Van Oss and van Ooyen (1997) used their two-cell model to investigate the effects of the combination between activity dependent neurite outgrowth and inhibition. They showed that this combination can account for multistability, which they associated with normal and pathological end states of network development. This model has the characteristics that are considered to underlie epigenetic variance. A mathematical description of the model and its behavior is given in Appendix A. Here we limit ourselves to an informal description.

The two-cell model contains one excitatory and one inhibitory unit or cell (set out graphically in Figure 2.1). More complicated (network) versions of this model have been used in simulating biological, structural properties of the developing nervous system (van Ooyen et al., 1995; van Ooyen & van Pelt, 1996). The two-cell model is based on the behavior of populations of neurons, and was developed in order to replace the network model with its numerous differential equations with a simpler model that still displays the characteristics and behavior of this network model. A unit may thus represent a population of neurons (see also, Wilson & Cowan, 1972; Ghosh, Chang, & Liano, 1998). Comparable two-neuron models have been used to study working memory. Kirillov, Myre, and Woodward (1991) examined the functioning of inhibitory-feedback networks as programmable memory devices using a 1000-neuron model and observed rich dynamic behavior and multi-stability. In order to focus on collective behavior rather than on the behavior of individual neurons they developed a simplified two-neuron model of this network model. In subsequent research (Kirillov, Myre, & Woodward, 1993) they studied the behavior of this two-neuron model and concluded that “[m]any of the [...] results generalize to N-neuron interconnected models” (p. 449).

The interpretation of a unit representing a population of neurons can be justified on biological grounds; in many areas of the brain, neurons are organized in populations of neurons with similar properties. For example, this is the case in the somatosensory cortex (Mountcastle, 1957), the visual cortex (Hubel & Wiesel, 1962), and in pools of motor neurons (Kandel, Schwartz, & Jessel, 2000).

As mentioned, the two-cell model of van Oss and van Ooyen describes activity-dependent neurite outgrowth, one of the many dynamical processes involved in shaping neuronal morphology. Excitatory and inhibitory inputs take the membrane potential towards a finite maximum and minimum potential, respectively. The excitatory unit is connected to itself (with weight w_{xx}), which can be taken to represent reciprocal excitation between excitatory neurons. For simplicity, reciprocal inhibition between inhibitory neurons is not modeled (weight $w_{yy} = 0$), i.e., the inhibitory unit is not connected to itself. In its most simple form, the connection between the inhibitory unit and the excitatory unit is modeled as symmetric (weight $w_{xy} = w_{yx}$).

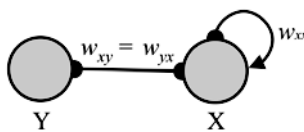


Figure 2.1 The two-cell model, where unit Y is interpreted as a population of inhibitory neurons and unit X as a population of excitatory neurons. X is connected to itself with weight w_{xx} . In contrast, Y is not connected to itself (mutual inhibition is not modeled). The connection between X and Y is modeled as symmetric ($w_{xy} = w_{yx}$). In the simulations, $w = w_{xx} = w_{xy} / p$.

A unit’s output is the mean firing rate, which is modeled as a sigmoidal function of the membrane potential. Parameters determine the steepness of the function as well as a low sub-threshold firing rate. The latter can be interpreted as spontaneous activity as a result of synaptic noise or fluctuations in membrane potential. Furthermore, increasing neurite outgrowth is thought to imply increasing connection strength. In turn, as connection strength increases, the amount of input that a cell receives through this connection also increases. Hence, the system is characterized by feedback. Finally, the dynamics of the connection strength are considerably slower than those of neuronal activity. Therefore, connection strength can be considered as a slowly varying parameter.

Using their model, van Oss and van Ooyen (1997) investigated occurrences of bifurcations in neuronal development. Such occurrences imply that individual networks may develop via different

pathways, dependent on initial conditions. Van Oss & van Ooyen studied the behavior of the network as a function of the parameters that determine the membrane potential at which neurite outgrowth is 0 (ε), and the relative strength of the inhibitory connection (p) (see Appendix A for further details). They found bifurcations, multistability, and rich dynamic behavior, including oscillations and transient jumps.

Empirical studies (see e.g. van Ooyen & van Pelt, 1994) have shown that, under normal conditions, developing cultures of dissociated cortex cells display a transient overproduction, or overshoot, of synaptic connections. An initial stage of neurite outgrowth and synapse formation is followed by a period of a considerable retraction of synapses towards a final stable state. In contrast, when a developing culture is deprived of electrical activity for a certain amount of time, neurite outgrowth is enhanced. In this case retraction of synapses does not take place, even if electrical activity is restored. This suggests there may exist a critical period after which electrical activity no longer results in retraction of synaptic connections. These results imply that multistability exists, because differences in initial conditions (i.e., differences in exposure to electrical activity) result in different stable developmental pathways (i.e., differences in neurite outgrowth).

Due to the relative simplicity of the model, van Oss and van Ooyen (1997) were able to construct a bifurcation diagram, in which areas in the parameter plane (ε , p) are associated with qualitatively different dynamic behavior of the model. These areas are demarcated by bifurcations. The realistic nonlinear characteristics of this model of neuronal development and the knowledge of its dynamics render it very suitable to study the generation of nonlinear epigenetic variance in a simulation experiment within a behavioral genetic design. Moreover, the systematic bifurcation analysis gives us good insight in the dynamics of the model that are relevant to the interpretation of the results of behavioral genetic analyses. We retained all model assumptions, so as to ensure that the bifurcation diagram described the model.

The model has several characteristics, which help to illustrate the theoretical point that epigenetic processes constitute a source of variance. First, due to the reciprocal interactions and the sigmoid activation functions, the model is non-linear. The specific properties of the model that may give rise to epigenetic variance are the occurrence of bifurcations (the possibility that small differences in parameter values, e.g. small differences in enzyme concentrations, result in qualitatively different phenotypes), and the presence of multistability (initial differences can result in different developmental pathways). The existence of qualitatively different possible phenotypes given one genotype implies that members of a MZ twin pair may follow different developmental pathways. Second, the model displays properties of self-organization. Third, the model describes development as a deterministic process. This is important theoretically, because it means that the sensitivity to initial conditions does not arise from any randomness, i.e., the epigenetic variance is not attributable to an external random process that introduces noise into the system.⁴

Using the two-cell model of van Oss & van Ooyen (1997), we aimed to simulate twin data in the form of time series. These time series were generated under various assumptions concerning starting values, parameter values, and degree of genetic control in order to create nonlinear epigenetic variance. In addition, we addressed another question of interest in this context: what consequences do these processes have for the estimated heritabilities and environmentabilities in the standard twin model?

2.6.1 Twin Simulations Applying The Two-Cell Model

Method Parameter values, the sigmoid function (see equation 3 in Appendix A), and the form of the differential equations constituting the two-cell model (see equations 1, 2, and 4 in Appendix A) give rise to the non-linear epigenetic process of the development of phenotypic traits. These traits are x , the time averaged membrane potential of the excitatory unit, y , the time averaged membrane potential of the inhibitory cell, and w , the connection strength between excitatory neurons. The variances of the parameters ε and p are attributable to genetic and environmental individual differences within the population. That is, individual differences in ε and p satisfy the standard behavior genetic model (see

⁴ This is not to say that developmental processes are noise-free.

above). Thus, individual differences in ε and p are the causes of individual differences in the development of phenotypic traits x , y , and w . Starting values of x , y , and w were set at 0.

Phenotypic time series were generated for 200 MZ and 200 DZ twin pairs using a simple additive model: $\varepsilon_i = \varepsilon_{g,i} \sqrt{a} + \varepsilon_{c,i} \sqrt{b} + \varepsilon_{e,i} \sqrt{(1-a-b)} + m_{\varepsilon}$, and $p_i = p_{g,i} \sqrt{a} + p_{c,i} \sqrt{b} + p_{e,i} \sqrt{(1-a-b)} + m_p$, with $0 \leq a \leq 1$, $0 \leq b \leq 1$, and $a + b \leq 1$, where ε_i and p_i are the individual values of the parameters ε and p , respectively, and m_{ε} and m_p are the sample means of the parameters. The subscripts g , c , and e refer to the additive genetic, shared environmental, and nonshared environmental components of a parameter, with regression coefficients \sqrt{a} , \sqrt{b} , and $\sqrt{(1-a-b)}$, respectively.⁵ Assuming that the additive genetic and environmental components of a parameter are uncorrelated and sampled randomly from the standard normal distributions, heritability h^2 equals a , common environmentability c^2 equals b , and unique environmentability e^2 equals $(1-a-b)$. MZ twin correlations of the additive genetic, shared, and nonshared environmental components equal 1 (100% additive genetic resemblance), 1, and 0, respectively. The same procedure was followed to generate 200 DZ twins, except the DZ twin correlations of the additive genetic components equals 0.5.

In matrix notation (e.g. for the parameter p) this can be written as:

$$\mathbf{p} = \begin{bmatrix} \sqrt{a} & \sqrt{b} & \sqrt{(1-a-b)} & 0 & 0 & 0 \\ 0 & 0 & 0 & \sqrt{a} & \sqrt{b} & \sqrt{(1-a-b)} \end{bmatrix} \cdot \begin{bmatrix} p_{g,1} \\ p_{c,1} \\ p_{e,1} \\ p_{g,2} \\ p_{c,2} \\ p_{e,2} \end{bmatrix} + \begin{bmatrix} m_p \\ m_p \end{bmatrix}$$

With covariance matrix

$$\Sigma_p = \begin{bmatrix} a \cdot \sigma_{p_g}^2 + b \cdot \sigma_{p_c}^2 + c \cdot \sigma_{p_e}^2 & r_g \cdot a \cdot \sigma_{p_g}^2 + b \cdot \sigma_{p_c}^2 \\ r_g \cdot a \cdot \sigma_{p_g}^2 + b \cdot \sigma_{p_c}^2 & a \cdot \sigma_{p_g}^2 + b \cdot \sigma_{p_c}^2 + c \cdot \sigma_{p_e}^2 \end{bmatrix}$$

Where subscripts 1 and 2 refer to each of the members of a twin pair and r_s denotes the genetic resemblance.

In simulating the data, we chose a heritability of 0.5 for both parameters p and ε . Furthermore, referring to the epigenetic picture and to non-linearity, initial conditions may be very similar. However, in real biological systems exactly equal initial conditions are impossible. This would require an infinite amount of information (or energy), which is biologically implausible (Molenaar & Rajmakers, 1999). Therefore, we set unique environmentability to a low, but nonzero, value (i.e., to 0.01). As a consequence, common environmentability was set to a value of 0.49. This procedure implies that in the absence of nonlinearity, standard behavior genetic analyses of the phenotypic measures should be expected to yield a heritability estimate of 0.5, a common environmentability of 0.49, and a unique environmentability of 0.01. However, given the occurrence of bifurcations and sensitivity to initial conditions, additional (i.e., epigenetic) variance is expected to arise.

The differential equations were numerically solved using the variable time step integrator Lsoda (Petzoldt, 2003). Subsequently, phenotypic twin correlations of x , y , and w were obtained at timepoints $t = 0$ to 20000 (by $t = 20000$ all networks have reached their final stable states). Regular oscillations can and do occur in these measures, which are a consequence of switches between two states. Latency shifts in these oscillations complicate statistical analyses: At certain points of time some twin members may show behavior that is out of phase or even in anti-phase, whereas the signals

⁵ One usually would implement environmental influences in a network by input of external activity. However, in doing so, the bifurcation diagrams would no longer apply to the model. In addition, this point is not relevant to the hypothesis that non-linear epigenetic processes constitute a source of variance.

over time may be highly similar. Such occurrences could lower twin correlations a bit when one would sample the raw measures at an arbitrary time point. We consider this as a kind of measurement error. In order to minimize such error, we derived alternative phenotypic measures. These are the mean of the signal over a certain period of time and the relative power. The mean signal is thus a smoothed signal, where high frequency oscillations have been filtered out. The power of a signal is a time average of energy (energy per unit time), where energy is defined by the area under the signal. Relative power is the power of one frequency band relative to that of other frequencies. In this manner we could distinguish (almost) non-oscillating signals (frequencies < 0.1) from oscillating ones (frequencies ≥ 0.1). In order to calculate the two alternative phenotypic measures, time was divided into 40 equal intervals: $[0, 500)$, $[500, 1000)$, ..., $[19500, 20000)$. Twin correlations were calculated in each time window.

In simulation 1 we chose region 5b within the (ε, p) -plane as region in which variance was to be created in parameters ε and p . This region is shown in Figure A.2 (see Appendix A). In this region one point attractor and two stable limit cycles exist. Such a limit cycle can be viewed as a switching between two states. With respect to epigenetics, we note that the system may follow multiple developmental pathways. However, which path is followed depends on the parameter values. A second reason for choosing region 5b was that connection strength grows to finite values, which is biologically more plausible than infinite growth. A third reason was that in this region the occurrence of overshoot is possible. As noted above, overshoot is a widespread phenomenon in empirical studies.

The means of parameters ε and p were set at 0.52, and 0.42, respectively. This parameter combination is located approximately in the centre of region 5b. In this way, the variance of the parameters could be taken as large as possible (0.0005 for both parameters). In the interest of biological plausibility, non-varying parameter values were set identical to those in the study of van Oss and van Ooyen (1997), i.e., $h = 0.1$, $\theta = 0.5$, $\alpha = 0.1$, and $b = 0.00005$. An exception was made for the value of q , which was set at 0.05.⁶ This parameter determines the outgrowth rate (see Appendix A). The use of lower values would slow down outgrowth and, thus, greatly increase the number of computations. Figure 2.2 depicts the behavior of x (left) and y (middle) for a number of parameter values for $t = 19800$ to $t = 20000$ as well as the development of w from $t = 0$ to $t = 20000$. Distinct behavior can be discerned, which is due to the existence of different types of attractors within one region.

In simulation 2 we chose region 5a as parameter region. Region 5a differs only from region 5b in that the limit cycles are absent. Only the point attractor exists, hence multistability is not present. We set the parameter means of ε and p to values of 0.8, and 0.3, respectively. The variances of parameters ε and p as well as other parameter values were identical to the values used in simulation 1. Figure 2.3 depicts the behaviors of x (left), y (middle), and w (right) from $t = 0$ to $t = 20000$ for these parameter values. We carried out simulation 2 to compare the differences between the amount of unexplained variance in case of multistability with the amount of unexplained variance in case of monostability. This difference can be regarded as the amount of nonlinear epigenetic variance.

Results To determine discordance between twins, we used the relative power of x . A twin pair shows discordant behavior if the one member of a twin pair displays oscillating behavior, whereas the other member does not. Twin correlations were based on the filtered (smoothed) signals. The filtered signals of x and y still showed some oscillating behavior. As explained above, oscillations may lead to latency shifts, which yield slight overestimates of unexplained variance (i.e., due to what we above have denoted measurement error). In order to minimize the effects of such error, we here mainly concentrate on the analyses of the filtered signal of w , but it should be mentioned that the other phenotypic measures gave similar results.

As is common in behavior genetic research, we decomposed phenotypic variance into latent factors by fitting an ACE twin model, where A stands for additive genetic effects, C for common, or shared, environmental effects, and E for nonshared environmental effects. We did so over each of the 40 time intervals. In addition, in each simulation two stepwise regression analyses were carried out on

⁶ As compared to the results of simulations using the original value of q (0.005), using the value of $q = 0.05$ did not give rise to qualitative different behavior of the system, or to computational artifacts.

the filtered signal of w , over the last time interval ($19500 \leq t < 20000$). To describe the amount of variance explained by the model, we calculated the adjusted squared multiple correlation coefficient ($R^2_{adjusted}$) between all of the predictors and the dependent variable. We calculated the amount of unexplained variance as $(1 - R^2_{adjusted}) * 100\%$. In the regression model, the predictors were the variables $p_g, p_c, p_e, \varepsilon_g, \varepsilon_c$ and ε_e . As above the dependent variable was the filtered signal of w . In the first analysis, the linear regression model (henceforth, referred to as ‘G+E model’) includes solely main effects for all independent variables. In addition to main effects, the second regression model (henceforth, referred to as ‘G×E model’) includes interaction terms for all possible combinations for all independent variables.

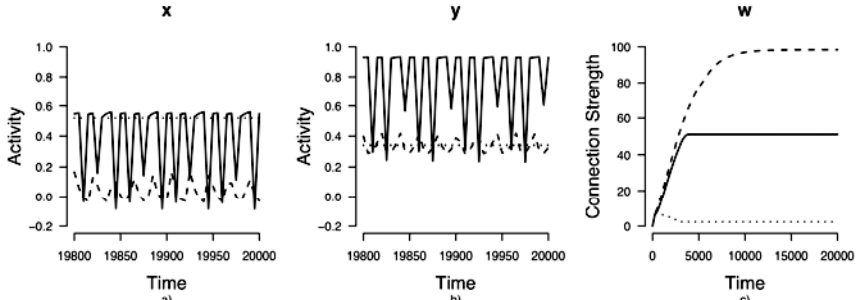


Figure 2.2 The behavior of x (a), y (b), and w (c) of developing networks in case of multistability. Parameter values are $\varepsilon = 0.52$, and $p = 0.435$ (straight lines), $p = 0.420$ (dashed lines), and $p = 0.402$ (dotted lines).

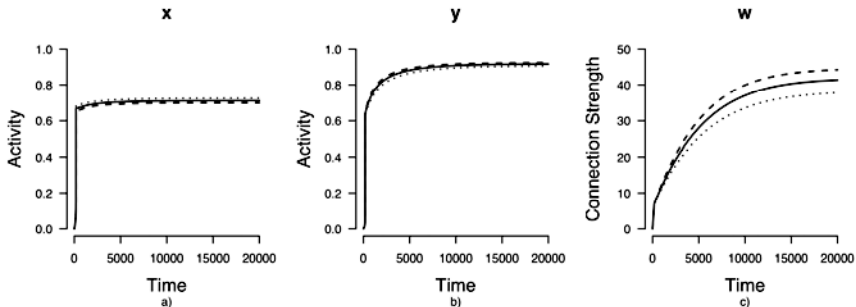


Figure 2.3 The behavior of x (a), y (b), and w (c) of developing networks in case of monostability. Parameter values are $\varepsilon = 0.8$, and $p = 0.315$ (straight lines), $p = 0.300$ (dashed lines), and $p = 0.282$ (dotted lines).

Simulation 1: subregion 5b In simulation 1, multiple stable attractors were present. Simulations using the two-cell model gave rise to bifurcations and multistability. The presence of bifurcations implies that small differences in parameter values could result in qualitatively distinct behavior; differences in developmental pathways and differences in final stable states (i.e., oscillating versus non-oscillating behavior). Twin members could thus follow discordant developmental pathways. At the end state, 27.5% of the MZ twin pairs, and 33% of the DZ twin pairs showed discordant behavior. In addition, even in the absence of noise, with time a substantial and increasing amount of unsystematic (nonlinear epigenetic) variance arose, which was attributed to the nonshared component in a linear behavior genetic analysis.

The presence of bifurcating processes resulted in a lowering of twin correlations over time. Figure 2.4 illustrates the development of these correlations with respect to the filtered signal of w , together with the development of observed heritabilities and environmentabilities. As one can see, relatively high initial correlations (MZ correlations) are affected less than relatively low initial correlations (DZ correlations). In other words, compared to DZ twin similarity, MZ twin similarity was better preserved. As a consequence, observed common environmentabilities decreased to zero,

whereas heritabilities and unique environmentabilities increased over time. Although not depicted, the development of twin correlations of other phenotypic measures yielded qualitatively the same picture.

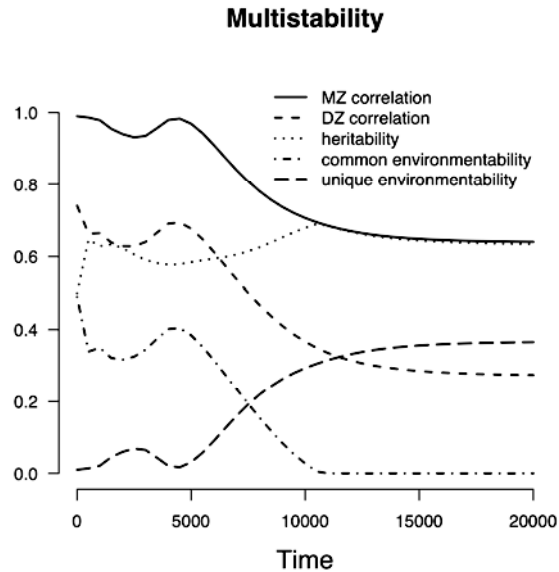


Figure 2.4 The development of MZ and DZ twin correlations, observed heritabilities and observed environmentabilities of the filtered signal of w in case of multistability.

Fitting an ACE-model to the twin covariance matrices of the filtered signal of w at the end state yielded good fits ($\chi^2(3) = 0.495$, $p = 0.91$). The variance attributed to the nonshared environmental component increased substantially (to 36.6%). The variance attributed to genetic effects also increased (to 63.4%), whereas estimated shared environmental variance had dropped to 0.00%. Dropping the shared environment component (C) from the model did not alter the model fit.

These results are in concordance with those of the stepwise regression analyses: In the G+E regression model on the filtered signal of w at the end state, a large part of the variance remained unexplained (58.1% in MZ twins and 63.3% in DZ twins). The model that included interaction terms (GxE model) did little to decrease the unexplained variance (53.1% in the MZ twins, and 62.5% in the DZ twins). In other words, GxE interaction did little to account for the residual variance. Thus, nonlinear epigenetic variance was not explained by genotype-environment interaction.

As in latent variable modeling, in the regression analyses the genetic components (p_g and ε_g) explained a significant part of the variance in the dependent variable, the filtered signal of w . However, in contrast to latent variable modeling, in the regression analyses the shared environmental components could explain a significant part of the variance. Hence, we may conclude that the effects of shared environmental influences were not detectable in a standard twin design.

Simulation 2: subregion 5a In simulation 2, one stable (point) attractor was present. Simulations using the two-cell model revealed the consequences of the absence of bifurcations and multistability. Differences in parameter values did not result in qualitatively different phenotypes or different developmental pathways. As a consequence, discordance between twins was 0. Furthermore, nonlinear epigenetic variance did not arise. Behavior genetic models yielded good fits and (nearly) all variance was explained.⁷

⁷ Since we described just a single simulation in each of the series of experiment, we could not quantitatively test the amount of non-linear epigenetic variance against the null-hypothesis of an unexplained variance of 0. To do so, each simulation should be repeated applying a full Monte Carlo design with sufficient numbers of replications.

Figure 2.5 illustrates the development of phenotypic twin correlations of the filtered signal of w , together with the observed heritabilities and environmentabilities. Twin correlations remained stable over time. As a result, observed heritabilities and environmentabilities accurately reflect the initial genetic and environmental structure. The results in terms of twin correlations obtained with the other phenotypic measures were largely the same.

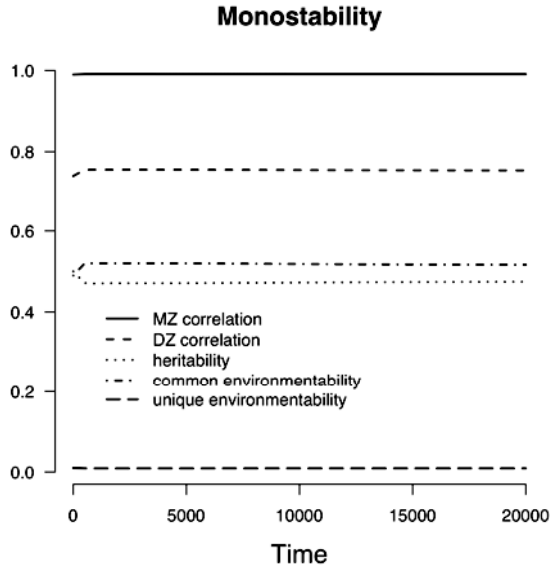


Figure 2.5 The development of MZ and DZ twin correlations, observed heritabilities and observed environmentabilities of the filtered signal of w in case of monostability.

Fitting an ACE-model on the filtered signal of w at the end state yielded perfect model fit ($\chi^2(3) = 0.00$, $p = 0.99$). The percentage of variance attributed to genetic effects was 47.5%, whereas the percentages of variance attributed to the shared and nonshared environmental components were 51.7% and 0.90%, respectively. These results are in concordance with the results from the regression analyses: The G+E regression model on the filtered signal of w at the end state explained nearly all of the variance (99.95% for the MZ twin data, 99.94% for the DZ twin data). The G×E regression models yielded about the same results: 99.99% of both the MZ and DZ twin data was explained. As expected, both genetic components (p_g and ε_{g_s}) and shared environmental components (p_c and ε_{c_s}) of the parameters were good predictors of the filtered signal of w .

Conclusion In simulations 1, we found that nearly all the variance that was attributed to unshared environmental effects in the twin model, was actually due to nonlinear epigenetic variance. This variance was due specifically to the disproportional relationships between causes and effects within the nonlinear process. Furthermore, we established that nonlinear epigenetic variance is distinct from variance due to genotype-environment interaction. Specifically, the interaction in our regression analyses did little to account for any of the variance. In conclusion, ultimate genetic and environmental causes of phenotypic variance were not detected in the standard twin design.

However, we carried out our simulations more than once and found comparable results. Hence, we consider our corresponding qualitative comparisons as most indicative.

2.7 Discussion

In the present chapter, we reviewed the literature on empirical evidence that suggests that non-linear (epigenetic) processes during ontogenesis account for a substantial portion of phenotypic variance. Such processes may account for a part of the ubiquitous nonshared environmental variance in twin studies of psychological traits. Second, we simulated twin data using a biological realistic model of neurite outgrowth, which displayed the characteristics that were hypothesized to underlie nonlinear epigenetic variance. The results of our simulations demonstrate that the existence of multiple attractors due to bifurcations gives rise to phenotypic variance in simulated neuronal development. This variance cannot be attributed to genetic or environmental components of the parameters, to measurement error, nor to any other external random process that introduced noise into the system. Hence, the variance can be interpreted as nonlinear epigenetic variance. In the standard behavior genetic (twin) model, this variance is subsumed under the nonshared environmental component.

In simulation 1, the existence of multistability and the related sensitivity to initial conditions gave rise to nonlinear epigenetic variance, which caused the twin correlations to decrease over time. The variance was unsystematic, thus remained unexplained in the regression analyses. The actual contributions of the genetic and environmental factors to the parameters in the model were not recovered in the standard twin model. The depressing effects of nonlinear epigenetic variance were greater on DZ than on the MZ twin correlation. As a consequence, over time heritabilities appeared to increase, and shared environmentabilities appeared to decrease to zero. In simulation 2, the absence of multistability ensured that we could recover the genetic and environmental contributions to the parameters well.

Our results are in concordance with the empirical evidence we reviewed, in which a substantial portion of phenotypic variance, provisionally attributed to unshared (nonshared) environmental influences, actually remains unexplained. This variance may be due to nonlinear sources of variance, which will include endogenous molecular or cellular processes. The hypothesis that non-linear epigenetic processes represent an appreciable source of variance is consistent with the fact that nonshared effects have proven quite hard to identify (Turkheimer & Waldron, 2000).

The results of the simulations are also consistent with the common findings in behavior genetic studies in psychology. That is, over time the estimated relative contribution of nonshared variance to phenotypic variance increases, whereas shared variance decreases to zero. As a consequence, estimated heritabilities increased, which is often observed in longitudinal twin studies (e.g. Bouchard & McGue, 2003). Finally, monozygotic twins were more than twice as similar as dizygotic twins, which is also frequently observed (Turkheimer, 2004).

The consequences of the presence of nonlinear epigenetic variance may be far reaching. The exact influences on initial conditions will be generally untraceable in standard behavior genetic modeling (of twin data, say), because the effects are unsystematic. Moreover, because the effects of nonlinear epigenetic processes may result in changes in the environmental variance over time, investigators might be inclined to seek explanations in terms of environmental factors. The same applies to the search for genetic factors. Again, due to the effects of nonlinear epigenetic processes, genetic variance may change over time. The standard interpretation of changes in heritability (say in terms of the ACE model) may be sought in specific genetic hypotheses, such as the switching on/off of genes (see also Eaves et al, 1999), while the ultimate causes lie elsewhere. Or, given DZ correlations which are markedly low compared to the MZ correlations, investigators may assume the presence of genetic interaction effects such as dominance or epistasis, whereas these may be absent (see also Turkheimer & Gottesman, 1996).

In the traditional behavior genetic model, genetic effects, shared and nonshared environmental influences are subject to a linear model, which yields the usual decomposition of phenotypic variance. A further decomposition of nonshared environmental variance into linear nonshared environmental variance and non-linear (epigenetic) variance would further increase our understanding of what we currently denote as nonshared environmental variance. Figure 2.6 depicts a schematic representation of this. Since their effects will be traceable in principle, measured nonshared influences can be incorporated in the model. In contrast, nonlinear influences act unsystematically and, as a consequence, these will difficult to trace back.

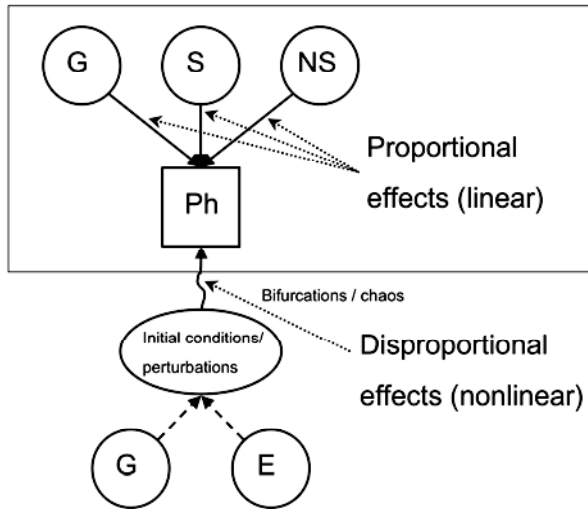


Figure 2.6 Phenotype (Ph) as a function of linear and nonlinear influences. In a linear behavior genetic model, the environmental component is decomposed into shared environment (S) and nonshared environment (NS). Error variance is subsumed under the nonshared component. In contrast to the modeled linear (proportional) effects, chaotic and bifurcating (epigenetic) processes will have unsystematic (disproportional) effects. These will be difficult to distinguish from error. The genetic (G) and environmental (E) influences on initial conditions or perturbations will be hard to detect. Although the ultimate influences on phenotype are only genetic and environmental, nonlinear (epigenetic) processes constitute a distinct and independent source of variance.

One solution to this problem, within the context of the present model, is to categorize the networks into classes according to their qualitative behaviors, which depend on the network's attractor. One can then fit a linear behavior genetic model to the data within each class. Within each class, at each point of time, the genetic and environmental contributions to the parameters can be recovered quite well. In theory, this can be achieved by fitting mixture models, which allows one to identify latent classes and fit the standard twin models within these classes. Whether this is actually viable in twin data is an open question, but this does provide an interesting perspective on the recent interest in mixture modeling of twin data (Gillespie & Neale, 2006; Muthén, Asparouhov, & Rebollo, 2006).

Our interpretation of nonshared environmental variance as consisting in part of non-linear epigenetic variance is consistent with Molenaar et al. (1993), who consider nonlinear epigenetic processes as a third source of variance, alongside genetic and environmental influences. According to the definition of nonshared variance in behavior genetics, non-linear epigenetic variance is subsumed under the nonshared environmental component even though initial conditions may be determined mainly by genetic effects and shared environmental influences. However, the ultimate causes (sources) of phenotypic differences are thus only genetic and environmental. Hence, to refer to nonlinear epigenetic variance as a third source is a matter of definition.

One important issue concerns the scalability of nonlinear epigenetic processes. Since the processes we simulated were low-level processes, it is important to consider how nonlinear effects may accumulate and combine. Such effects can average out to produce a kind of statistical macro-level behavior (that may show stage/phase transitions), or they can amplify each other as they do in chaotic systems (e.g. in a system such as the weather system). In chaotic epigenetic systems the genetic structure initially present will be destroyed, i.e., twin correlations will approach zero, a result not frequently observed in empirical studies (Molenaar & Raijmakers, 1999). The role of chaos in development may thus indeed be limited, as Eaves et al. (1999) argue. However, if within a nonlinear system only a limited number of bifurcating processes are present, e.g. a limited number of stage transitions, critical periods, or developmental pathways, a different picture may arise. In that case,

differences in (initial) conditions may only have an effect at critical points (bifurcation points), even when they are very small. At other points, differences in conditions may not affect development, even when they are very large. Our review of the literature indicated that initial conditions are of great importance, whereas phenotypes are often stable over time. These findings would support such an account.

One possible step researchers may take to investigate whether nonlinear (epigenetic) processes contribute to nonshared variance in a trait is to study the developmental trajectory of that trait. Ontogenesis invariably involves self-organizing processes, and self-organization invariably arises in nonlinear systems. Given that bifurcations (stage/phase transitions) are a common characteristic of nonlinear dynamics, the presence of critical periods or stage transitions strongly suggest that the process is nonlinear. Van der Maas and Molenaar (1992; see also Gilmore, 1981) discuss in considerable detail the detection, using catastrophe flags, and the classification of stage transitions and the ways to distinguish between transitions due to nonlinear dynamics and mere acceleration in growth (e.g. growth spurts). We believe that these can be used to study complex human behavior, such as Piagetian cognitive development, motor development, and language development. The use of a longitudinal twin design, would allow one to study dynamics of development by means of the catastrophe flags, and relate these to changes in the nonshared environmental covariance structure.

Another issue concerns the generalizability of our simulation experiments. We studied the effects of nonlinear epigenetic processes in an unsupervised, self-organizing network. Within neural network modeling, many networks are supervised systems, which are generally not self-organizing systems (but see van der Maas, Verschure & Molenaar, 1990; Raijmakers & Molenaar, 2004; Pollack, 1991; Rodriguez, Wiles, & Elman, 1999; Daucé, 2007). Since, non-linear epigenetic processes were considered to involve self-organization, nonlinear epigenetic variance may be expected to be less important in supervised systems. However, to conceive the whole organism as fully supervised systems is implausible. Indeed, in real biological systems (fully) supervised networks may exist, but they will be coupled with and thus dependent on unsupervised or mixed supervised/unsupervised networks. There is no reason to expect that nonlinear epigenetic variance will not arise in these systems. Hence, we may find nonlinear epigenetic variance at all levels, biological as well as psychological, just as bifurcations (phase transitions and stage transitions) are found at all these levels. Kelso stresses repeatedly:

“[O]ver and over again nature uses the same principles of self-organization to produce dynamic patterns on all scales. The precise patterns that form may differ from one scale of observation to another, but the basic principles are the same.” (Kelso, 1995, p. 24).

Indeed, he described bifurcations at molecular levels in the activity of ion channels, at psychological levels, in perception, motor coordination, speech, language acquisition, learning, working memory, and cognition, and even at the level of interindividual behavior, for instance in case of social coordination.

Furthermore, (critical) periods may exist, before the inception of any supervision, during which sensitivity to supervision is developed. This suggestion is compatible with van Oss & van Ooyen's (1997) account of their simulation experiments, in which they study the existence of critical periods. As mentioned above, under normal conditions, developing cells display an overproduction of connections followed by a period of retraction. When a developing culture is deprived of electrical activity for a certain amount of time, retraction does not take place, even if electrical activity is restored. Hence, in such a case supervision may have a different effect. Further simulation studies addressing these issues will elucidate the role of nonlinear epigenetic variance in supervised versus unsupervised learning.

We consider it possible that genetic influences and shared environmental events are causes of nonshared effects. For example, if shared environmental events have influence on a nonlinear system, they may act as nonshared influences and thus might have nonshared effects. Perhaps shared events have a greater chance to result in shared effects in MZ twins (pushing them towards to identical or similar attractors) whereas shared events have a greater chance to result in nonshared effects in DZ twins (pushing them towards nonidentical or different attractors). MZ correlations may

increase, while DZ correlations may increase less or may even decrease. This would further increase heritability and nonshared environmentability, and decrease shared environmentability. In that case, shared environmental factors that do not differ between children growing up in the same family may explain why children growing up in the same family are different and why pairs of identical twins become different.

In sum, we demonstrated the emergence of nonlinear variance in a bifurcating developmental process. We interpreted this variance as epigenetic variance. The presence of nonlinear epigenetic variance had clear effects on the twin correlations, which in turn affected the estimated heritabilities and environmentabilities. These were found to be comparable to those commonly reported in the literature. In conclusion, we believe that it is important to be aware of the role of nonlinear (epigenetic) processes in psychological development. Theoretically, these provide a challenging perspective on the sources of individual differences, and the interpretation of variance components. We believe that this perspective will ultimately enrich behavior genetic studies, by raising new research questions, and by reducing the gap between (linear) statistical modeling and developmental (nonlinear systems) theories of individual differences.