Towards an integration of evolutionary psychology and developmental science : new insights from evolutionary developmental biology

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TOWARDS AN INTEGRATION OF EVOLUTIONARY PSYCHOLOGY AND DEVELOPMENTAL SCIENCE

New insights from evolutionary developmental biology

Annemie Ploeger

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Towards an integration of evolutionary psychology and developmental science

New insights from evolutionary developmental biology

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aan de Universiteit van Amsterdam
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prof. dr. D.C. van den Boom
ten overstaan van een door het college voor promoties
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Annemie Ploeger

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Promotor:	Prof. dr. H.L.J. van der Maas
Co-promotores:	Dr. F. Galis Dr. M.E.J. Raijmakers
Overige leden:	Prof. dr. C. Kemner Prof. dr. M. van Lambalgen Prof. dr. M.W. van der Molen Prof. dr. R. Wiers Dr. C.J.M. Egas Dr. H. Looren de Jong

Faculteit der Maatschappij- en Gedragswetenschappen (FMG)
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CHAPTER 1

GENERAL INTRODUCTION

It was in 1996 during my stay at the Florida Atlantic University (FAU) in the USA, that I first learnt about evolutionary psychology. As a student of developmental psychology, I started working on my Master's thesis in the lab of Howard Hock, who is a renowned professor in the field of visual perception. I arrived at FAU to investigate experimentally dynamic aspects of vision, as I was interested in a dynamic systems approach to development. Dynamic systems theory is a mathematical theory that describes the behavior of complex dynamical systems, such as the behavior of human beings. Within this theory, developmental outcomes are explained as the spontaneous emergence of coherent, higher-order forms through recursive interactions among lower-level components (Lewis, 2000). The emergence of higher-order forms occurs by phase transitions, and visual perception was an excellent subject to study such phase transitions.

In Florida, I hoped to meet people with whom I could discuss the dynamics of development, and to develop a new research program on how to study the dynamical aspects of the human mind. With the presence of the Center of Complex Systems at FAU, at the time directed by Scott Kelso, I certainly met those people, and I had a very inspirational time. Rather coincidently, I took a course on evolutionary psychology, taught by the professors David Bjorklund and Robin Vallacher, and this course influenced my scientific thinking more than any other course I had taken in Florida or at home in Amsterdam. This was quite surprising, because at high school I was a *gymnasium-alpha* student, without biology in my curriculum, and my knowledge of evolutionary theory was vague at best, as was my understanding of the relevance of evolution for psychology. The book we read for the course was *The Adapted Mind: Evolutionary Psychology and the Generation of Culture*, edited by Barkow, Cosmides, and Tooby (1992). From the very first sentence I read in the book, to the very last, I was overwhelmed by all the new theories and new experiments, all following from evolutionary thinking. As many students in psychology, I had always been displeased by the fragmentation of the research in the field: many interesting experiments and findings, but all quite isolated and lacking a unifying view on how the mind works. Dynamic systems theory was one way to

integrate different areas in psychology, and evolutionary psychology appeared to be another way to integrate the diverse array of facts and findings in psychology and other social sciences.

Evolutionary psychology

In *The Adapted Mind*, evolutionary psychology is defined as 'simply psychology that is informed by the additional knowledge that evolutionary biology has to offer, in the expectation that understanding the process that designed the human mind will advance the discovery of its architecture' (Cosmides, Tooby, & Barkow, 1992, p. 3). It continued with: 'It unites modern evolutionary biology with the cognitive revolution in a way that has the potential to draw together all of the disparate branches of psychology into a single organized system of knowledge' (p. 3). During the aforementioned course, we also read an article by Buss (1995), who stated that 'although psychologists assume that the human mind is a whole and integrated unity, no metatheory subsumes, integrates, unites, or connects the disparate pieces that psychologists gauge with their differing calipers. An important new theoretical paradigm called *evolutionary psychology* is emerging that offers to provide this metatheory' (p. 1). I was thrilled by the possibility of evolutionary psychology as a metatheory for psychology. Actually, it was not the first time that I was thrilled by a theory. From the very first start of my study in psychology, I liked the developmental theory of Jean Piaget.

Jean Piaget

Piaget, the father of developmental psychology, proclaimed that children's development proceeds in stages, each stage characterized by qualitatively different kinds of behavior and cognition. The differences in behavior and cognition arise because underlying each stage is a domain-general structure that constrains the way the child thinks and explores its environment at a certain age. Interestingly, Piaget used to be a biologist. Only after finishing his dissertation on mollusks, did he embark on his studies in psychology. However, his interest in biology remained, leading him to write books, among many others on child development, entitled *Biology and Knowledge* (1971), *Behavior and Evolution* (1978), and *Adaptation and Intelligence* (1980a). In 1983 Piaget wrote that his theory of development 'is impossible to understand if one does not begin with analyzing in detail the biological presuppositions from which it stems and the epistemological consequences in which it ends' (p. 103). Thus, Piaget can be viewed as an evolutionary psychologist *avant la lettre*.

But do Piaget and the well-known evolutionary psychologists such as Cosmides, Tooby, and Buss, agree with each other on the implications of evolutionary theory for psychology? To answer this question, we first need to acknowledge that Piaget does not play a role in the work of the main evolutionary psychologists. In *The Adapted Mind*, a book of 666 pages, Piaget is only mentioned twice, and in the other works of the main evolutionary psychologists, he is not mentioned at all. So in some way, Piaget has not inspired the main evolutionary psychologists with his writings on evolution. Why not?

Integrated Causal Model

To understand this, we first need to know a bit more about the principles of evolutionary psychology. As our starting point, we take the *Integrated Causal Model* as proposed by evolutionary psychologists Tooby and Cosmides (1992). The tenets of this model are:

1. 'the human mind consists of a set of evolved information-processing mechanisms instantiated in the human nervous system;
2. these mechanisms, and the developmental programs that produce them, are adaptations, produced by natural selection over evolutionary time in ancestral environments;
3. many of these mechanisms are functionally specialized to produce behavior that solves particular adaptive problems, such as mate selection, language acquisition, family relations, and cooperation;
4. to be functionally specialized, many of these mechanisms must be richly structured in a content-specific way' (Cosmides & Tooby, 1992, p. 24).

In a later paper, Cosmides and Tooby (1994) gave some additional reasons why functionally specialized mechanisms are more likely to evolve than a single domain-general mechanism. First, what counts as the best solution differs from domain to domain. There is no domain-general criterion for what is right or wrong. For example, someone with a domain-general learning mechanism succeeds to find out that intercourse is necessary for reproduction. He has sex with everybody he meets. This strategy will not be optimal, because, for instance, having sex with one's relatives is counterproductive. Suppose the person finds out with his domain-general learning mechanism that having sex with relatives is not a good strategy. He now may conclude that all interaction

with relatives is wrong. This behavior would also be selected out, because helping relatives favors the survival of one's own genes. What counts as a success and failure in relation to fitness, depends on the specific domain.

Second, someone with a single domain-general learning mechanism has, initially, to treat all perceptual information equally, as he has no specific knowledge about the information. It is impossible for an individual to learn all specific knowledge in one life-time. For example, it is impossible for a child to acquire a complex skill such as language so quickly only by trial and error. The child must possess some functionally specialized mechanism(s) that facilitates language acquisition.

Third, as organisms with a single domain-general learning mechanism have no specific knowledge, they have to evaluate all possible alternatives in every situation, which leads to a combinatorial explosion of possibilities. Having to think that long before one can act, is unlikely to be very adaptive.

In short, Cosmides and Tooby (1994) proclaim that in the course of evolution, human beings have encountered a diverse set of specific psychological problems, and it is likely that specific psychological mechanisms to solve these problems emerged through natural selection. Therefore, it is likely that our mind is composed of a multitude of specialized psychological mechanisms, like our body has different organs that are functionally specialized. There is no such thing as a general solution, because there is no such thing as a general problem (Symons, 1992; Buss, 1995).

Structuralism

It is interesting to note the difference between the Integrated Causal Model and Piaget's theory on child development. Piaget's theory has been called structuralism, because he believes that there are *domain-general* homogeneous structures which are characterized by laws that pertain to all cognitive, social and moral aspects during a given developmental epoch (Piaget, 1970). This theory appears to contradict the Integrated Causal Model, which claims that the human mind consists of evolved *domain-specific* mechanisms to solve recurrent problems encountered in the evolutionary past. According to Piaget, the only innate abilities are reflexes (Piaget & Inhelder, 1969). For example, sucking is behavior that the infant shows spontaneously, which does not have to be learned. Piaget states that abilities that require experience are not innate; the child learns these by an active exploration of the environment. By

exploring the environment the child constructs schemata, i.e., mental representations of external events. By encountering a new event, the child will first try to assimilate the environmental information in existing schemata. If the information does not fit into a present schema, the child has to accommodate to the environment by constructing a new schema. Piaget called the process of assimilation and accommodation *adaptation*. The purpose of adaptation is to reach a balance of assimilation and accommodation, which is called *equilibrium*.

Piaget and evolutionary psychologists agree that the child is not born as a blank slate, but this is where the agreement ends. According to Tooby and Cosmides (1992), cognitive psychologists replaced the blank slate metaphor with 'blank cognitive procedures' (p. 29). Piaget claimed that the infant's ability to assimilate and accommodate is innate, but he also proclaimed that these abilities are content-free and general-purpose. As Piaget (1980b) stated: 'Fifty years of experience have taught us that knowledge does not result from a mere recording of observations without a structuring activity on the part of the subject. Nor do any a priori or innate cognitive structures exist in man; the functioning of intelligence alone is hereditary and creates structures only through an organization of successive actions performed on objects' (p. 23).

Annette Karmiloff-Smith

Piaget died in 1980, so unfortunately we shall never witness a debate between him and evolutionary psychologists. However, it is clear that they would have had much to disagree about. Fortunately, Piaget had many followers, and many of them are active researchers at the moment. One of them, Annette Karmiloff-Smith, trained as a developmental psychologist in Piaget's lab in Geneva, recognized that Piaget put too little emphasis on innate abilities: 'Why would Nature have endowed every species except the human with some domain-specific predispositions?' (Karmiloff-Smith, 1992, p. 1), but she also contended that evolutionary psychologists put too much emphasis on domain-specific innate abilities. The position of evolutionary psychologists on evolved domain-specific psychological mechanisms, in the literature often referred to as *modules*, has been called the *massive modularity thesis* (Sperber, 1994), because evolutionary psychologists believe that the mind consists of many different evolved domain-specific psychological mechanisms, or modules. Karmiloff-Smith (1992) believes that the adult mind consists of many modules, a belief based on brain studies that show modularity of different brain regions.

But she does not believe that infants are born with a modularized brain. She proclaims that children develop by *gradual modularization*, i.e., by actively exploring the environment children gradually develop neural circuits that are modular in nature. For example, it is possible to develop a 'piano play module', a neural circuit that specializes as the result of intensive piano playing. It is self-evident that this is not an evolved module, but a module developed by experience. With her theory, Karmiloff-Smith reconciles Piaget's idea that development requires an active exploration by the child with the idea of modularity of the adult brain, but she does not believe that infants are born with a modular mind. She recognizes the role of some domain-relevant biases, but considers the massive modularity position of evolutionary psychology as too strong (Karmiloff-Smith, 1998). This is just one example in the literature that shows that there is quite a big gap between evolutionary and developmental psychology.

David Bjorklund

There have appeared two ways to deal with this gap. The first approach, as advocated by David Bjorklund, was to adopt the framework as defined by evolutionary psychologists, and to propose new hypotheses related to developmental psychology derived from this framework (Bjorklund & Pellegrini, 2000). Central in this approach, named evolutionary developmental psychology, is the idea that there were different adaptive pressures at different times during individual development. The fruitfulness of this approach was shown in a special issue of the *Journal of Experimental Child Psychology* in 2003, which covered tests of evolutionary hypotheses over the whole lifespan, with topics such as infants'ability to detect and act upon the direction of eye gaze of another human face (Farroni, Mansfield, Lai, & Johnson, 2003), strategies of control, aggression, and morality in preschoolers (Hawley, 2003), children's impaired performance on false-belief tasks with a predator-avoidance content (Keenan & Ellis, 2003), sexual segregation and integration in early adolescence (Pellegrini & Long, 2003), and mechanisms of inbreeding avoidance (Weisfeld, Czilli, Phillips, Gall, & Lichtman, 2003).

Lickliter and Honeycutt

The second approach, as advocated by Lickliter and Honeycutt (2003a), took the opposite direction. They denied that evolutionary psychology, as proposed by Cosmides, Tooby and Buss, has any value, because it is an approach that ignores development. They proposed an alternative, the developmental

systems approach: 'Development is not the result of the interaction of genetic and environmental factors, as neither operate as independent causes; rather, development results from the bidirectional and dynamic transaction of genes, cells, tissues, organs, and organisms during the course of individual ontogeny' (Lickliter & Honeycutt, 2003b, p. 869). Lickliter and Honeycutt argued that evolutionary psychology is too much a gene-centered, predeterministic approach to the study of the human mind. The gene-centered approach should be replaced by the probabilistic epigenesis approach, i.e., the idea that each level of an organism (e.g., genetic, neural, behavioral, social) is influenced by, and interacts with each adjacent level (see also Gottlieb, 2000).

As expected, evolutionary psychologists were not very pleased with this criticism. Buss and Reeve (2003) demonstrated the ongoing success of evolutionary psychology by providing a long list of new empirical discoveries made by evolutionary psychologists. In addition, they argued that the developmental systems approach is rather vague and obscure, and does not give rise to testable predictions. Cosmides, Tooby and Barrett (2003) countered Lickliter and Honeycutt (2003a) by arguing that evolutionary psychology does acknowledge the important role of development in phenotypic outcomes.

Evolved probabilistic cognitive mechanisms

The only researcher among the commentators who tried to reconcile the two approaches was Bjorklund (2003). He argued that developmental systems theorists perceive an incompatibility of evolved psychological mechanisms, as proposed by evolutionary psychologists, and probabilistic epigenesis, as proposed by developmental systems theorists. In the view of developmental systems theorists, the idea that the human mind consists of many evolved psychological mechanisms leaves too little room for environmental and developmental influences, whereas evolutionary psychologists argue that developmental systems theory cannot predict species-typical behavior and cognition. Bjorklund, Ellis, and Rosenberg (2007) tried to reconcile these opposite views by proposing the concept of evolved probabilistic cognitive mechanisms, defined as 'cognitive mechanisms that are functionally organized to solve recurrent problems faced by ancestral populations, are highly probable when species-typical environments are encountered (i.e., when developmentally relevant features of the environment are in the range typically encountered during a species' evolution), and are products of emerging developmental systems that have evolved over the course of the ontogenies of

our ancestors'(p. 22). This definition acknowledges that natural selection played a role in the evolution of species-typical traits, but it also acknowledges that development is always an interaction among different levels of organisms. Evolved probabilistic cognitive mechanisms *prepare* an organism for life in a species-typical environment, but they are not *preformed* (Bjorklund et al.).

Evolutionary developmental biology

Despite the attempts of Bjorklund and colleagues to bridge the gap between evolutionary psychology and developmental systems theory, there is still a long way to go to reconcile these positions. Interestingly, one approach in evolutionary biology, the evolutionary developmental (commonly abbreviated as evo-devo) approach, has, so far, been ignored in the debate about evolutionary psychology. Evo-devo biology 'forges a synthesis of those processes operating during ontogeny with those operating between generations (during phylogeny)' (Hall & Olson, 2003, p. xiii). It includes topics such as the processes leading to the rise and evolution of embryonic development, the role of embryonic development in evolutionary modification and evolutionary novelties, the origin of life history stages, the interaction of genotypes and phenotypes, and the co-evolution of development and ecology. To appreciate the contribution of evo-devo biology, I first outline some history of evolutionary biology.

With the publication of his book *The Origin of Species* in 1859, Charles Darwin was among the first to recognize the importance of natural selection in evolution: the forms of organisms that are best adapted to the environment increase in frequency relative to less well adapted forms over a number of generations (definition by Ridley, 2004). However, he did not know the mechanism of inheritance, as was later revealed in the work of Gregor Mendel. Mendel's discovery of the laws of inheritance gave rise to the field of genetics. In 1942, Julian Huxley published a book called *Evolution: The Modern Synthesis*, which integrated the fields of evolutionary biology and genetics, by recognizing that evolution can be explained by small genetic changes that result in variable forms that are acted upon by natural selection. The Modern Synthesis has also been called the neo-Darwinian evolutionary theory.

With the Modern Synthesis, we know that forms do change, and that natural selection is a force, but we do not know *how* forms change (S.B. Carroll, 2005). In order to understand this, we have to know how forms develop. This was

studied by embryologists, but researchers in the fields of evolutionary biology and embryology did not join forces until the 1970s. Stephen Jay Gould's book *Ontogeny and Phylogeny*, published in 1977, was the first step towards an integration of the fields. In the 1980s, the two fields became inseparable in the light of the discovery of genes that controlled development. These genes appeared to be similar across a wide range of species (McGinnis, Garber, Wirz, Kuroiwa, & Gehring, 1984; McGinnis, Levine, Hafen, Kuroiwa, & Gehring, 1984). This research was the start of the field of evo-devo biology (S.B. Carroll, 2005).

Thus, evo-devo biologists take the neo-Darwinian evolutionary theory as a starting point, but they argue that it is not a complete theory of evolution (S.B. Carroll, 2005; Müller & Wagner, 1991, 2003). Evo-devo biologists want to understand both which variants were better adapted to local circumstances than others, and how variants arose in the first place. Neo-Darwinian theory does not provide an explanation for the latter, i.e., the origin of evolutionary novelty.

Wagner (2000) argued that the neo-Darwinian theory of evolution and evo-devo biology have different explanatory power, and showed this with two examples. The first example concerns the stable sex ratio; in almost every species, there are as many females as males (Bell, 1982). How can we explain this stable sex ratio? Wagner argues that the 1:1 sex ratio can best be explained by using the neo-Darwinian approach. Suppose that there are fewer females than males in a given population. Because the females are the rare sex, the average female will have more offspring than the average male. Any genetic variant that increases the offspring sex ratio in favor of the female sex, will be selected, leading to more females. This process is stable when there are as many females as males (Fisher, 1930). In this example, the occurrence of natural selection explains why there is a 1:1 sex ratio. Knowledge about developmental mechanisms determining the sex of organisms does not add much to the explanation of the stable sex ratio. Developmental mechanisms causing the sex of an organism (Bell, 1982) can be very different among species (e.g., dependent on environmental temperature). However, because the sex ratio is stable among many different species, none of these mechanisms causes a change in sex ratio. Thus, according to Wagner, in this example, the neo-Darwinian approach has more explanatory power than the developmental approach.

The second example concerns the origin of eyespots on butterfly wings. The eyespots are a relatively recent evolutionary novelty, which serves to deter predators. Evolutionary developmental biologists (Keys et al., 1999) found two developmental events that are necessary for the development of eyespots on the wings[1]. The neo-Darwinian explanation for the emergence of the eyespots would be that butterflies with eyespots had a greater chance to survive, and hence eyespots were selected. However, we do not learn from this account how the eyespots arose in the first place. The evo-devo study of Keys et al. offers new insight in the developmental mechanisms that cause the emergence of eyespots. Thus, in this example, the developmental approach has more explanatory power, because it tells us something about the mechanisms that contributed to the origin of the novelty.

What is the crucial difference between the two examples? Wagner (2000) explained that sex ratio is a simple quantitative variable; in the evolution of sex ratio, there were no qualitative changes in genetic properties. In contrast, the origin of eyespots is a qualitative innovation, which goes together with a radical change in the genetic properties. An explanation in terms of population or quantitative genetics (i.e., the neo-Darwinian approach) is not informative. Evo-devo research is necessary to know how forms evolved.

Back to the metatheory

I started this introduction with a description of evolutionary psychology as a metatheory. What followed suggested that not all psychologists welcomed the ideas of evolutionary psychology with open arms. Especially developmental psychologists were critical, because evolutionary psychologists seem to discard the role of development in the unfolding of psychological mechanisms. If evolutionary psychology does not pay enough attention to development, what is left of the claim of evolutionary psychology as a metatheory?

As mentioned above, evolutionary developmental biology takes the neo-Darwinian evolutionary theory as its starting point. The neo-Darwinian theory is also the starting point for evolutionary psychologists, but for them it is also

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[1] These developmental events are '1) a modulation of hh expression along the proximal-distal axis of the wing disc, and 2) a relaxation of ci repression by en' (Wagner, 2000, p. 96-97).

the endpoint. Their main research method is reverse engineering, which means providing an account of: (1) what counts as a biologically successful outcome in a given situation, (2) the recurrent structure of the ancestral world that is relevant to the behavior to be explained, (3) of the organization of recurrent features that comprise the suspected adaptation, (4) what happens when the suspected adaptation interacts with the world, and (5) how well the design in ancestral conditions resulted in a successful outcome (Tooby & Cosmides, 1992). As proclaimed by Buss and Reeve (2003), this approach has been quite successful in discovering mechanisms that had eluded other psychologists. However, the method of reverse engineering is not conducive to explanations of the development of a mechanism. One may contend that evolutionary psychology is a young field, and has yet to address development. However, given the metatheoretic ambition of evolutionary psychology, the present lack of a developmental perspective is undesirable. Although Piaget's theory did not turn out to be true on every count (Feldman, 2004), his theory was a true metatheory; it predicted behavior and cognition for different ages groups and different domains, and it predicted the developmental pathway of the behavior and cognition. The promise of evolutionary psychology as a metatheory has yet to be realized with respect to the explanation of psychological development.

With this statement, need we relinquish evolutionary psychology as a metatheory? In chapter 2 of this dissertation I will address to this question. In short, the answer to this question is 'no', but evolutionary psychology has to broaden its scope in order to become a fruitful metatheory for psychology. It has to include theories and facts delivered by evolutionary developmental biology and dynamical systems theory to be able to contribute to the main issues in psychology. Evolutionary developmental biology provides a rich array of theories and facts on modularity (Kreimer, Borenstein, Gophna, & Ruppin, 2008; Callebaut & Rasskin-Gutman, 2005; Schlosser & Wagner, 2004), phase transitions (Coveney & Fowler, 2005; Camazine et al., 2001; Stadler, Stadler, Wagner, & Fontana, 2001), novelties (Moczek, 2008; Osorio & Retaux, 2008; Müller & Wagner, 2003), individual differences (Allen, Beldade, Zwaan, & Brakefield, 2008; Hallgrímsson, 2003; Stern, 2000), and plasticity (Badyaev, 2007; Wagner, 2005), all subjects of major interest for evolutionary psychology and psychology in general. Without incorporation of these facts and theories within the metatheory of evolutionary psychology, it will remain wanting as a metatheory.

Testable predictions

Buss and Reeve (2003) have complained that developmental systems theory does not generate testable predictions. To show that this is not true for the application of evo-devo biology to psychology, we (Frietson Galis, Han van der Maas, Maartje Raijmakers, and myself) have tested three hypotheses derived from evo-devo thinking. In chapter 3, we provide evidence for the hypothesis that the savant syndrome, despite its positive aspects, did not spread in the population because of a developmental constraint. The savant syndrome is a condition in which individuals have one or more areas of expertise, ability or brilliance that is in contrast with the individual's general capacities (Treffert, 2000). A developmental constraint is a mechanism that limits the possibility of a phenotype to evolve (Maynard-Smith et al., 1985). The developmental constraint is the result of high interactivity among body parts during a particular stage of embryological development, called *early organogenesis*. During this stage, a mutation or an environmental disturbance does not only affect a single phenotypic trait, but several traits (Sander, 1983). A potential positive mutation, such as a mutation that causes the positive aspects of savant syndrome, is not naturally selected because of the negative side-effects (e.g., the development of mental retardation or autism). The finding that individuals with savant syndrome often have autism, mental retardation and several physical anomalies supports our hypothesis.

In chapter 4 we argue that schizophrenia is the result of disturbances during early organogenesis. Due to the high interactivity of body parts during this stage, we expect that individuals with disorders that originate from disturbances during this stage, have several physical and mental anomalies. During early organogenesis, all organs start to develop, including the brain, as well as the limbs and the vertebrae. We show that schizophrenia is not only a disorder of the brain, but a disorder that includes multiple anomalies, of body parts that become established during early organogenesis. In chapter 5 we show that the same results are found in individuals with autism. We show that concrete hypotheses can be derived from evo-devo thinking that are relevant to psychology. We conclude this thesis with a discussion of the value of the evo-devo approach for psychology.

CHAPTER 2

IS EVOLUTIONARY PSYCHOLOGY A METATHEORY FOR PSYCHOLOGY? A DISCUSSION OF FOUR MAJOR ISSUES IN PSYCHOLOGY FROM AN EVOLUTIONARY DEVELOPMENTAL PERSPECTIVE[2]

Abstract

Evolutionary psychology has been proposed as a metatheoretical framework for psychology. We argue that evolutionary psychology should be expanded if it is to offer new insights regarding the major issues in psychology. Evolutionary developmental biology can provide valuable new insights into issues such as the domain-specificity of the human mind, the nature-nurture debate, stages in development, and the origin of individual differences. Evolutionary developmental biology provides evidence for the hypotheses that domain-general and domain-specific abilities co-occur, that nature and nurture interact in a dynamic and nonadditive way, that stages occur in development, and that individual differences are the result of pleiotropic effects during development.

Evolutionary psychology has been advanced as a metatheory for psychology, that is, as a unifying theory that can accommodate a diversity of facts and findings from all fields within psychology (Cosmides, Tooby, & Barkow, 1992; Buss, 1995). The general idea is that psychological characteristics (e.g., sex specific mate preferences), like biological characteristics, have evolved over a

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long period of time, and should be seen as adaptations to the social and ecological circumstances that characterize human existence. The main tenet of evolutionary psychology is that the human mind comprises a collection of psychological adaptations, which arose through the process of natural selection. Another tenet is that humans have encountered distinct problems in different evolutionary periods, and that the specific solutions to these problems have resulted in a multitude of functionally specialized, domain-specific mechanisms in the brain. This is known as the *massive modularity assumption* (Sperber, 1994).

Since the rise of evolutionary psychology, many hypotheses about evolved psychological mechanisms have been derived and tested. Buss and Reeve (2003) pointed out that evolutionary psychologists have made many discoveries that had eluded other psychologists. These discoveries mostly concern issues related to social exchange, mate choice, sexual behavior, relationship maintenance, and parental care. The interpretative framework, and the possibilities of making new discoveries offered by the evolutionary perspective, have certainly been fruitful.

However, in order to function as a metatheory in psychology, evolutionary psychology should both identify important research questions that are often missed in other perspectives, and address the present major issues in psychology. In this chapter, we consider the present contribution of evolutionary psychology to four major issues in psychology. These issues are:

- Does the human mind consist mostly of domain-specific abilities, or is the mind domain-general?
- What is the influence of nature and nurture on the human mind?
- Does development proceed in stages or gradually?
- How do individual differences arise?

As our point of departure, we examine three approaches to evolutionary psychology. Tooby and Cosmides (1992) presented a comprehensive framework for the field of evolutionary psychology. Buss (1995, 2003) presented a similar framework, in terms more suitable for a general audience. Pinker (1997), working within this same framework, provided evolutionary explanations for many psychological phenomena. To ease presentation, we refer to the general framework of these researchers as *mainstream evolutionary psychology*. This should not be taken to imply that all evolutionary

psychologists subscribe to this framework, but most, if not all, do take this framework as a point of reference.

We contend that mainstream evolutionary psychology at present is not sufficiently elaborated to address the major issues in psychology. We show that certain tenets and ideas of mainstream evolutionary psychology are inconsistent with certain empirical facts pertaining to these issues. However, we maintain that these inconsistencies do not disqualify evolutionary psychology as a metatheory for psychology. We attribute these inconsistencies to the fact that mainstream evolutionary psychology embraces a limited subset of ideas from evolutionary biology, and is therefore lacking in scope. We argue that the inclusion of theoretical concepts and empirical findings from the field of evolutionary developmental biology can remove these inconsistencies and broaden the scope of evolutionary psychology such that it can serve as a proper metatheoretical framework for psychology. This chapter is organized as follows. First, we present a brief introduction to mainstream evolutionary psychology. Second, we describe evolutionary developmental biology. Third, we discuss the implications of both views for four major issues in psychology.

Mainstream evolutionary psychology

Mainstream evolutionary psychology starts with the tenet that evolution by natural selection is at present the only viable scientific explanation of the existence of complex biological and psychological mechanisms (Buss, 1995, 2003; Pinker, 1997). Hypotheses derived from the theory of evolution by natural selection have been confirmed many times, and so this theory is generally considered to be as well-established (e.g., Dawkins, 1986; Mayr, 1982; Williams, 1966). As discussed in the next section, evolutionary developmental biologists do not disagree with this tenet, but argue that it is incomplete; they maintain that there are additional processes that influence the evolution of complex traits (Müller & Wagner, 1991, 2003).

The second tenet of mainstream evolutionary psychology is that psychological theories imply psychological mechanisms, e.g., information-processing devices and decision rules (Buss, 1995). For example, Skinner's behaviorist theory implies a very general learning mechanism. This mechanism must have evolved in some way. Mainstream evolutionary psychologists define a psychological mechanism as a set of processes within an organism that exists because it solved a particular problem of survival or reproduction in ancestral

times (Buss, 2003). Examples of putative evolved psychological mechanisms are male's desire for sexual variety (Schmitt & 118 Members of the International Sexuality Description Project, 2003), male sexual and female emotional jealousy (Buss, Larsen, Westen, & Semmelroth, 1992), and child-directed speech (Fernald, 1992).

For example, Schmitt et al. (2003) offered an evolutionary explanation for the finding that men, in general, express greater desire for sexual variety than women. This universal sex difference can be explained in terms of differential reproductive success: men, who have sex with many different women, will have on average more offspring than men, who have sex with few women. Women do not tend to have more offspring by having sex with many different men, because they experience relatively long periods of infertility due to pregnancy and breastfeeding. For them, it is more important to have a stable relationship for keeping protection and resources.

The third tenet of mainstream evolutionary psychology is the so-called massive modularity assumption. This tenet holds that the human mind consists of many different domain-specific psychological mechanisms. It is based on the idea that the confrontation in the evolutionary past with domain-specific problems gave rise to domain-specific, functionally specialized psychological mechanisms (Buss, 1995; Tooby & Cosmides, 1992). Therefore, many different psychological mechanisms are supposed to exist, just like many organs exist in the body that perform specific functions. Although the ultimate criterion is fitness, no general mechanism for fitness exists, because environmental conditions change over time, and differ from place to place (Symons, 1992). In other words, there is no such thing as a 'general solution', because there is no such thing as a 'general problem' (Buss, 1995). The massive modularity hypothesis is important in the debate on the domain-specificity of the mind, which we discuss below. First, we provide a brief account of evolutionary developmental biology.

Evolutionary developmental biology

In the wake of the synthesis of Darwin's theory of natural selection and genetics, most biologists have come to consider themselves to be neo-Darwinians. The central tenets of the neo-Darwinian theory are that evolutionary change occurs because of genetic mutations, and that adaptive variants get 'fixed' in the population through natural selection. Although neo-

Darwinian theory enjoys a considerable following (e.g., Dennett, 1995), it is not free of controversy (e.g., Gould, 2002). One controversy concerns the role of natural selection, which is, in the neo-Darwinian approach, the most important force in evolution. Neo-Darwinians argue that complex biological forms and organs arise as a result of the retention, by natural selection, of genetic changes that cause small gradual changes in phenotypic features, which in turn increase the individual's fitness to procreate in its environment. The transmission of these genetic changes from parents to offspring increases the frequency of these phenotypic features in the population. Due to the accumulation of small advantageous features, complex forms and organs, such as the eye, evolve.

Mainstream evolutionary psychologists adhere to the neo-Darwinian approach. In their theorizing, they neglect another important approach in evolutionary biology, namely the evolutionary developmental approach. This is defined as a 'synthesis of those processes operating during ontogeny with those operating between generations (during phylogeny)' (Hall & Olson, 2003, p. xiii). The starting point in evolutionary developmental biology is the thesis that new variants emerge before natural selection can do its work. The relevance of natural selection is not disputed, but evolutionary developmental biology provides a better account of the evolutionary origin of new forms, than does neo-Darwinian theory (Müller & Wagner, 1991, 2003). Natural selection does not explain *how* individual variants arise or how they evolved. Here knowledge about development may help us address these issues (S.B. Carroll, 2005).

Several evolutionary developmental biologists have argued that individual development and behavior can be viewed as the initiator of evolutionary change (Gottlieb, 2002, 2003; Weber & Depew, 2003). Developmental change leads to new behavior, which may be better suited to certain environmental conditions. The new behavior brings out latent possibilities for physiological or morphological change. As was put forward by Gottlieb (2003), the issue is whether the original change in behavior requires a genetic mutation. Neo-Darwinian theory is guided by the tenet that only a change in genetic structure can be the initiator of evolutionary change (Crick, 1970). Gottlieb (2002, 2003) used the study of the evolution of the apple maggot fly (*Rhagoletis pomonella*) to illustrate that a genetic mutation is not required to produce new behavior. Originally, the female apple maggot fly laid her eggs on hawthorns. When domestic apple trees were introduced, females started to lay their eggs on these as well (a phenotypic change). At present, there are two variants of the

apple maggot fly, one that lays its eggs on apples and the other on haws. The two variants no longer mate with each other, because apples mature earlier than haws, so the mating seasons are different. This change in developmental timing has given rise to genetic changes (i.e., differences in gene frequencies) in the two populations (Feder, Roethele, Wlazlo, & Berlocher, 1997).

Note that these genetic changes occurred after the new phenotypic behavior emerged, i.e., the phenotypic behavioral change provided the impetus for the genetic change. Note also the clear difference with Lamarckian theory, which states that acquired characteristics are transmitted biologically to the offspring. The evolutionary developmental point of view is that new behaviors (phenotypic changes) create new possibilities to deal with environmental conditions, which set the stage for later genetic change.

Another issue that requires an evolutionary developmental solution is the origin of novelties. For example, consider the origin of eyespots on butterfly wings, a relatively recent evolutionary novelty, which serve to deter predators. The neo-Darwinian explanation for the emergence of the eyespots would be that butterflies with eyespots had a greater chance to survive, and hence eyespots were selected. However, as Wagner (2000) stressed, we do not learn from this account how the eyespots arose in the first place. An evolutionary developmental study offered new insight in the developmental mechanisms that cause the emergence of eyespots (Keys et al., 1999). This study showed that eyespots evolved as new patterns that develop from special organizers called foci. An organizer is a signaling center that directs the development of parts of the body. Formation of these organizers is associated with novel expression patterns of a signaling protein, its receptor, a transcription factor, and a related gene. These novel expression patterns break the existing regulatory circuits of the butterfly wing. The general message of this study is that the redeployment of pre-existing regulatory circuits may serve as a general mechanism underlying the evolution of novelties. This study provides an example of how the evolutionary developmental biology approaches the developmental mechanisms that underlie evolutionary change. The neo-Darwinian approach in contrast can only tell us about the selection of existent traits.

It is important to emphasize that the neo-Darwinian and the evolutionary developmental approaches are complementary rather than opposite. Most evolutionary biologists cannot be classified as either neo-Darwinian or

evolutionary developmental. Although we recognize that the two approaches are largely complementary, in the remainder of this chapter we will emphasize their differences, to accentuate the different contributions the two approaches can make to four major issues mentioned above.

Evolutionary biology and four major issues in psychology

This section contains four parts, each addressing a major issue in psychology. The issues are concerned with the domain-specificity of the mind, nature and nurture, stage-wise versus gradual development, and individual differences. We discuss each issue from the perspective of mainstream evolutionary psychology and the perspective of evolutionary developmental biology.

Domain-specificity versus domain-generality of the mind

The issue of the domain-specificity of psychological abilities has been discussed intensively, both in psychology in general, and in the field of evolutionary psychology. Domain-specificity refers to the extent to which a mechanism is tailored to handle some particular and narrow range of inputs. One view emphasizes domain-specificity of the brain, i.e., the view that different brain regions work more or less independent from each other (e.g., Gazzaniga, Ivry, & Mangun, 2002). Another view emphasizes domain-specificity of cognition, i.e., the view that knowledge about someone's ability for a specific aspect of cognition tells you little about other specific cognitive abilities of that person (e.g., Carey, 1985). Still another view emphasizes the domain-specificity of innate bodies of knowledge, for example, the knowledge that newborns possess about physical entities of the world (e.g., Spelke, 1994; Gelman & Williams, 1998). Finally one view emphasizes the domain-specificity of processes that solve a particular psychological problem (e.g., Buss, 1995).

In this last view, a domain-general process is viewed as one that plays a role in a wide range of domains, and is independent of the content of the domain involved. The processes of assimilation and accommodation as proposed by Piaget (1952) are examples of domain-general abilities. Assimilation is a process by which a new experience is perceived in accordance with existing knowledge. Accommodation is a complementary process by which a new experience can no longer be perceived in accordance with existing knowledge, resulting in a change in the existing knowledge. The two processes are independent of the kind of experience or the kind of existing knowledge. In contrast, a domain-specific process solves problems only in a single domain,

and is dependent on the content of the domain. For example, Cosmides and Tooby (1992, 2005) proposed a cheater detection ability, which is functionally specialized to help people to detect cheaters. When people have to solve logical problems in the form of 'If P then Q', they perform best if the logical problem consists of a situation in which a cheater has to be detected. Cosmides and Tooby concluded that humans do not have a domain-general logical-problem-solver ability that is independent of the content of the problem, but do have a cheater detection ability, which solves a specific adaptive problem.

Mainstream evolutionary psychologists are not always clear about the particular kind of domain-specificity to which they refer (see Samuels (1998) and Fodor (2000) for an analysis of this problem). However, in general they refer to domain-specificity in the last sense, i.e., domain-specificity of processes that solve a particular psychological problem. In the remainder of the chapter, we refer to this meaning of domain-specificity.

Mainstream evolutionary psychology's view

An important tenet of mainstream evolutionary psychology is the massive modularity assumption. This tenet holds that our minds consist of many domain-specific devices in order to solve domain-specific adaptive problems that human beings have encountered in their evolutionary past. This tenet does not exclude the possibility of the existence of some domain-general abilities. It asserts only that we should expect many domain-specific abilities. However, Cosmides and Tooby (1994) advance three reasons that domain-general processes that solve adaptive problems are unlikely. First, what counts as the best solution differs from domain to domain. There is no domain-general criterion for what generates an adaptive or maladaptive outcome. What counts as a success or a failure in terms of fitness depends on the specific domain. Second, individuals, equipped only with domain-general problem solving mechanisms initially have to treat all perceptual information equally, as they have no specific prior knowledge about the information. It is impossible for an individual to learn all necessary specific knowledge in one life-time. In this connection, Cosmides and Tooby referred to Chomsky's (1975) theory, which states that it is impossible for a child to learn a language by trial and error. Third, since organisms with only domain-general abilities have no specific knowledge, they have to evaluate all possible alternatives in every situation, which leads to a combinatorial explosion of possibilities. Having to think a long time before one can act is not adaptive. This line of reasoning has

given rise to the massive modularity assumption, which states that the human mind consists of many functionally specialized, domain-specific mechanisms.

Empirical evidence for domain-general abilities

The massive modularity assumption of mainstream evolutionary psychology has given rise to an intense debate (for an overview and references, see Barrett and Kurzban, 2006). Although mainstream evolutionary psychologists argue that the evolution of domain-general abilities is unlikely, there is ample empirical evidence for the existence of domain-general abilities. Bjorklund and Pellegrini (2002) mentioned speed of processing, working memory, inhibition, and general intelligence as possible domain-general abilities. Habituation, statistical learning, associative learning, and metacognition are other examples. We will present empirical evidence for the existence of these putative domain-general abilities in the remainder of this section. This evidence does not exclude the existence of domain-specific abilities, but it suggests that domain-general abilities also exist.

Speed of processing. The amount of time that people need to perform distinct tasks show developmental similarities across those tasks. For example, Hale (1990) compared performance on four different tasks (choice reaction time, letter matching, mental rotation, abstract reasoning), and found that it is possible to predict the response latencies of the younger children from the response latencies of the older children, no matter which task was involved (for similar research, see Kail, 1986, 1991). Other evidence for the domain-generality of speed of processing comes from studies in which factor analysis revealed a higher-order general mental speed factor (Danthiir, Wilhelm, Schulze, & Roberts, 2005; Roberts & Stankov, 1999).

Working memory. The hypothesis that working memory is domain-general has been tested with a so-called latent variable approach (Kane et al., 2004). In this approach, multiple tasks are used to measure the putative construct, in order to statistically remove the irrelevant variance (e.g., due to measurement error) of individual tasks. Kane et al. found that verbal and visual-spatial working memory share about 80% of their variance, leaving little room for variance that can be attributed to domain-specific components (see also Hambrick, Kane, & Engle, 2005). Swanson and Sachse-Lee (2001) found that children with and without reading disabilities who were matched on central executive processing did perform similarly on all domain-specific working memory tests (e.g., verbal, visual-spatial). These results imply that reading disability is the result

of impaired domain-general executive processing, and not the result of domain-specific impairment in verbal working memory (see also Swanson, Howard, & Saez, 2006).

Inhibition. Inhibition has also been proposed as a domain-general ability (Bjorklund & Kipp, 2002). It is argued that inhibition, like other domain-general abilities, plays a facilitating role in cognition. That is, without a certain amount of inhibition, people would not be able to perform higher-order cognitive tasks. Band, van der Molen, Overtoom, and Verbaten (2000) found that subjects of several ages performed equally well on inhibition tasks in different domains. A general ability to inhibit responses seems to be present at the age of 5 (for similar results, see Van den Wildenberg and van der Molen, 2004).

General intelligence. The construct of general intelligence ('g') is based on the finding that an individual who has a high score on a specific test (e.g., a verbal test), will, in general, get a high score on another specific test (e.g., a mathematical test). The idea of general intelligence is an old one (Spearman, 1904) and has received a lot of attention (Jensen, 1998). General intelligence has also been discussed from an evolutionary perspective. From this perspective, general intelligence is required for dealing with variant patterns in nature, and for integrating information across different domain-specific abilities (Geary, 2005). Recent evidence for the existence of general intelligence is provided by a study in which a large sample was tested on three well-known batteries of intelligence tests that cover different aspects of cognitive ability (Johnson, Bouchard Jr., Kreuger, McGue, & Gottesman, 2004). The main result was that the correlations among the second-order 'g'-factors of the three different test batteries were very high, ranging from .99 to 1.00. Based on this study, and several other studies (for a review, see J.B. Carroll, 1993), it can be concluded that there is ample evidence for general intelligence.

Habituation. Habituation involves a decreased strength of a response as a result of repeated presentation of a stimulus. Habituation occurs regardless of the nature of the stimulus, for example in the language domain (e.g., Bijeljac-Babic, Bertoncini, & Mehler, 1993), the visual domain (e.g., Kirkham, Slemmer, & Johnson, 2002) and the music domain (e.g., Hannon & Trehub, 2005).

Statistical learning. Statistical learning takes place in both children and adults when they try to structure information from the environment. Human beings,

as well as non-human primates (Newport, Hauser, Spaepen, & Aslin, 2004), quickly discover statistical regularities of their environment. For example, when visual stimuli are presented in pairs, infants quickly discover this statistical regularity, as measured by habituation studies (Kirkham et al., 2002). Infants can also detect statistical patterns in musical stimuli (Hannon & Trehub, 2005), and language (Bijeljac-Babic et al., 1993; see Saffran, 2003, for a general overview of research on statistical learning and language).

Associative learning. Associative learning is the ability to learn connections between stimuli that often occur together. Most research on associative learning concerns infants' ability to learn categories. Infants as young as 3 months can form categories when presented with different visual stimuli (see Quinn & Eimas, 1996, for an overview). Networks in which these results are simulated are based on a single domain-general associative learning mechanism (Mareschal & French, 2000). These networks can also be used for video image compression (Cottrell, Munro, & Zipser, 1988), text compression (Schmidhuber & Heil, 1996), and the detection of fault diagnoses in marine diesel engines (Sharkey, Sharkey, & Chandroth, 1996), showing the domain-generality of the networks.

Metacognition. Metacognition is the ability to evaluate and change one's own performance. Schraw, Dunkle, Bendixen, and Roedel (1995) tested undergraduates in five different domains (knowledge of U.S. presidents, geographical distances between American cities, vocabulary, prominent sport figures and popular music stars). Subjects were asked to provide a confidence rating for each test item, immediately after completing each of the five tests. The confidence rating is supposed to express metacognition. Partial correlations among confidence scores on each of the five tests, with performance covariation statistically removed, were all significant. This result is inconsistent with the hypothesis that metacognition is based on knowledge and expertise in a particular domain (see also Veenman & Verheij, 2003).

Conclusion. The presented research findings are consistent with the view of speed of processing, working memory, inhibition, general intelligence, habituation, statistical learning, associative learning, and metacognition as domain-general abilities. These are abilities that help human children and adults to deal flexibly with varying environmental conditions (Geary, 2005). These research findings suggest that evolutionary psychologists' massive modularity assumption is incorrect.

Evolutionary developmental biology's contribution

Modularity is a central theme in evolutionary developmental biology (e.g., Callebaut & Rasskin-Gutman, 2005; Schlosser & Wagner, 2004). Modularity is defined as 'the properties of discreteness and dissociability among parts and integration within parts' (West-Eberhard, 2003, p. 56). The concept of modularity in evolutionary developmental biology usually refers to morphology, i.e., the form and structure of an organism. This may seem removed from the discussion in psychology, in which modularity usually refers to functions, i.e., cognitive abilities. However, morphology also includes the structure of the brain, and the functions that accompany the different parts of the brain (for an evolutionary developmental perspective on the modularity of functional modules in the brain, see Redies and Puelles, 2004). So the discussion about modularity in evolutionary developmental biology is certainly relevant to the discussion in psychology.

An ongoing discussion in evolutionary developmental biology, related to the discussion on domain-specific versus domain-general abilities, concerns the coexistence of modularity and pleiotropy. Pleiotropy refers to cases in which a single gene has effects on more than one phenotypic trait. Wagner (1996) argued that a module has the following properties: (1) it serves a particular functional role; (2) it is relatively independent from other modules, and (3) pleiotropic effects are more frequent within a module than across modules.

Wagner (1996) argued that the elimination of pleiotropic effects is a necessary condition for evolution, i.e., modularity is a necessary condition for evolution. Evolution is only possible if one module can be changed without changing the whole organism. However, Hansen (2003) disagreed with this. He argued that the elimination of pleiotropic effects reduces the number of genes that can influence the module, and thereby reduces its mutational target size. According to Hansen, modularity is beneficial for the individual modules, but not beneficial for the whole organism. He hypothesized that evolvability (i.e., the capacity to respond to a selective challenge) is maximized by variable pleiotropic effects. Eliminating pleiotropic effects may increase the evolvability of one module, but reduce the evolvability of another. Thus, Hansen concluded: 'It has been almost universally accepted that biological organisms are "modular", but the fact remains that pleiotropy across characters is a ubiquitous property of biological variation' (p. 91-92).

Griswold (2006) showed with simulation experiments that under some conditions an increase in pleiotropy enhanced evolvability, whereas under other conditions an increase in modularity enhanced evolvability. The condition that is probably found most often in nature is that some traits are under stabilizing selection, whereas other traits are under directional selection (Wagner, 1988, 1996). Stabilizing selection occurs when individuals with an average value for a trait have higher fitness than individuals with an extreme value; under stabilizing selection, the trait will remain constant. Directional selection occurs when individuals with an above or below average value for a trait have higher fitness than individuals with an average value. For example, Darwin's famous finches were adapting their beak shape (i.e., directional selection) while conserving other body parts (i.e., stabilizing selection; Grant, 1986). Griswold found that evolvability is enhanced when an increase of pleiotropy is associated with traits that are under directional selection, but not under stabilizing selection. When a mutation is beneficial for two or more traits, which only occurs when the mutation has pleiotropic effects, then the increase in fitness is larger and the mutation gets fixed faster.

Hansen (2003) and Hansen, Armbruster, Carlson, and Pélabon (2003) proposed a model to explain the relationship between modularity and pleiotropic effects, and how this relationship affects the evolvability of a system. It is beyond the scope of this chapter to discuss this technical model in detail, but an example illustrates the idea. It has been found that the lens of the eye, commonly seen as a clear example of a separate module, has pleiotropic links with other traits. For example, in amphibians, the lens is formed by interactions with tissues from the retina and even heart mesoderm. Furthermore, crystalinnes, proteins that make up 30 to 40% of the mass of the lens, are not specialized for their role in lens formation, because they also have functions in other cells. In other words, crystalinnes are domain-general. The process where a single gene has pleiotropic effects in that it produces a protein that has several different functions, is called co-option, and this process is regarded as fundamental to the evolution of new traits (e.g., Gerhart and Kirschner, 1997; Raff, 1996; True & Carroll, 2002).

Other evolutionary developmental researchers also conclude that modularity is not the only path to evolvability. Evolutionary developmental biologist West-Eberhard (2003) criticized mainstream evolutionary psychology explicitly for its rigid use of the concept of modularity. She argued that modularity, and connectedness or integration, are two sides of the same coin. Biological

modules, such as body parts, are never pure modules, because they are always connected to some degree to other body parts. She preferred to refer to biological entities or behavioral traits in terms of their modular properties, and not in terms of actual separate modules.

Ancel and Fontana (2000) presented results of simulation studies which show that strong modularity leads to a strong decline in variation, and finally to an evolutionary dead-end. We will discuss their research more extensively in the section on individual differences. Nagy and Williams (2001) presented experimental support for the idea that organisms possess both modular and nonmodular developmental mechanisms. They stated that there is ample evidence for the modularity of the segments that make up the principle body axes of vertebrates, and for the modularity of the major body parts that arise from the segments, e.g., the limbs. That is, the genes that underlie the segments of the body axes, and the development of each particular body part can be specified. The body parts themselves can be divided into smaller units, but the genes underlying these smaller units are not specific, i.e., there is no one-to-one relation between specific genes and specific parts of the limb. That is, the genes that underlie the smaller parts of limbs are 'domain-general'.

Simulation studies by Kauffman (1993) support the idea that organisms have both domain-general and domain-specific properties. Kauffman described the capacity of a system to evolve in terms of fitness landscapes that are characterized by a degree of ruggedness. Fitness landscapes are used to describe the relationship between genotypes and their fitness. Fitness landscapes are two-dimensional representations, with genotypes on the x-axis, and the degree of fitness on the y-axis. Genotypes that resemble each other are close together on the x-axis, whereas genotypes that are very different are far away from each other on the x-axis. Genotypes with a high fitness have a high value on the y-axis, whereas genotypes with a low fitness have a low value on the y-axis. The ruggedness of the fitness landscapes is indicative of variation in the fitness conferred by similar genotypes. A smooth landscape expresses the similar fitness conferred by similar genotypes.

Kauffman's (1993) simulation study revealed that very smooth landscapes and very rugged landscapes lead to low evolvability. An intermediate degree of ruggedness results in optimal evolvability. In terms of domain-specific and domain-general abilities, we may explain this as follows. A very smooth landscape represents a system with stable fitness. Such a system consists of

domain-specific modules that have proved to be adaptive. There are few pleiotropic effects across the different modules, so the modules will not easily break down due to negative pleiotropic effects. As long as there are no significant environmental changes, such systems do well. However, when the environment changes significantly, these modules are inflexible and cannot improve by means of positive pleiotropic effects. Such a system has low evolvability. In terms of domain-specificity, systems with only domain-specific abilities have low evolvability. On the other hand, a very rugged landscape represents a system with a single domain-general ability. In this kind of system, a small change affects the fitness of the whole system, resulting in many different peaks and valleys in the fitness landscape. This system also has a low evolvability, because a single negative change in the system can reduce the fitness of the system as a whole dramatically. A system with both domain-specific and domain-general abilities has the greatest evolvability.

Conclusion

We showed that there is ample empirical evidence for the existence of several domain-general abilities. In addition, we showed that the evolutionary developmental approach provides models that can explain the existence of both domain-specific and domain-general abilities. We conclude that, if evolutionary psychology is to provide a metatheoretical framework for psychology that can address the existence of both domain-specific and domain-general abilities, it will have to include elements of the evolutionary developmental approach.

Nature and nurture

Present-day psychologists subscribe neither to the idea that the mind is a tabula rasa, nor to the idea that the mind is completely genetically determined. Today, the nature-nurture debate is about how genetic and environmental influence interact in the development of phenotypes (e.g., Li, 2003), or about the question whether it makes sense to break up the environmental and the genetic in separate components (Lickliter & Honeycutt, 2003; Oyama, 2000).

Mainstream evolutionary psychology's view

Mainstream evolutionary psychologists proposed the *Integrated Causal Model* to explain the interaction between nature and nurture (Tooby & Cosmides, 1992). This model contends that the human mind consists of a set of evolved functionally specialized content-specific information-processing mechanisms

that generate human culture. Thus, Tooby and Cosmides regard evolved psychological mechanisms as the basis of human culture: 'content-specific information-processing mechanisms generate some of the particular content of human culture, including certain behaviors, artifacts, and linguistically transmitted representations' (p. 24). According to mainstream evolutionary psychology, evolved psychological mechanisms and the environment cannot be split up in two different components: because of their evolved psychological mechanisms, humans create an environment that reflects the operation of their evolved architecture. Thus, mainstream evolutionary psychology rejects the dichotomies of the genetic and environmental, the biological and social, and the nativist and environmental. In general, mainstream evolutionary psychologists have little to say about the relation between their proposed evolved psychological mechanisms and genes. They study the mechanisms at the behavioral and the cognitive level, and leave the question open about how the mechanisms actually develop.

Evolutionary developmental biology's contribution

Evolutionary developmental biologists hold the view that there is a dynamic interaction between genes and environment. As Sterelny and Griffiths (1999) state: 'No one supposes that a plant will grow in just the same way no matter what sort of light or nutrients it receives' (p. 13). Sterelny and Griffiths distinguish two kinds of interaction. The first kind of interaction is additive: a small genetic change will result in a small change in the outcome, and a large genetic change will result in a large change in the outcome (i.e., a linear relationship between genetic change and phenotypic change). This kind of interaction is referred to in statements such as: 'If we keep the environment equal, then differences in outcomes are attributable to differences in genes (and vice versa)'.

The second kind of interaction is nonadditive, which means that a small genetic change may lead to a large difference in outcome (i.e., a nonlinear relationship between genes and outcomes). The phenotypic expression of some genes can be strikingly different in different contexts. This can be illustrated in depictions of identical twins with obviously different lengths and weights (Gottlieb, 2000, p. 96). Sterelny and Griffiths (1999) state that most scientists think of interactions between genes and environment in an additive way, although it is most likely that interactions happen in nonadditive ways.

Gaertner (1990) provided empirical evidence for the existence of nonadditive interaction. He noted that efforts to standardize laboratory animals so far have been unsuccessful. He found that when genetic variability is reduced by using inbred strains, and when the amount of food is held constant, the weight of mice is still highly variable. It is estimated that 70 to 80 percent of the range of body weight is due to a third source (i.e., in addition to genetic and environmental sources) of variability. Archer et al. (2003) compared variability in phenotypic traits between cloned pigs (Duroc swines) and non-cloned controls. Remarkably, for many traits variability was equal for cloned and non-cloned pigs, for example body weight, number of teats, skin type, hair growth, and several blood parameters such as calcium. For some blood parameters, variability was even larger for cloned pigs than for non-cloned controls.

Molenaar, Boomsma, and Dolan (1993) argued that this third source probably comprises self-organizing processes. The process of self-organization is often recognized in evolutionary theorizing that is strongly related to evolutionary developmental biology (e.g., Camazine et al., 2001; Kauffman, 1993, 1995; Solé & Goodwin, 2000). It has also been recognized in psychological theorizing (Kelso, 1995; Lewis, 2000; Smith & Thelen, 1993; Thelen & Smith, 1994), but, as Kenrick (2001) pointed out, it is mostly ignored in mainstream evolutionary psychology. In self-organizing systems, patterns appear through interactions internal to the system, without intervention of external directing influences. In technical terms, self-organization refers to 'a set of dynamical mechanisms whereby structures appear at the global level of a system from interactions among its lower-level components' (Solé & Goodwin, 2000, p. 151). This means that patterns appear without a blueprint of the patterns themselves.

From an evolutionary point of view, we arrive at the concept of self-organization in order to explain recurrent patterns in nature. Kauffman (1993, 1995) noted that the patterns on the trunk of a tree, the patterns on shellfish, and the stripes on the skin of the zebra or the tiger look so alike, while neo-Darwinists claim that evolution takes place based on random mutations and the selection of good variants. Based on the neo-Darwinist idea, one would expect much more variant patterns in nature. However, to the contrary, there is increasing evidence for extreme homology, that is, extreme conservation of ancient patterns (Gould, 2002; Gerhart & Kirschner, 1997). Random mutations and natural selection are not sufficient to explain these recurrent patterns. Models that include the concept of self-organization, however, can do so.

Conclusion

We showed that there is empirical evidence for the existence of a third source of variance that can neither be explained by genetic nor by environmental influences. It has been proposed that self-organization plays an important role in creating variance. Mainstream evolutionary psychologists, and the neo-Darwinian approach to evolution, at least at present, have yet to develop explicit models for nonadditive interaction and self-organization. Because evolutionary developmental biology provides these models, we argue that we need this approach in order to achieve a metatheoretical framework based on evolutionary psychology, which can bring new input into the discussion about the role nature and nurture in explaining the human mind.

Stage-wise versus gradual development

A third major issue in psychology is whether children's development proceeds in a stage-wise or in a continuous fashion. A stage is defined by a discrete period of time, in which the child is characterized by a qualitative different functioning compared to the functioning in other periods. Piaget was the major proponent of stage-wise psychological development (Piaget & Inhelder, 1969). He proposed a theory in which development includes four major stages. As described by Flavell (1982), a developmental period is called a stage, if the child's cognition is homogeneous at any point during that period. That is, the mind operates consistently at a single, uniform level of complexity and cognitive developmental maturity. Thus, one of the questions concerning stages is whether children possess homogeneous cognitive abilities over extended periods of time. Another question is whether the transition from one period to the next is abrupt, rather than continuous or gradual.

Mainstream evolutionary psychology's view

Mainstream evolutionary psychologists have not addressed the issue of stage-wise development. However, it is possible to give an evolutionary interpretation of stage-wise development by comparing the development of humans with the development of primates. For example, Bjorklund and Pellegrini (2002) mentioned Piaget's work in reference to Parker and McKinney's (1999) view on primate cognition. Piaget (1952) distinguished six substages in the sensorimotor period, the first stage of development. Parker and McKinney studied the existence of these six sensorimotor substages in humans, great apes, and monkeys. They concluded that all primates follow the

same sequence of sensorimotor stages. Bjorklund and Pellegrini related this finding to the issue of domain-specific versus domain-general abilities. They contended that 'intelligence is multifaceted, and that a Piagetian-like domain-general intelligence exists alongside other more domain-specific abilities, which have their own phylogenetic history' (p. 143). This suggests that there is a relation between the debate on the domain-specificity of the mind and the debate on stage-wise development. Stages, as defined by Piaget, are domain-general. From the discussion on domain-specific versus domain-general abilities, we doubt that mainstream evolutionary psychology will subscribe to this aspect of Piaget's theory. Another part of Piaget's stage theory concerns the existence of abrupt transitions from one stage to the other. Because mainstream evolutionary psychologists have not addressed this issue, we cannot evaluate their point of view.

Empirical evidence for the existence of stages in development

The first question is whether there is empirical evidence for homogeneity of cognition in children's development. This is one of the most controversial aspects of Piaget's theory (see Feldman, 2004, for a review). Piaget (1950) acknowledged the fact that children at a single point in development show different levels of cognitive skills on different, but also on highly similar tasks. He called this phenomenon *horizontal décalage*, referring to the inability of the child to solve a particular problem, although the child can solve a similar problem involving the same operations. For example, the ability of conservation, that is, the ability to understand the permanence of the quantity of a substance in spite of changes of the form, is highly variable depending on what kind of substance is used. Conservation of number, mass and length is reached between the age of 7 and 8, conservation of weight between the age of 9 and 10, and conservation of volume between the age of 11 and 12.

However, infants and older children differ both quantitatively and qualitatively. Current researchers in the Piagetian tradition have tried to reconcile the research findings of general qualitative differences between children of different ages, and the findings of specific abilities that can differ remarkably from domain to domain (Case, 1991; Feldman, 2004; Karmiloff-Smith, 1992). As explained in the discussion of domain-specificity of abilities, empirical evidence favors a position in which both domain-specific and domain-general abilities are admitted. In relation to the stage debate, this means that we have to adapt Piaget's strict idea of domain-general stages to an

idea of stages that contain both domain-specific and domain-general elements (see Feldman, 2004, for a similar view).

The second question is whether abrupt transitions from one stage to another take place. Because the idea of domain-general stages is controversial, this question is hard to answer. It is impossible to study transitions from one stage to the other without clearly defined stages. However, if we abandon the idea of strict domain-general stages, we can ask whether the development within a domain is continuous or discontinuous. We need no longer to speak of stage transitions, because we do not exactly know how to define a stage, but we can speak of phase transitions.

Phase transitions are defined as points of instability and turbulence, where old patterns break down and new ones appear (Lewis, 2000; van der Maas & Molenaar, 1992). The concept of a phase transition is derived from dynamic systems theory, and has its roots in physics. In physics, a phase transition is the observation of sudden changes in physical properties, for example the transitions between solid (e.g., ice), liquid (e.g., water), and gaseous (e.g., steam) phases. Note that the independent variable, i.e., temperature, changes continuously, whereas the dependent variable changes discontinuously. The concept of a phase transition can be applied to cognitive development as well. In child development, a phase transition is the observation of sudden changes in cognitive properties, for example knowledge or skills. There is ample evidence for the existence of phase transitions in cognitive development.

For example, Jansen and van der Maas (2001) showed that a phase transition takes place in the development of proportional reasoning as measured by the balance scale task (Siegler, 1981). In the balance scale task, children are confronted with a scale and are asked to predict the side to which it will tip, in view of a given configuration of weights. Clearly this movement depends on the number of weights that is put on either side, and on the distance between the weights and the fulcrum. Children use several different rules to solve items of the balance scale task. Initially, they focus mostly on the number of weights (Rule I). Later, they focus only on the distance between the weights and the fulcrum (Rule II). Finally, children use both dimensions to predict the movement (Rule III, i.e., adding distance and weights, and the correct Rule IV, i.e., multiplying distance and weight).

Jansen and van der Maas (2001) tested 6- to 10-year-olds on the balance scale task to study the phase transition from Rule I to Rule II. They hypothesized that children who do not spontaneously use Rule II, can be encouraged to adopt this rule by making the distance dimension more salient. The salience of the distance dimension increases, as the distance between one of the weights and the fulcrum increases. Children received a series of five distance items, in which the distance between one of the weights and the fulcrum gradually increased. A phase transition was observed: some children who initially only used Rule I, switched to using Rule II when the distance between the weight and the fulcrum increased.

Phase transitions have also been observed in the domains of language development (Dromi, 1987; Ruhland, 1999; Ruhland & van Geert, 1998), motor development (Smith & Thelen, 1993; Vereijken & Adolph, 1999; Wimmers, Savelsbergh, Beek & Hopkins, 1998), analogical reasoning (Hosenfeld, van der Maas, & van den Boom, 1997) and physical growth (Hermanussen & Burmeister, 1993; Lampl, 1993; Lampl & Johnson, 1993). Thus, although there is little empirical evidence for the existence of strict Piagetian stages, there is ample evidence for the existence of phase transitions occurring within more specific domains.

Evolutionary developmental biology's contribution

The main question in evolutionary developmental biology regarding the stage debate is how stage-wise development is related to the evolvability of populations. As defined above, evolvability is the ability to respond to a selective challenge (Hansen, 2003). This ability requires the capacity to produce the variation that can serve as the input for natural selection. Evolutionary developmental biologists would like to know whether evolvability is dependent upon the nature of development, i.e., whether development proceeds in a stage-wise or a continuous fashion (Stadler, Stadler, Wagner, & Fontana, 2001).

Kauffman (1993, 1995) has contributed to this issue. As described in the discussion on the domain-specificity of abilities, his simulation studies provided evidence for the idea that a system with both domain-specific and domain-general abilities has the greatest evolvability. Interestingly, these simulation studies also provided evidence for phase transitions in evolution. The simulations are built upon the idea of random graphs. In a random graph, a set of dots, or nodes, is connected at random with a set of lines. Imagine that

we have a hundred nodes, and that only a few nodes are connected by lines. Then imagine that we increase the number of lines, so more and more nodes become interconnected. After a while the nodes start to become interconnected into larger clusters. With up to fifty lines, the number of nodes that are interconnected within a single cluster is relatively limited. However, when the number of lines exceeds fifty, a "giant cluster" suddenly forms. Kauffman's simulation studies revealed a general finding: as the ratio of lines to nodes passes 0.5, a phase transition happens from relatively small clusters to relatively large clusters of interconnected nodes.

According to Kauffman (1993, 1995), this kind of phase transitions always occurs when individually simple elements get connected, and start to form more meaningful complex wholes. As evolution is mostly about the formation of complex systems composed of simple elements, Kauffman claimed that phase transitions are at the heart of evolution. Kauffman's model has enjoyed a lot of attention in the literature. Many specific changes of his model have been proposed, but phase transitions remain central to all variations of this model (e.g., Aldana, 2003; Solé, Salazar-Ciudad, & Garcia-Fernández, 2002).

Why would this theory be of interest for psychology? In the section about nature and nurture, we explained why self-organization is an important concept in the explanation of development. Kauffman's (1993, 1995) simulation studies demonstrated that complex wholes start to form when individually simple elements are connected. We have seen that self-organization, i.e., the nonlinear interaction among small-scale elements, plays an important role in this process. Kauffman's work also demonstrated that phase transitions characterize the process of interacting individual elements, which result in complex wholes. The emergence of self-organization from phase transitions, often called phase shifts or bifurcations, has been demonstrated mathematically (Scheinerman, 1996), and applies to physical, chemical, and biological systems (Kelso, 1995; Nicolis, 1977; Prigogine & Stengers, 1983; Thelen & Smith, 1994). The general idea is that complex systems arise by means of nonlinear interactions among local elements, and these self-organizing processes always occur by means of phase transitions. So, if self-organization is ubiquitous in nature, phase transitions are also ubiquitous.

If complex systems arise by means of self-organization, and thus by means of phase transitions, it would seem unavoidable that individual development is characterized by self-organization and phase transitions. We illustrate this

idea with an example concerning infant kicking (Thelen & Smith, 1994). During the first year of life, infants kick their legs in rhythmic succession, seemingly caused by nonspecific behavioral arousal. The traditional explanation of this kicking is that it is controlled by a Central Pattern Generator (CPG), a group of neurons in the spinal cord that could generate locomotion without sensory input (for references, see Thelen and Smith, 1994). An important aspect of the CPG is that it leads to precise alternation between flexor and extensor neurons in the limbs. However, in studying the muscles in the infants' legs, Thelen and colleagues did not find this pattern of alternation. Instead, they found that at the initiation of the flexion movement, both the flexors and the extensors of the hip, knee, and ankle joints contracted simultaneously. Moreover, they observed no muscle contraction at the initiation of the extension part of the kick.

According to Thelen and Smith (1994), the leg completed the kick, not because of a CPG prescribing how to end the kick, but because of the spring qualities of legs. That is, legs store elastic energy during the flexion movement. Combined with the pull of gravity, this energy caused the leg to extend. Because there is no agent that prescribes the kicking trajectory, the cyclic kicking movements can be viewed as self-organized. In addition, because of the recurrent nature of this cyclic movement, it can be said to be a stable pattern. Infants must overcome this pattern in order to learn to crawl, stand up, and walk. Specifically, to execute these movements, infants must be able to move the joints of the knee, ankle, and hip independently.

Thelen (1985) found that the pairwise correlations between knee-ankle, hip-ankle, and hip-knee movements were moderate to high up to about month 8. In the last months of the first year, this coupling decreased dramatically, indicating strong individual actions of the different joints. A phase transition occurred from strong inter-limb coupling to independent action of the joints. This research shows that self-organization in development is amenable to empirical study, and that phase transitions from relatively simple behavior to more complex patterns take place, as a consequence of interactions among local elements.

Conclusion

Empirical evidence for the domain-generality of Piagetian stages is lacking, but we showed that there is ample evidence for phase transitions occurring within specific domains of development. Evolutionary developmental biologists relate

phase transitions to the evolvability of traits, making phase transitions an important subject for both researchers in the domain of evolution and researchers in the domain of development. They also show, along with mathematicians and physicists, that self-organization and phase transitions go hand in hand, putting the concept of phase transitions in a larger framework. We conclude that if we want to arrive at a metatheoretical evolutionary psychology, we must be able to give an evolutionary rationale for the occurrence of phase transitions in development.

Individual differences

The study of individual differences is a major part of psychological research. Most studies focus on individual differences in intelligence and personality. The question that remains unresolved is: how do individual differences arise?

Mainstream evolutionary psychology's view

Mainstream evolutionary psychology studies the universal architecture of the mind. Regarding individual differences, Tooby and Cosmides (1990, 1992) emphasized the distinction between evolved mechanisms and manifest behavior. While there are individual differences in manifest behavior, the underlying set of evolved psychological mechanisms is universal. Individual differences are due to different environmental input, not to differences in the cognitive architecture. For example, children raised in England speak English and children raised in the Netherlands speak Dutch, but the underlying ability to learn language is the same in all children. To know how the mind works, we have to unravel the common cognitive architecture. Thus, we have to identify and explain the universals, not the individual differences.

Tooby and Cosmides (1990) argued that genetically based individual differences are an unrepresentative subset of human features, and are only quantitative variation of domain-specific psychological mechanisms. There must be enough variation in the population to combat parasites[3], and to be able to react to changes in the environment, but this variation must be

[3] Species that reproduce asexually, and thus have offspring that is genetically identical, are vulnerable to parasites. Once parasites 'crack' their genetic code, all of their offspring and kin will also pass away. Asexually reproducing species have a short life, so parasites have not enough time to crack the genetic code.

superficial from the point of view of the functional design of the organism, so as not to interfere with it. Tooby and Cosmides also argued that human groups do not differ substantially in the genes they possess. Natural selection is a process that eliminates variation. They stated: 'Those interested in studying complex psychological mechanisms should be most interested in design features that are inherited, but not heritable' (p. 38). They followed with: 'From the point of view of natural selection, it does not matter whether an alternative strategy is activated in an individual by a gene, an environmental cue, or a cognitive assessment of the situation. All that matters is that the innate mechanism is designed such that the right alternative is activated under the right circumstances' (p. 43).

But if there is little room for variation, how can people adapt to changing environments so well? Where does this plasticity come from? Tooby and Cosmides (1992) have argued as follows: 'The solution to the paradox of how to create an architecture that is at the same time both powerful and more general is to bundle larger numbers of specialized mechanisms together so that in aggregate, rather than individually, they address a larger range of problems. Breadth is achieved not by abandoning domain-specific techniques but by adding more of them to the system' (p. 113). In sum, mainstream evolutionary psychologists' point of view is that plasticity is the result of massive modularity, not of large differences between individuals.

Evolutionary developmental biology's contribution

The discussion of individual differences in evolutionary developmental biology centers around the study of mutation-selection balance, i.e., the balance between the number of mutations (i.e., variation or individual differences) and the number of adaptations within a system (e.g., Turelli, 1984; Zhang & Hill, 2005). The conflicting fitness effects (i.e., sometimes positive, but often negative) of mutations suggest small genetic variation, but the opposite is true. In natural populations, variation is typically large, and attributable to genes for 20 to 60 percent (i.e., heritability is .2 to .6; Mousseau & Roff, 1987).

An appealing idea is that the loss of variation due to natural selection is compensated for by many new mutations (i.e., the mutation-selection balance). Different models for this balance have been proposed, but some of them have assumptions that predict much higher mutation rates than are observed in nature (Kimura, 1965), and some of them predict less variation than is observed (Turelli, 1984). Recently a model was proposed that can

account for the observed mutation rate (Zhang, Wang, & Hill, 2004a; Zhang & Hill, 2005). Recall that all genes have pleiotropic effects, i.e., they have an effect on more than one trait. It is not feasible to describe all pleiotropic effects of any gene on all traits. However, it is possible to assess the effects of a gene on the focal trait (i.e., the trait that is influenced by that particular gene mostly), and the effects of a gene on fitness. The latter effect includes all pleiotropic effects. These two effects of genes are the basis of Zhang et al.'s (2004a) model, called the joint stabilizing and pleiotropic selection model. Predictions derived from this model fit well to empirical observations (Zhang, Wang, & Hill, 2004b). Thus, recently evolutionary developmental biologists have developed a model that can explain the balance between the generation of individual differences and the elimination of individual differences by natural selection. So far, empirical results that fit well within the model are often based on studies of the fly *Drosophila*. The next step is to study whether the same results can be found in other species, including human beings.

Another issue that evolutionary developmental biology addresses is how people, or organisms in general, are able to adapt to changing environments. Mainstream evolutionary psychologists suggested that plasticity is the result of massive modularity, not because of large individual differences (Tooby & Cosmides, 1992). However, they did not provide empirical support for this statement. Can evolutionary developmental biology provide this support? West-Eberhard (2003) argued that modularity can contribute to the emergence of plasticity. For example, a multi-segmented leg is more flexible than a single-segment, or a less segmented leg. She followed the same line of reasoning in relation to behavioral flexibility: 'Modularity in behavioral sequences permits a great diversity of combinations to characterize the flexible repertoire of an individual' (p. 59). She referred to a model of courtship behavior of grasshoppers, in which courtship is organized in more or less independent modular phases. This organization permits sensitivity to environmental conditions (Otte, 1972).

Research by de Kroon, Huber, Stuefer, and van Groenendael (2005), focusing on plasticity in plants as the result of modularity, is consistent with West-Eberhard's theory. De Kroon et al. showed that plasticity in plants is the result of changes at the modular level, that is, at the level of structural and functional subunits of the plant, rather than changes that influence the whole plant. Chipman (2002) presented similar results in a study of different anuran species (i.e., tailless amphibians, frogs and toads). He showed that the plasticity of

anuran development is attributable to the modular nature of anuran development. Modules can shift in time and space, without affecting other modules. Different arrangements of modules give rise to a large degree of plasticity.

Of course, the step from plants, grasshoppers, and frogs to human behavior and cognition is large, but these species can be used as models for studying the relation between modularity and plasticity. Another way of studying this relation that has been used by evolutionary developmental biologists is by means of simulation experiments. Ancel and Fontana (2000), using this method, showed that natural selection leads to a decrease in plasticity, which as a side effect, results in modularity. They used an empirically simple model of RNA sequences folding into different shapes to illustrate their ideas about the relation between natural selection, plasticity and modularity. In this model, the RNA sequence represents an individual's genotype and the folded shape represents an individual's phenotype. The RNA sequence can fold into several different RNA shapes under environmental fluctuations (i.e., temperature fluctuations).

In the simulation experiments it was assumed that the fitness value of a particular RNA shape is reflected by the amount of time the RNA sequence spends in it. The RNA sequence was regarded as plastic if it can fold into many different shapes. However, when the RNA sequence folded quickly into many different shapes, it did not spend much time in each shape individually. The more alternative shapes were possible, the less time the RNA sequence spent in each shape, including the advantageous ones. When the RNA sequence stayed in the advantageous shapes for extended periods, the simulation studies revealed that the number of possible shapes (under different environmental circumstances) was reduced very quickly, i.e., there was a rapid loss of plasticity. As a side effect, the advantageous shapes appeared to show great modularity (i.e., they contained several structural units that are thermophysically and genetically independent). To summarize, optimal structures have low plasticity and show strong modularity. Although modularity leads to quantitative improvement of a trait it also prevents significant structural modifications of that trait. Once modules are available evolutionary novelty is reduced to combinatorial arrangements of the modules.

Thus, according to Ancel and Fontana (2000), the emergence of modularity implies a reduction of evolvability because it leaves little room for significant

structural changes that improve the phenotype. This finding is consistent with the proposal of Hansen (2003), which was discussed in the section on domain-general versus domain-specific abilities. Hansen advanced, and provided evidence for, the view that modularity is not the best evolutionary solution; it reduces the mutational target size.

Based on these results, it is unlikely that plasticity is the result of extreme modularity, as this would reduce the mutational target size considerably. Conversely, it is also likely that plasticity is only possible given a certain degree of modularity. Modules can be changed without affecting other modules, leaving room for plasticity within a module. As was discussed in earlier sections, the results of Kauffman's (1993, 1995) simulation experiments offer a compromise that explains the existence of both stability and plasticity within a single system. In his random networks, plasticity depends on the degree of connectedness among the elements of the network. If the network is sparsely connected, the system exhibits clear order. The network quickly falls into very short cycles, and is very stable. Although stable behavior emerges, this behavior is very simple. When the degree of connectedness is very high, the network behaves in a chaotic way. There is a certain order, but when the network is very dense, this order cannot easily be detected. The network is too plastic and clear patterns are not discernible. This behavior also is not very interesting. Only when the network has an intermediate density, discernable interesting patterns emerge. Kauffman claimed that networks *at the edge of chaos* behave in a realistic manner, that is, they serve as a model for life processes. Only systems with an intermediate degree of connectedness of elements can evolve.

To illustrate the relevance for psychology, this idea of connectedness plays an important role in a new model for general intelligence proposed by van der Maas et al. (2006). Van der Maas et al. explain general intelligence with a nonlinear dynamic model adapted from mathematical ecology. Simulation experiments show that the positive correlations between scores on cognitive tasks are not caused by a single underlying biological or cognitive source, but by the positive mutual interactions between cognitive modules during development. It appears that such a developmental process results in the same pattern of positive correlations between tasks on which the famous 'g'-factor is based. The dynamic model, however, also explains additional phenomena in the development of intelligence, such as the hierarchical factor structure of intelligence and the increase in heritability of 'g'. Thus, simulation studies such

as Kauffman's (1993, 1995) have also been shown to be successful in a psychological context.

Conclusion

Mainstream evolutionary psychologist have argued that to unravel our cognitive architecture, we have to study universals rather than individual differences. The evolutionary developmental approach provides detailed models about the mutation-selection balance, which predict the genetic variation for different traits in different populations. Another contribution of this approach is that it provides some evidence for the hypothesis that modularity increases plasticity. However, it also shows that *massive* modularity does not necessarily do so; systems with a moderate degree of modularity have the greatest evolvability.

Discussion

The first aim of this chapter was to evaluate the role of evolutionary psychology as a metatheory for psychology. We argued that mainstream evolutionary psychology, as advanced by Tooby and Cosmides (1992), Buss (1995, 2003) and Pinker (1997), will have to address the major issues in psychology, if it is to fulfill this role. Here we considered four such issues. We judge mainstream evolutionary psychology to be deficient in this respect. The discussed deficiency should not be construed to imply that evolutionary psychology has no role to play in the general discussions in psychology. As discussed by Buss and Reeve (2003), evolutionary psychology certainly has identified important research questions, which were largely missing in the general research agenda of psychology. However, we do contend that the scope of mainstream evolutionary psychology requires broadening, if it is to contribute to the solution of the major issues in psychology. We judge the present strict adherence of mainstream evolutionary psychology to the neo-Darwinian approach to be overly restrictive. The neo-Darwinian approach is undoubtably indispensable, but it does not represent the whole field of evolutionary biology. We argued in favor of expanding the scope of mainstream evolutionary psychology to include the theory of evolutionary developmental biology.

The second aim of the chapter was to demonstrate how the inclusion into mainstream evolutionary psychology of concepts and findings from the field of evolutionary developmental biology does result in the desired metatheory. So

far, alternatives to mainstream evolutionary psychology, such as developmental dynamics (Lickliter & Honeycutt, 2003), have not been welcomed with open arms. For example, Buss and Reeve (2003) judged Lickliter and Honeycutt's proposal to be 'obscure' (p. 851), and stated that they failed to provide clear hypotheses. While Lickliter and Honeycutt's proposal may have not included specific hypotheses or predictions, it is not true that evolutionary developmental biology cannot furnish these. We derived several hypotheses, which are relevant to the major issues in psychology. The first hypothesis is that domain-general and domain-specific mechanisms co-exist, and that the ability to evolve requires both classes of mechanisms. The second hypothesis is that the interaction between nature and nurture is largely nonadditive, and that self-organization constitutes an important third source of variance. The third hypothesis is that development is characterized by phase transitions. The fourth hypothesis is that individual differences are largely attributable to pleiotropic effects that are incorporated in recent models that describe the balance between selection and mutations. As discussed, these hypotheses are consistent with many empirical results.

One might argue that research in the field of evolutionary developmental biology is concerned mainly with nonhuman organisms, and that the link with human development is therefore tenuous. Certainly most research in evolutionary developmental biology is not concerned with humans, but this does not mean that this research cannot provide input that is relevant study of human development and evolution. Moreover, for ethical reasons many hypotheses about the relationship between genetics and development cannot be tested on human beings, so animal research is the only way to get a better insight into this relationship.

Another possible objection against the inclusion of concepts and findings from evolutionary developmental biology in mainstream evolutionary psychology might be that the former is relatively new and therefore characterized by a lack of general consensus (e.g., this is the case with respect to the issue of modularity). Evolutionary developmental biology cannot be expected to provide clear-cut answers to all the unresolved questions in psychology. However, a clear contribution can be made, because evolutionary developmental biology provides other, potentially fruitful, perspectives on the major debates.

For example, in evolutionary psychology the discussion concerning the issue of modularity often takes the form of a philosophical debate, in which logical arguments are advanced concerning the likelihood of the evolution of domain-specific (modular) versus domain-general structures (e.g., Cosmides & Tooby, 1994; Fodor, 2000). In evolutionary developmental biology, this discussion takes the form of a biological debate about how modules actually develop and evolve, and how these modules are biologically related to each other (e.g., Wagner, 1996; Griswold, 2006). In contrast to the philosophical debate, this biological debate is more strongly embedded in empirical findings. Thus evolutionary developmental biology can provide an empirical basis for the various arguments in the philosophical debate, and thus bring the debate closer to a resolution. Moreover, evolutionary developmental biologists have used a wider diversity of research methods to study basic issues, such as modularity. For example, simulation experiments and mathematical modeling are often used as research tools by evolutionary developmental biologists (e.g., Kauffman, 1993, 1995; Hansen, 2003). Such tools have hardly been explored by evolutionary psychologists.

Another advantage of the evolutionary developmental approach is that its incorporation in the metatheoretical framework will free evolutionary psychology from the accusation of simply providing 'just-so stories', i.e., ad hoc functional explanations of current cognition and behavior. Evolutionary developmental biology provides theory and empirical findings concerning the actual development and evolution of structures. It also lessens the emphasis of evolutionary psychology on the end-products of development, i.e., the final adaptations that help human beings to survive and reproduce. The perspective of evolutionary developmental biology includes the role of evolution in the ontogenesis of adaptations. Specifically, evolutionary developmental biology provides psychology with a general framework concerning development, and the interaction of ontogenesis and evolution. This general perspective emphasizes the roles of self-organization and phase transitions, which give rise to partly modular structures with a balanced number of pleiotropic connections between them. This creates a greater mutational target size, and so greater evolvability.

CHAPTER 3

WHY DID THE SAVANT SYNDROME NOT SPREAD IN THE POPULATION? A PSYCHIATRIC EXAMPLE OF A DEVELOPMENTAL CONSTRAINT[4]

Abstract

A developmental constraint is a mechanism that limits the possibility of a phenotype to evolve. There is growing evidence for the existence of developmental constraints in the biological literature. We hypothesize that a developmental constraint prevents the savant syndrome, despite its positive aspects, from spreading in the population. Here, the developmental constraint is the result of the high interactivity among body parts in an early stage in embryological development, namely early organogenesis or the phylotypic stage. The interactivity during this stage involves all components of the embryo, and as a result mutations that affect one part of the embryo also affect other parts. We hypothesize that a mutation, which gives rise to the development of the positive aspects of the savant syndrome (e.g., an impressive memory capacity), will virtually always have a deleterious effect on the development of other phenotypic traits, (e.g., resulting in autism and/or impaired motor coordination). Thus, our hypothesis states that the savant syndrome cannot spread in the population, because of this developmental constraint. The finding that children with savant syndrome often have autism and physical anomalies, which are known to be established during early organogenesis, supports our hypothesis.

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A developmental constraint is a developmental mechanism or process that limits the ability of a phenotype to evolve, or biases it along certain pathways (Maynard-Smith et al., 1985; Amundson, 1994, 2005; Beldade et al., 2002; Schwenk and Wagner, 2003). In the biological literature, the evidence for the existence of developmental constraints is growing (Amundson, 2005). In the psychological literature, the concept of constraint is often considered, but is generally accorded a different meaning. In this chapter, we first explain the different conceptualizations of the term constraint in fields of psychology and biology. Then we discuss biological examples to illustrate the concept of developmental constraint, and we present what we contend to be an instance of a developmental constraint in the psychiatric context. Specifically, we hypothesize that it is a developmental constraint that prevents the positive aspects of the savant syndrome to become established in the population through the process of natural selection.

Conceptualizations of the concept of constraint

In the psychological literature, the term constraint is generally used in the context of learning. Keil (1981), in a now classic article on constraints on knowledge and cognitive development, defined constraints as 'formal restrictions that limit the class of logically possible knowledge structures that can normally be used in a given cognitive domain' (p. 198). Although the use of the term *limit* seems to imply that constraints hinder the child in its learning, it is rather believed that constraints facilitate learning. This is because constraints guide the learner towards a non-random selection of logically possible characterizations of information (see also Keil, 1990). For an instance of such a constraint, Keil (1981) refers to Chomsky's (1965) work on children's language acquisition. Here constraints are thought to be necessary to enable children to develop language as quickly and easily as they do. Moreover, constraints have been called *learning enablers* (Gelman & Williams, 1998). Thus, as was put forward by Bjorklund and Pellegrini (2002), constraints help children to make sense of certain types of information, and are likely to be the outcome of natural selection.

In the field of biology, the concept of developmental constraint is accorded a different meaning. Here, developmental constraints are related to the relative imperviousness of existing developing structures to modifying or reorganizing influences (Raff, 1996). Although many different biological variants are imaginable, only a limited number of variants seem to arise. From an

evolutionary perspective, this is remarkable, because an abundance of variation may be expected, as it is variation upon which natural selection acts.

Biological examples of developmental constraints

A biological example of a developmental constraint is the fact that we have five, and not more, fingers (Galis, van Alphen, & Metz, 2001). This is remarkable, because a common anomaly at birth is the presence of an extra finger or toe (e.g., in humans 0.1-0.2%; Castilla et al., 1996). Thus, there is variation in the number of digits, but extra digits have never become a stable pattern. An easy conclusion would be that extra digits do not have a selective advantage. However, extra digits may well be advantageous for climbing, digging, or swimming, and they have no apparent disadvantages. In fact, many animals have evolved extra digital structures, but these are never 'true' digits, but rather are modified wrist bones or extra phalanges (Galis et al., 2001; for example, the 'panda's thumb', see Gould, 1980). Thus there appears to be a developmental constraint on digit number that cannot easily be explained in terms of natural selection.

Galis et al. (2001) hypothesized that this developmental constraint is due the fact that limb patterning occurs very early in embryonic development, namely during early organogenesis (sometimes referred to as the phylotypic stage). This stage is characterized by intense inductive signaling, a process of massive response induction among cells. The result is that genetic mutations in one part of the embryo affect other parts of the embryo (so-called *pleiotropic effects*). If a mutation for an extra digit occurs in this stage, it is very likely that changes in another part of the body also occur, usually with deleterious effect. Infants born with an extra digit often have other congenital abnormalities, such as spina bifida, cleft lip, microcephaly, 13 trisomy syndrome, Meckel syndrome, and Down syndrome (Castilla et al., 1998). Polydactyly is also associated with serious abnormalities in other animals (for references, see Galis et al., 2001). This is probably the reason for the (indirect) selection against extra digits.

There are several other examples of developmental constraints in the biological literature. For instance, there is a developmental constraint that prevents parthenogenesis in mammals, i.e., the production of offspring solely from maternal germ cells (Kono et al., 2004). Without bi-parental parenting there is unequal expression of imprinted genes from maternal and paternal

alleles (Tilghman, 1999). Some genes are differently imprinted in maternal and paternal chromosomes, and both imprintings are necessary for normal development. For example, if chromosome 15q13 misses paternal imprinting, the result is the Prader-Willi syndrome (Butler & Palmer, 1983); if maternal imprinting is missing, the result is Angelman syndrome (Williams et al., 1990).

A third example of a developmental constraint was established in the fruit fly *Drosophila*. Genes that are expressed only during early embryonic development have been duplicated significantly less often during evolution than genes expressed in the later larval stage (Yang & Li, 2004). The duplication of genes is regarded as a major source of evolutionary change, so there appears to be a developmental constraint that prevents modification of early embryonic development. In a study of the worm *C. Elegans*, Yang and Li also found that genes expressed early in development have been duplicated less than those expressed late in development.

A psychiatric example of a developmental constraint

An example of a developmental constraint in psychiatry is related to the savant syndrome. Sufferers of this rare syndrome are often referred to as idiot savants, retarded savants, or autistic savants. They combine a serious disability, often mental retardation and/or a pervasive developmental disorder, such as autism, with a spectacular ability, which stands in stark contrast with the handicap (Treffert, 2000). The ability is highly developed in a narrow range, such as music or art performance, calendar calculating, mathematics, and mechanical or spatial skills, coupled with a phenomenal memory within the area of the skill itself (Miller, 1999; Treffert, 1999, 2000). In some savants, the skills are remarkable only in contrast to the handicap (Treffert calls such savants *talented*). In other savants, the skills would be remarkable even if observed in an otherwise normal person (Treffert calls savants with these skills *prodigious*). The skills themselves would probably be advantageous for many individuals by increasing the survival and reproductive chances. However, because these skills co-occur with a disability, natural selection does not favor these abilities.

We hypothesize that the savant syndrome has a genetic basis, and that the genes involved in the development of this syndrome have pleiotropic effects (i.e., affect more than one phenotypic trait). Furthermore, we hypothesize that the side-effects of this syndrome are unavoidable due to its developmental origin in the highly interactive early organogenesis stage. The exceptional skill

associated with the syndrome is itself a positive pleiotropic effect. However, this positive pleiotropic effect is always accompanied by negative pleiotropic effects, which nullify any selective advantage. The negative pleiotropic effects serve as a developmental constraint; because of this constraint, the savant syndrome cannot spread in the population, despite its positive aspects.

As our hypothesis is based on the supposition that the savant syndrome has a genetic basis, we first must establish this. Nurmi et al. (2003) reported that autism combined with savant syndrome is genetically linked to chromosome 15q11-q13, but Ma et al. (2005) could not replicate this finding. Despite this controversy about the specific genes involved in savant syndrome, there is little reason to doubt that the savant syndrome has a genetic basis. Savant syndrome is linked to autism (Treffert, 2000; Heaton & Wallace, 2004), and the genetic basis of autism is well-established (for a recent review, see Klauck, 2006). For example, Steffenburg et al. (1989) found a concordance rate for autism of 90% in identical twins, compared with 0% in fraternal twins in a Scandinavian sample. Bailey et al. (1995) found a concordance rate of 73% in identical twins, compared to 0% in fraternal twins in a British sample. Based on a large number of family and twin studies, Bailey et al. (1996) estimated the heritability of autism to be at least 90%. Thus, because of the co-occurrence of autism and the savant syndrome. it seems very likely that the savant syndrome also has a genetic basis.

Second, our hypothesis presupposes that the positive aspects of the savant syndrome are accompanied by negative aspects. There is ample support for this hypothesis, as was reviewed by Miller (1999) and Treffert (2000). Characteristics of savants include pervasive developmental disorders, such as autism, convulsions, visual impairment, deafness, Tourrette syndrome, epilepsy, schizophrenia, and language disorder or delay. Most savants are mentally retarded, although there are some exceptions (Heavey et al., 1999; Young & Nettlebeck, 1994). All studies on savants indicate that subjects with remarkable abilities in a narrow range suffer disabilities that prevent them from living independently, and, importantly from an evolutionary perspective, prevent them from acquiring a partner and enjoying reproductive success. For example, fifty percent of the savants have autism (Treffert, 2000), a disorder that clearly prevents sufferers from attracting and retaining sexual partners (Larsen & Mouridsen, 1997; Keller & Miller, 2006). Some have argued that autism is not a necessarily a harmful disorder, because people with autism outperform people without autism on numerous perceptual, reasoning, and

comprehension tasks (Gernsbacher et al., 2006). However, as long as people with autism do not benefit from this superiority in attracting sexual partners, the disorder will be harmful from the evolutionary perspective (i.e., selectively disadvantageous). Because of the disabilities of the savant, whether these include autism or other handicaps, the exceptional skill of the savant will not spread in the population. This is not because of selection against the exceptional skill, but because of selection against the accompanying severe disabilities.

Third, our hypothesis posits that the pleiotropic effects originate in the early organogenesis stage, i.e., very early in embryological development. Pleiotropic effects in this stage generally serve as a much stronger developmental constraint than pleiotropic effects in later embryological stages, because that have more pervasive effects (Galis & Metz, 2001). Support for this idea comes from several sources. First, many savants have brain anomalies (for an overview, see Treffert, 2000, pp. 193-198). Most savants with brain damage have left-side abnormalities. Because the brain starts to develop during early organogenesis (O'Rahilly & Müller, 2006), these findings are relevant to our hypothesis (this is not to say that savants may not suffer brain damage later in life, due to accident or disease). Second, an interesting finding is that many savants were born prematurely (Treffert, 2000). Although the exact reason why babies are born prematurely is often unknown, it is known that premature birth is usually related to disturbances during early organogenesis (Galis et al., 2006). So the combination of premature birth and savant syndrome suggest disturbances during early organogenesis. Third, it is important to establish that savant syndrome co-occurs with physical anomalies, besides brain anomalies, that are known to be established during early organogenesis, such as extra digits. Although a systematic study of physical anomalies in savants has yet to be conducted, from carefully reading of case histories, it emerges that many savants have physical anomalies. Treffert (2000) provides an overview of 90 savants. Some cases are described in great detail; others in a few sentences. Treffert mentioned physical abnormalities which we have listed in Table 3.1. Some savants have more than one physical abnormality. It should be noted that Treffert did not entertain any explicit hypothesis concerning the co-occurence of savant syndrome and physical anomalies, so the anomalies listed in Table 3.1 are not the result of a systematic study. A systematic study of physical anomalies in savants would presumably result in a more extensive list.

Fourth, an important finding for our hypothesis is that savant syndrome co-occurs with Williams syndrome (Gillberg & Rasmussen, 1994), a genetic disorder characterized by deviant facial features and a heart defect. The origin of this disorder lies in abnormalities in neural crest development, which occurs during early organogenesis.

Table 3.1 Physical anomalies in savants (n = 90), as mentioned in Treffert (2000)

Physical anomaly	**Number of savants with anomaly**
Blindness or other visual defect	23
Motor disorder or delay	10
Disproportions in heads	7
Epilepsy	6
Deafness or other hearing defect	4
Disproportions in hands	3
Mute	3
High-arched feet	2
High-arched palate	2
Diabetes	1
Hypothyroid	1

Fifth, indirect evidence is provided by findings that characteristics that frequently co-occur with savant syndrome, such as autism and delayed language, have also been reported to co-occur with having an extra digit (Kumandas et al., 2004), other congenital abnormalities (Arndt et al., 2005; Miller et al., 2005; Wier et al., 2006) and minor malformations (Rodier et al., 1997) that are known to be established during early organogenesis. The co-occurrence of congenital abnormalities and characteristics of the savant syndrome provides support for the hypothesis that the savant syndrome is the result of pleiotropic effects in early embryological development. For example, autism co-occurs with Down syndrome or trisomy 21 (Ghaziuddin, 1997) and Patau syndrome or trisomy 13 (Konstantareas & Homatidis, 1999), i.e., two chromosomal abnormalities that have been reported to co-occur with an

increase in digit number (Castilla et al., 1998). This evidence is consistent with the hypothesis that the savant syndrome did not spread in the population due to pleiotropic effects in the early organogenesis stage.

Discussion

We hypothesize that the failure of the savant syndrome to become established in the population through natural selection is due to a developmental constraint, as the concept is used in biology. The developmental constraint has its origins in the negative side-effects that are induced during the early organogenesis stage. These nullify the positive, potentially fitness enhancing, aspects of the savant syndrome. As we have only considered a few lines of support, further research is clearly necessary to test this hypothesis. This research should include a systematic assessment of physical anomalies that are known to be established in the early organogenesis stage in savants. These physical anomalies include, among others, polydactyly, midline disorders, such as cleft lip and spina bifida, congenital heart defects, the absence or incomplete development of one or more kidneys, or ear tags (Opitz, 1985). This research would also have clinical relevance, as the presence of physical anomalies might lead to more alertness towards severe psychiatric disorders, such as autism.

We have also shown that the biological conceptualization of a developmental constraint is relevant to psychiatric research. It is well known that if a mutated gene becomes active in the early organogenesis stage, its effects usually concern many phenotypic traits (Galis & Metz, 2001). In chapter 4 and 5, we examine the effects of mutations during the early organogenesis stage on the development of schizophrenia and autism. The vulnerability of the early organogenesis stage is the source of many disorders, both psychiatric and physical.

A remaining question is how disturbances in early embryological development may lead to psychiatric disorders that appear later in life. It is well-known that prenatal influences are correlated with the development of disorders such as autism (Glasson et al., 2004) and schizophrenia (M.C. Clarke et al., 2006). But can disturbances in embryological development explain the age of onset of disorders? Why is autism diagnosed as early as 18 months, while schizophrenia usually appears in early adulthood? Because autism and other developmental disorders are multigenic, this question is hard to answer. These disorders are

the result of multiple interactions among the effects of genes during both prenatal and postnatal life, leading to complex disorders with many characteristics. The problem of unraveling the influences of genes and interactions among genes on the development of disorders remains to be addressed. In the case of schizophrenia, there are already some findings that point in the direction of a specific gene, ZNF74, that is related to the age of onset of schizophrenia (Takase et al., 2001). For research on savants, it would be most interesting to get similar findings regarding autism.

CHAPTER 4

THE ORIGINS OF SCHIZOPHRENIA: A VIEW FROM EVOLUTIONARY DEVELOPMENTAL BIOLOGY

Abstract

Schizophrenia is a multigenic disorder, which implies that phenotypic effects of genes underlying this disorder are due to interactions among these genes during development. We present an evolutionary developmental account of this disorder. In evolutionary developmental biology, both genetic effects and developmental processes are considered in explaining the evolution of phenotypes. Work in this field has revealed that there is a stage in embryological development, which takes place between day 20 and 40 after fertilization, that is characterized by intense interactions among cells. This stage is called early organogenesis. Because of the intense interactions, mutations that are expressed during this stage are generally deleterious. It is hypothesized that schizophrenia is the result of genetic and environmental disturbances during early organogenesis. Evidence has shown that there is a significant association between the development of schizophrenia and brain defects, major and minor congenital anomalies, other medical comorbidities, prenatal infections, and maternal obstetric complications. These abnormalities are usually established during early organogenesis, suggesting that schizophrenia has its origins very early in embryological development.

Many studies have established that the risk of schizophrenia is largely genetically determined (e.g., Sullivan, Kendler, & Neale, 2003) and that several genes appear to be involved, i.e., it is a multigenic disorder (e.g., Freedman et al., 2001). At present, studies focus on the identification of those genes (for a review, see Berry, Jobanputra, & Pal, 2003). Several evolutionary hypotheses have been proposed in an attempt to explain the genetic etiology of schizophrenia (Polimeni & Reiss, 2003). Some hypotheses propose that schizophrenia originally was an adaptive trait. For example, some symptoms of

schizophrenia (e.g., hallucinations, hearing voices) were seen as divine properties, which in ancient times afforded an individual greater status and eventually higher reproductive success (Polimeni & Reiss, 2002). Others have proposed that it is unlikely that schizophrenia is adaptive, because it is associated with factors that are indicative of harmful mutations (Keller & Miller, 2006).

These evolutionary explanations of schizophrenia generally do not take into account the fact that schizophrenia is a developmental disorder. Understanding the evolutionary origins of schizophrenia requires a genetic analysis that is embedded in a developmental perspective. Because more than one gene is involved, the phenotypic effects of the genes depend on the interactions among the effects of each gene during development. Given the involvement of many genes, the effects of a single gene can vary considerably depending on the general genetic background of the individual. Therefore, it is necessary to study the interactions among the effects of genes in order to understand the evolution of schizophrenia.

To elucidate the relevant interactions among the effects of genes during development, and to understand how these have evolved and continue to be maintained in evolution, we require an approach that combines knowledge about the evolution and about the development of phenotypes. Evolutionary developmental biology is such an approach, as it forges a synthesis between processes acting on individual development and processes acting on evolutionary time scale (Hall & Olson, 2003). Most research in this field has focused on the development and evolution of the embryo. In this chapter, we outline the unique contribution of evolutionary developmental biology to the elucidation of the origins of schizophrenia. Research in evolutionary developmental biology has revealed that the embryological stage of early organogenesis is particularly susceptible to disturbances. This susceptibility is due to the fact that genetic and environmental effects during this stage differ greatly in scope from these effects during other stages (Sander, 1983; Raff, 1994). We hypothesize that schizophrenia develops as a consequence of dysregulation during early organogenesis. First, we present evolutionary developmental biology research on the vulnerability of early organogenesis. Second, we review research findings that provide support for the hypothesis that schizophrenia results from the vulnerability of early organogenesis.

Vulnerability of early organogenesis

There is a remarkable stage in embryological development in which many different species (all vertebrates, including humans) look more similar than during earlier or later stages (Sander, 1983). This stage, called early organogenesis, marks the inception of organ formation. The organs that start to develop in this stage are called primordia. In humans, this stage starts with neurulation (i.e., the process of formation of the central nervous system) around day 20[5] after fertilization and ends around day 40. Before this stage, embryos look remarkably different across species, and after this stage, development diverges again. Apparently, the stage of early organogenesis is strongly conserved during evolution, leaving limited room for variation across species (see Richardson et al., 1997, for discussion of variation of this stage). What is the reason behind this conservation?

It has been hypothesized that this conservation is the result of intense interactivity among different parts of the embryo during early organogenesis (Sander, 1983; Raff, 1994). During early organogenesis, a mutation that affects one part of the organism will also affect other parts. Suppose that a mutation has an effect on the developing kidney such that the efficiency of the kidney is increased. This is potentially a beneficial mutation, as it confers to the carrier a relatively higher fitness than to an individual who is not a carrier. However, if this mutation is expressed during early organogenesis, it will almost invariably affect other parts as well, such as, for example, the developing digestive or visual system. The phenomenon that a single mutation causes several phenotypic effects, is known as pleiotropy. Now if the mutation that leads to a more efficient kidney, has negative pleiotropic effects, resulting, say, in a deficient digestive or visual system, then the ultimate fitness of the carrier depends on the trade-off of beneficial and deleterious effects. In terms of evolutionary fitness, the positive effects of the better kidney may be counteracted by the negative effects of a deficient digestive or visual system. The result is that the vast majority of mutations expressed during early organogenesis are deleterious, making this stage susceptible to disturbances.

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[5] The start of neurulation in human embryos is generally listed as 18 days after fertilization, when neurulation has started in one quarter of the embryos (O'Rahilly & & Müller, 1981). Neurulation has started in most embryos at 23 days after fertilization (O'Rahilly & Müller, 2006).

Besides genetic mutations, these disturbances can also be environmental influences that affect the expression of genes. Because mutations that are deleterious will not be selected, this stage remains conserved during evolution (Sander, 1983; Raff, 1994).

Empirical evidence for the hypothesis that early organogenesis is susceptible to disturbances was collected by Galis and Metz (2001). Reviewing the literature, they found a strong association between mortality and disturbances of early organogenesis. For example, when hamsters are treated with sodium retinate on the days before early organogenesis, less than 25% of the hamsters die. However, when treatment occurs during the first days of early organogenesis, mortality increases up to 100%. When treatment occurs after these days, mortality drops quickly to previous levels (Shenefelt, 1972). Several studies revealed that in different species a peak in mortality occurs after treatment with a substance that interferes with development (e.g., methanol; for references, see Galis & Metz) during early organogenesis. In the surviving embryos, significantly more anomalies (such as head malformations and eye abnormalities) were found when the treatment occurred during, rather than before or after, early organogenesis (for references, see Galis & Metz). Note that in this research the abnormalities are environmentally induced. The main factor that determines which abnormalities are induced during embryogenesis appears to be the timing of the disturbance and not the type of disturbance (i.e., genetic or environmental; Wilson, 1965; DeSesso & Harris, 1996).

Another hypothesis related to the vulnerability of early organogenesis is that extra digits (i.e., polydactyly) did not evolve because of intense interactions during early organogenesis (Galis, van Alphen, & Metz, 2001; Lande, 1978; Wright, 1968). Structures that function as extra digits have evolved in association with digging, swimming, and tree-climbing (e.g., see the mole *Talpa europea,* and the sea turtle *Chelone*). This suggests that these structures have an evolutionary advantage. Interestingly, these evolved digit-like structures are never 'real' digits, but, for example, modified wrist bones or connective tissue. The selection of these extra digit-like structures suggests that such structures are advantageous. But it is puzzling why no real digits have been selected, given that polydactyly is a common anomaly at birth (0.1-0.2%, Castilla, Lugarinho, da Graça Dutra, & Salgado, 1998). If polydactyly were advantageous, it might easily have evolved in at least some species.

Did polydactyly not evolve as a stable trait because of negative pleiotropic effects during early organogenesis? Limb development starts during early organogenesis. For example, in mice, limb development starts on day 8 after fertilization, and digits are clearly visible on day 10 and 11 after fertilization (Ngo-Muller & Muneoka, 2000). This is exactly the time that interactivity among cells in embryo mice is most intensive (Theiler, 1989). The classic staging tables of Keibel (1897-1938) show that limb development occurs during early organogenesis in several species, including lapwings, sand lizards, deer, mice, chickens, and humans (for humans, see also O'Rahilly & Gardner, 1975). In general, in most amniotes, a class of species comprising reptiles, birds, and mammals, limb development occurs during early organogenesis.

The association between polydactyly and many abnormalities in different species, including humans, constitutes support for the hypothesis that extra digits did not evolve because of negative pleiotropic effects during early organogenesis. In humans, an extra digit is often associated with other anomalies, such as cleft lip and cleft palate, and at least 119 disorders and syndromes, including Down, Meckel, and Patau syndrome (Biesecker, 2002; Castilla et al., 1998). Moreover, Opitz et al. (1987) estimated that 90% of the human embryos and fetuses with polydactyly die prenatally. The co-occurrence of polydactyly and other abnormalities has also been reported in mice and chickens (Grüneberg, 1963), and in dogs (Bonnett, Egenvall, Olson, & Hedhammar, 1997; Kolbjornsen, Press, & Landsverk, 1994).

Other support comes from studies that compared amniotes (reptiles, birds, and mammals) and amphibians. In amphibians, limb development does not occur during early organogenesis, but at a later stage. This implies that mutations related to limb development do only have pleiotropic effects within the module (i.e., unit) of limb development, but hardly have pleiotropic effects on other parts of the body. Indeed, several studies showed that there is much more variation in limb development in amphibians than in amniotes (Gollmann, 1991; Hanken, 1982, 1983; Rienesl & Wagner, 1992; Shubin, Wake, & Crawford, 1995). Thus, there is considerable evidence that polydactyly in amniotes did not evolve because of negative pleiotropic effects during early organogenesis.

The hypothesis that early organogenesis is a vulnerable stage because of the intense interactions is consistent with current ideas on the importance of modularity in evolution (e.g., Callebaut & Rasskin-Gutman, 2005; Schlosser &

Wagner, 2004). Modularity states that the body consists of different semi-independent units which are characterized by a relative absence of interactions from the outside and much larger interaction within the units. In terms of pleiotropy, modularity means that there are more pleiotropic effects within a unit than there are between units. Modularity is regarded as an important condition for evolutionary change, because it allows individual units to change without affecting other units. If in a given unit a mutation has beneficial effects, the individual unit is able to evolve, because the mutation does not directly affect the functionality of the other units. In the absence of modularity, a mutation could affect many different units, which would generally result in deleterious effects in one or more of the other units.

The intense interactivity among parts, or the absence of effective modularity, which constrains the evolution of new phenotypes, is observed mainly during early organogenesis. Why is the stage of early organogenesis more conserved than earlier and later stages? At earlier stages there are fewer interactions because organ primordia have yet to develop. Body parts in later stages are characterized by a relatively high degree of modularity. A high degree of modularity implies that the effects of mutations will mainly be limited to the module itself and not to other parts of the organism, which in turn increases the possibility of evolution of the component parts (Wagner, 1996).

We conclude from the studies by Galis and Metz (2001), Galis, van Alphen and Metz (2001), and other work by Galis and colleagues (e.g., the remarkable absence of variation in the number of cervical vertebrae, Galis et al., 2006) that there is ample support for the hypothesis that the vulnerability of early organogenesis is due of the absence of effective modularity in this stage.

Schizophrenia and vulnerability of early organogenesis

In this section, we review evidence for the hypothesis that schizophrenia is the result of a disturbance, either genetically or environmentally induced, during early organogenesis. First, we need to introduce some terminology.

Terminology

Schizophrenia is a psychiatric disorder characterized by symptoms, apparent for at least six months, that are either positive (delusions, hallucinations, disorganized speech, disorganized or catatonic behavior), or negative (affective flattening, poverty of speech, lack of desire, motivation or persistence) (DSM-

IV, American Psychiatric Association, 1994). Its lifetime prevalence is about 1%, and it usually emerges in late adolescence or early adulthood. Most studies discussed in this chapter concern people diagnosed with schizophrenia. A few studies concern people with schizophrenia spectrum disorders, which include schizotypical personality disorder (main symptom: odd behaviors, thinking, and beliefs), schizoid personality disorder (main symptoms: aloof of other people, not showing emotions), delusional disorder (main symptom: false beliefs about one's own body, worthiness, or other people), schizoaffective disorder (symptoms of schizophrenia, combined with episodes of depression) and schizophreniform disorder (symptoms of schizophrenia, but the episodes do not last longer than six months). Some researchers distinguish deficit from nondeficit schizophrenia (Kirkpatrick, Buchanan, McKenney, Alphs, & Carpenter, 1989). People diagnosed with deficit schizophrenia have primarily negative symptoms (e.g., affective flattening) compared to people diagnosed with nondeficit schizophrenia, who have primarily positive symptoms (e.g., delusions).

Despite decades of intense research, the cause or etiology of schizophrenia remains unknown. One major hypothesis is the neurodevelopmental hypothesis of schizophrenia (Weinberger, 1987). In the next section we show that this hypothesis is consistent with our hypothesis that schizophrenia is the result of the vulnerability of early organogenesis, but that our hypothesis includes the underlying mechanism that causes the neurodevelopmental deficits related to schizophrenia.

The neurodevelopmental hypothesis of schizophrenia

The neurodevelopmental hypothesis of schizophrenia postulates that schizophrenia is a developmental disorder related to a brain defect. The brain defect is the result of abnormal genetic or epigenetic events, and is influenced by a diverse set of environmental events, both prenatally and postnatally. The brain defect eventually leads to the symptoms of schizophrenia in adolescence or adulthood. The support for the neurodevelopmental hypothesis is abundant (e.g., Bloom, 1993; Weinberger, 1987), although it has met some criticism (e.g., Lieberman, 1999; Weinberger, 1996). The evidence, as summarized by McClure and Lieberman (2003), comes from several sources, such as the increased risk of schizophrenia due to obstetric events, and the brain pathologies that people diagnosed with schizophrenia show (we review this evidence below). Despite the evidence for the neurodevelopmental hypothesis of schizophrenia, it is

remarkable that the cause or etiology of schizophrenia remains unknown and the causation is apparently complex. In addition, despite numerous findings that are in agreement with the neurodevelopmental hypothesis, no unifying mechanism has been advanced (M.C. Clarke, Harley, & Cannon, 2006). Many pieces of the puzzle have been collected, but they have yet to be put together to form a consistent picture. We propose that the absence of effective modularity during early organogenesis provides the unifying mechanism of the development of schizophrenia. In this chapter we show that there is ample evidence for this proposal.

Support for the hypothesis that schizophrenia results from the vulnerability of early organogenesis can be found in the existence of phenotypic abnormalities that are known to be established in the stage of early organogenesis, and that are observed more frequently in people diagnosed with schizophrenia than in unaffected people. We review six categories of abnormalities that are associated with schizophrenia: neuropathology, major congenital structural anomalies, minor physical anomalies, medical comorbidities, prenatal exposure to infections, and maternal obstetric complications. For each category, we provide evidence that these abnormalities originated during early organogenesis. We only report data on humans, not on animals.

Neuropathologies associated with schizophrenia

It is well-known that the brains of people diagnosed with schizophrenia are significantly different from the brains of unaffected people. The neuropathology of schizophrenia has been reviewed extensively elsewhere (e.g., Harrison, 1999; Robertson, Hori, & Powell, 2006; Shenton, Dickey, Frumin, & McCarley, 2001), so we only discuss it briefly. A consistent finding regarding structural brain alterations is that the volume of several brain regions of people diagnosed with schizophrenia is abnormal. Shenton et al. (2001) reviewed 193 MRI studies in schizophrenia; a summary of the results is presented in Table 4.1 (a). Most robust findings were the enlargement of the cavum septi pellucidi in 92% of the studies, the enlargement of lateral ventricles in 80% of the studies, the reduction of the medial temporal lobe volume (including the amygdala-hippocampal complex) in 74% of the studies, and the enlargement of the third ventricle in 73% of the studies.

Table 4.1 Abnormalities in brain structures in schizophrenia found in MRI studies as reviewed by Shenton et al. (2001); see text for references of first appearance of brain structures; the stage of early organogenesis starts around day 20 after fertilization, and ends around day 40

Brain structure	**(a) Percentage of studies in which abnormality was found (in parentheses the number of studies involved)**	**(b) First appearance of brain structure in days after fertilization**
Reduction of olfactory bulbs	100 (1)	30
Enlargement of the cavum septi pellucid	92 (12)	28
Enlargement of lateral ventricles	80 (55)	28
Reduction of the medial temporal lobe volume	74 (49)	33
Enlargement of the third ventricle	73 (33)	28
Reduction of the superior temporal gyrus volume	67 (15)	120
Enlargement of the basal ganglia	64 (25)	33
Corpus callosum abnormalities	63 (27)	32
Reduction of the whole temporal lobe volume	61 (51)	33
Reversal of left greater than right planum temporal	60 (10)	70
Reduction of frontal lobe volume	60 (50)	33
Reduction of the parietal lobe	60 (15)	33
Reduction of the thalamus	42 (12)	35
Reduction of the occipital lobe	40 (9)	33
Reduction of the cerebellum	31 (13)	32
Reduction of whole brain volume	22 (50)	20

An overview of the timing of the first appearance of the brain structures that are affected in people diagnosed with schizophrenia is given in Table 4.1 (b). Most of this research was performed by O'Rahilly and Müller (2006, for an overview of their work). Recall that the stage of early organogenesis starts around 20 days and ends around 40 days after fertilization.

The first morphological indication of the nervous system appears around 20 days after fertilization, with the appearance of the neural groove (O'Rahilly & Müller, 1981, 2006). A few days later, the three major divisions (prosencephalon, mesencephalon, and rhombencephalon) are visible, and the neural crest begins to develop (Müller & O'Rahilly, 1983; O'Rahilly & Müller, 2006). The neural crest is a temporary embryonic structure that gives rise to a variety of structures, including connective tissues of the face. The development of the olfactory bulb starts between 26 and 30 days after fertilization, when the olfactory placodes become visible (Pearson, 1941; ten Donkelaar et al., 2006). The ventricular system begins its development around 28 days after fertilization (O'Rahilly & Müller, 1990; Müller & O'Rahilly, 2006). The cavum septum pellucidum, a fluid-filled cavity of the brain that separates the lateral ventricles, starts to develop on the same day as the ventricular system (Müller & O'Rahilly, 2006). The cerebellum first appears 32 days after fertilization (Müller & O'Rahilly, 1988a; O'Rahilly & Müller, 2006). Also after 32 days, the corpus callosum starts to develop with the formation of the lamina terminalis (O'Rahilly & Müller, 2006; Rakic & Yakovlev, 1968). The future cerebral hemispheres become identifiable at 33 days after fertilization (Müller & O'Rahilly, 1988b; O'Rahilly & Müller, 2006). This implies the start of the development of the frontal, parietal, temporal, and occipital lobes. Now also the basal ganglia become visible (O'Rahilly & Müller, 2006). The thalamus becomes visible around 35 days after fertilization, because of longitudinal zoning in the diencephalon (Müller & O'Rahilly, 1988c; O'Rahilly & Müller, 2006); ten Donkelaar et al., 2006). In short, many brain structures that are abnormal in people diagnosed with schizophrenia start to develop during early organogenesis. The two brain structures which development does not start in early organogenesis, do not necessarily contradict our hypothesis. The cerebral sulci (the planum temporale is part of the lateral sulcus) and the gyri appear relatively late in fetal development (O'Rahilly & Müller, 2006), but they develop from brain structures which appear during early organogenesis. It is possible that abnormalities in sulci and gyri are the result of abnormalities in brain structures that first appear during early organogenesis.

Major congenital structural anomalies

Although the distinction between major and minor congenital anomalies is somewhat arbitrary, a general characteristic of a major congenital anomaly is that it is structural with serious medical, surgical, or cosmetic consequences (e.g., Matalon, Schechtman, Goldzweig, & Ornoy, 2002). Below we provide a list of major structural anomalies that have been reported in the literature to co-occur with schizophrenia. The list includes DiGeorge syndrome, Prader-Willi syndrome, Huntington's disease, and polydactyly.

DiGeorge syndrome. The DiGeorge syndrome (also called velo-cardio-facial syndrome, or 22q11 deletion syndrome) results in craniofacial anomalies, glandular malformations, and cardiovascular defects (for a review, see Wurdak, Ittner, & Sommer, 2006). One out of four of the people with this syndrome develop schizophrenia (for a review, see Arinami, 2006). Murphy, Jones, and Owen (1999) found that 24% of 50 subjects with DiGeorge syndrome fulfilled the criteria for schizophrenia. Bassett et al. (2005) described clinical features of 78 adults with DiGeorge syndrome, and found that 23% were diagnosed with schizophrenia. Vorstman et al. (2006) examined 60 children (9 to 18 years) with this syndrome, and found that 27% had psychotic symptoms. Murphy (2002) concluded that DiGeorge syndrome is the highest known risk factor for the development of schizophrenia. People with this syndrome have similar brain abnormalities as people diagnosed with schizophrenia (Chow, Zipursky, Mikulis, & Bassett, 2002; van Amelsvoort et al., 2001). DiGeorge syndrome involves disturbances of normal development of the neural crest and the pharyngeal apparatus (Lindsay, 2001; Vitelli, Morishima, Taddei, Lindsay, & Baldini, 2002), which start to develop during early organogenesis (Müller & O'Rahilly, 1987).

Prader-Willi syndrome. Prader-Willi syndrome is characterized by motor and cognitive delay, obesity, small hands and feet, and several craniofacial malformations (e.g., Holm et al., 1993). D. Clarke (1998) found that 14.7% of 59 individuals with Prader-Willi syndrome were diagnosed with a psychotic disorder, including schizophrenia. Vogels et al. (2004) found that 16.2% of 37 individuals with Prader-Willi syndrome had a psychotic disorder. As mentioned above, limb development is established during early organogenesis (O'Rahilly & Gardner, 1975). Craniofacial malformations are the result of abnormal neural crest development (ten Donkelaar & Vermeij-Keers, 2006;

Chai & Maxson, 2006), which start to develop during early organogenesis (Müller & O'Rahilly, 1987).

Huntington's disease. Huntington's disease is characterized by choreiform movements, dementia, and a wide variety of psychiatric symptoms (for a review, see Naarding, Kremer, & Zitman, 2001). These symptoms most likely arise because of abnormalities in the basal ganglia (Vonsattel & DiFiglia, 1998). One of the related psychiatric symptoms is schizophrenia (Besson, Ebmeier, & Simpson, 1991). Luaute, Turpin, and Lucotte (1997) reported eight cases with both Huntington's disease and schizophrenia. Tsuang, DiGiacomo, Lipe, and Bird (1998) found that within a family in which Huntington's disease runs, several members had schizophrenia-like symptoms (e.g., hallucinations and delusions). The development of the basal ganglia starts during early organogenesis (O'Rahilly & Müller, 2006).

Polydactyly. Although polydactyly may seem a minor anomaly, it is in fact usually regarded as major, because most people with an extra digit have other severe anomalies (Biesecker, 2002; Castilla et al., 1998). Three articles report the co-occurrence of schizophrenia or psychosis and polydactyly. Cardno et al. (1998) described five cases of co-occurrence of schizophrenia and polydactyly. Purandare and Plunkett (1999) reported another case, and Bhatia (1999) two additional cases. To our knowledge, the association between polydactyly and schizophrenia has not been systematically studied yet. In humans, limb development starts around 16 days after fertilization, at the start of early organogenesis (O'Rahilly & Gardner, 1975), with the number of digits determined a few days later (Keibel, 1897-1938).

Klinefelter syndrome. Klinefelter syndrome is a condition characterized by an extra X chromosome in the male (47,XXY), or by more extra X chromosomes (48,XXXY and 49,XXXXY; for a review, see Lanfranco, Kamischke, Zitzmann, & Nieschlag, 2004). Affected males have several physical problems including microorchidism (small testicles), micropenis, sterility, gynecomastia (larger than normal breasts), clinodactyly (abnormal growth and development of the phalanges of the toes or fingers), acromicria (abnormally small fingers or toes), and taurodontism (tooth with enlarged body and pulp chamber and reduced root size). Warwick, Lawrie, Beveridge, and Johnstone (2003) described an individual with both Klinefelter syndrome and schizophrenia. The brain of this individual showed similarities with that of other people diagnosed with schizophrenia. Van Rijn, Aleman, Swaab and Kahn (2006) compared 32 men

with Klinefelter syndrome with 26 matched unaffected controls on schizophrenia-spectrum traits with the Schizotypal Personality Questionnaire. The Klinefelter group scored significantly higher on schizotypal traits compared to the healthy controls. During early organogenesis many events occur that influence the developmental of the human reproductive system (O'Rahilly, 1983a). For instance, primordial germ cells appear first between 16 and 20 days after fertilization, that is, at the very beginning of early organogenesis. At 33 days after fertilization, the primary urogenital sinus becomes distinguishable, which is also within the period of early organogenesis. Several of the physical problems of males with Klinefelter syndrome indicate a disturbance of early organogenesis, including heart diseases (e.g., mitral valve prolapse, Fricke, Mattern, & Schweikert, 1981) and rheumatic diseases (Rovensky, 2006). During early organogenesis the heart (O'Rahilly, 1971; Moorman & Christoffels, 2003), limb, and digit primordia (O'Rahilly & Gardner, 1975) start to develop.

Case studies. Many case studies report an association between a major congenital disorder and schizophrenia. Caluseriu et al. (2006) reported an adult with 6p25 deletion, characterized by ocular anomalies, hearing loss, craniofacial abnormalities, and sometimes mental retardation, who was diagnosed with schizophrenia. 6p25 deletion is related to neural crest development (Mears, Mirzayans, Gould, Pearce, Walter, 1996), which starts during early organogenesis (Müller & O'Rahilly, 1987). Babovic-Vuksanovic, Jenkins, Ensenauer, Newman, and Jalal (2004) reported a subject with a deletion of 18p, characterized by a round face, hypertelorism, down-slanted palpebral fissures, temporal narrowing, and small hands and feet, who was diagnosed with schizophrenia. Craniofacial malformations indicate disturbances during early organogenesis (ten Donkelaar & Vermeij-Keers, 2006; Müller & O'Rahilly, 1987). Also limb development starts during early organogenesis (O'Rahilly & Gardner, 1975). Nimgaonkar, Scott, Brar, Ganguli, and Chakravarti (1993) reported an individual with both schizophrenia and Treacher-Collins syndrome. This syndrome is characterized by several craniofacial malformations, which are the result of abnormal neural crest development, starting during early organogenesis. Kawanishi, Kono, Onishi, Ishii, and Ishii (1997) reported one case and Prior, Chue, and Tibbo (2000) reported two cases of co-occurrence of schizophrenia and Turner syndrome. This syndrome is characterized by a short stature, lymphoedema, and several oral and craniofacial malformations (Lopez, Bazan, Lorca, & Chervonagura,

2002). Again, the craniofacial malformations are the result of abnormal neural crest development, which starts during early organogenesis.

Myers and Pueschel (1994) reported one case, and Duggirala, Cooper, and Collacott (1995) six cases of Trisomy 21 (i.e., Down Syndrome) with schizophrenia. A review of medical problems of people with Trisomy 21 is given by Roizen and Patterson (2003). For example, 44% of the infants with Trisomy 21 have congenital heart disease (Freeman et al., 1998). The heart starts to develop during early organogenesis (O'Rahilly, 1971; Moorman & Christoffels, 2003). A major characteristic of Trisomy 21 is mental retardation, suggesting brain anomalies. Several studies showed brain abnormalities in people with Trisomy 21 (e.g., Aydin, Kabakus, Balci, & Ayar, 2007; Rachidi, Lopes, Delezoide, & Delabar, 2006). As was mentioned above, the brain starts to develop during early organogenesis (O'Rahilly & Müller, 2006). People with Trisomy 21 also show a diverse array of minor physical anomalies (e.g., Rex & Preus, 1982). The relation between minor physical anomalies, schizophrenia, and early organogenesis is explained in the next section.

Conclusion. There is considerable evidence that schizophrenia co-occurs with major congenital anomalies that originate from abnormal development during early organogenesis. In general, it is acknowledged that major congenital anomalies are the result of disturbances of early organogenesis (Opitz, 1985a; 1985b; Martínez-Frías, 1994).

Minor physical anomalies

In this section, we present an overview of studies on the relation between minor physical anomalies and schizophrenia. Minor physical anomalies, also called dysmorphic features, are morphological abnormalities that can be detected quite easily, but that are not life-threatening. In most studies, minor physical anomalies were assessed with the Waldrop Physical Anomaly Scale (Waldrop, Pedersen, & Bell, 1968; Waldrop & Halverson, 1971). The items of the Waldrop scale assess abnormalities in six different body regions: head, eyes, ears, mouth, hands, and feet. In Table 4.2, the 18 individual items of the original scale are summarized.

Table 4.2 List of minor physical anomalies assessed by the Waldrop Physical Anomaly Scale

Body region	**Anomaly**
Head	Electric hair
	Two or more whorls
Eyes	Epicanthus
	Hypertelorism
Ears	Low seated ears
	Adherent ear lobes
	Malformed ears
	Asymmetrical ears
	Soft and pliable ears
Mouth	High palate
	Furrowed tongue
	Smooth-rough spots on tongue
Hands	Curved fifth finger
	Single transverse palmar crease
	Index finger longer than middle finger
Feet	Third toe: longer than second toe / equal in length to second toe
	Partial syndactylia of two middle toes
	Gap between first and second toe

Although the Waldrop Physical Anomaly Scale has been used extensively, it has also met with a lot of criticism (Akabaliev & Sivkov, 2007; Krouse & Kauffman, 1982; Lane et al., 1997; Sivkov & Akabaliev, 2003a; Trixler & Tenyi, 2000). Concerns are that the scale includes subjective judgments (e.g., the definition of electric hair or a malformed ear), that it cannot be applied to other races than the Caucasian (e.g., black people never have electric hair), and that it cannot be applied to all age groups (e.g., many young children have epicanthus, and thus this cannot be considered as an abnormality at that age). In response to the criticisms of the Waldrop Physical Anomaly Scale, several researchers proposed new assessments. Generally, recent studies have included many more items than the 18 of the original Waldrop Scale. Most recent studies often have combined the Waldrop Scale with an anthropometric scale, based on the work of Farkas (1994). An anthropometric scale consists of multiple linear or angular measurements of craniofacial widths, lengths and depths, and categorical or ordinal scores of details of the eye, ear, nose, mouth, hand and foot morphology (Lane et al., 1997).

Table 4.3 presents an overview of the studies that showed significant differences between samples of people diagnosed with schizophrenia and unaffected controls on several measurements of minor physical anomalies. Note that not all minor physical anomalies are measured in every study, so comparison between studies of the individual anomalies is not possible. All studies included samples of people with a DSM-III-R or DSM-IV diagnosis of schizophrenia, assessed by a professional clinician. The study conducted by McGrath et al. (2002) included 180 people with psychotic disorders (schizophrenia, n=130; delusional disorder, n=5; atypical psychosis, n=5; depression with psychosis, n=9; bipolar disorder, n=21; and schizoaffective disorder, n=10). Interrater reliability was sufficient for all studies; only Elizarrarás-Rivas et al. (2003) did not report their interrater reliability.

Lane et al. (1997) presented the most extensive evidence for the presence of minor physical anomalies in people diagnosed with schizophrenia. In a large sample they found many different anomalies, in all parts of the body they assessed. McGrath et al. (2002) provided the study with the largest sample of people diagnosed with schizophrenia. Donovan-Lepore et al. (2006) provided the only study with a racially mixed schizophrenia sample. Many more studies than reported in Table 4.3 showed the presence of minor physical anomalies in people diagnosed with schizophrenia. Some of these studies did not report the individual minor physical anomalies, but only a total score of anomalies. For

example, Lohr and Flynn (1993) compared scores on a slightly modified Waldrop scale (17 items) of people diagnosed with schizophrenia (n=118; mean Waldrop score=1.53), people with mood disorders (n=33; mean Waldrop score= 1.21) and unaffected controls (n=31; mean Waldrop score=0.84). The difference between people diagnosed with schizophrenia and unaffected controls was statistically significant; the differences between any of the other groups were not. Waldrop scores for the people diagnosed with schizophrenia ranged from 0 to 7; the Waldrop scores for unaffected controls from 0 to 3. Similar results were found by Lohr, Alder, Flynn, Harris, and McAdams (1997), Green, Satz, and Christenson (1994), Weinstein, Diforio, Schiffman, Walker, and Bonsall (1999), and Gourion et al. (2003). Schiffman et al. (2002) studied a Danish birth cohort of children born between 1959 and 1961. In 1972, 265 children from this cohort were assessed for minor physical anomalies with the Waldrop Physical Anomalies Scale. In 1993, 242 subjects were assessed for their psychiatric status. Of the subjects with less than three minor physical anomalies in their childhood, 2.5% developed schizophrenia, and 12.4% another psychiatric disorder. Of the subjects with three or more minor physical anomalies in childhood, these percentages were significantly higher: 8.3% developed schizophrenia, and 16.5% another psychiatric disorder. Hennessy, Baldwin, Browne, Kinsella and Waddington (2007) used three-dimensional laser surface imaging to detect deviant craniofacial morphology in people diagnosed with schizophrenia. They found that the face of people diagnosed with schizophrenia is on average laterally broad and vertically short.

There are a few studies that do not report a significant relation between schizophrenia and minor physical anomalies. One study did not report a significant difference between people diagnosed with schizophrenia and controls (Alexander, Mukherjee, Richter, & Kaufmann, 1994). The sample consisted of 41 people diagnosed with schizophrenia, 8 people with bipolar disorder, 19 people with mental retardation and 14 unaffected controls. On a slightly modified Waldrop scale, only the scores of the mentally retarded subjects (mean = 6.2) were significantly higher than the scores of the unaffected controls (mean = 2.9). Christensen and Mortensen (2002) found a moderate, but statistically nonsignificant, increased risk of schizophrenia among people with cleft palate.

Table 4.3 Overview of studies that reported significantly more minor physical anomalies in people diagnosed with schizophrenia compared to unaffected controls

Minor physical anomalies[a]	Scale of measurement	Sample size of people diagnosed with schizophrenia	Sample size of control group	Reference
1, 27	Anthropometric	52 (32 Caucasian and 20 African American, USA)	52 (matched for gender, race and age)	Donovan-Lepore et al. (2006)
3, 5, 14, 16, 21, 24, 28, 29	Waldrop + extra items on facial and limb asymmetry	40 (France)	42	Gourion et al. (2004)
1, 2, 5, 10, 11, 12, 13, 15, 24, 27, 28, 39	Waldrop + anthropometric	20 (Mexico)	20 (matched for gender, ethnic origin, age and place of residence)	Elizarrarás-Rivas et al. (2003)
4, 11, 12, 21, 24, 33	Waldrop	76 (Bulgaria)	82	Sivkov & Akabaliev (2003b)
8, 16, 23, 35	Waldrop + extra items	30 (Hungary)	30 (matched for gender, ethnic origin and age)	Trixler et al. (2001)
1, 2, 5, 19, 20	Anthropometric	180 (people with psychosis; 130 of them with schizophrenia, Australia)	180 (matched for gender and age)	McGrath et al. (2002)
1, 5, 7, 11, 13, 16, 21, 23, 27, 28, 32, 34, 35, 37	Waldrop + extra items	60 (Scandinavia)	75	Ismail et al. (1998)
2, 4, 5, 6, 10, 11, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 30, 32, 34, 36, 38	Waldrop + anthropometric	174 (Ireland)	80	Lane et al. (1997)
9, 19, 23, 25, 27	Waldrop + extra items	50 (Hungary)	50 alcohol-dependent people (matched for gender, ethnic origin and age)	Trixler et al. (1997)
1, 21, 23, 24, 28, 29, 33, 35	Waldrop	67 (USA)	88	Green et al. (1989)

Legend of Table 4.3

[a]Anomalies:

Global head:

1, abnormal head circumference; 2, lower face abnormalities; 3, facial asymmetry; 4, electric hair; 5, abnormal hair whorls; 6, other hair abnormalities; 7, abnormal eyebrows; 8, flat occiput; 9, skin abnormalities; 10, nose abnormalities

Eyes:

11, epicanthus; 12, hypertelorism; 13, other eye abnormalities;

Ears:

14, low seated ears; 15, adherent lobes; 16, malformed ears; 17, asymmetrical ears; 18, soft and pliable ears; 19, ear protrusion; 20, other ear abnormalities;

Mouth:

21, high palate; 22, other palate abnormalities; 23, furrowed tongue; 24, smooth-rough spots on tongue; 25, other tongue abnormalities; 26, teeth abnormalities; 27, other mouth abnormalities;

Hands:

28, curved fifth finger; 29, single tranverse palmar crease; 30, other palm abnormalities; 31, index finger longer than middle finger; 32, fingernail abnormalities;

Feet:

33, third toe longer than or equal to second toe; 34, partial syndactylia of two middle toes; 35, gap between first and second toe; 36, toenail abnormalities; 37, other toe abnormalities; 38, abnormal pedal arches;

Global body:

39, abnormal length of arms

Besides these studies, the evidence that minor physical anomalies are more abundant among people diagnosed with schizophrenia than among unaffected people is overwhelming. What is the evidence that minor physical anomalies are established during early organogenesis?

Hand and feet. The upper limb bud first appears around 24 days after fertilization; the lower limb bud is present around 28 days after fertilization (O'Rahilly & Gardner, 1975). Many of the shape characteristics are determined early on, including the separation of the digits, or absence thereof in syndactyly (Grüneberg, 1963; Hall & Miyake, 2000).

Eye. During early organogenesis, many important parts of the eye are established (O'Rahilly, 1983b). For example, the optic primordium and the optic sulcus appear around 22 days after fertilization. The lens pit is formed around 32 days after fertilization, and around the same time the oculomotor nerve appears. The eyelid grooves appear around 37 days after fertilization.

Ear. During early organogenesis, also important parts of the ear are established (O'Rahilly, 1983b). The otic disc first appears around 20 days after fertilization. The vestibular part of the vestibulocochlear ganglion and vestibular nerve fibres can be distinguished around 28 days after fertilization. Auricular hillocks representing the tragus, crus helecis, helix, and antitragus are present around 37 days after fertilization.

Craniofacial development. The basic parts of the face (five facial swellings) first appear around 25 days after fertilization (for an overview, see Larsen, 2001). Many craniofacial abnormalities are derived from abnormal neural crest development (ten Donkelaar & Vermeij-Keers, 2006; Chai & Maxson, 2006). In humans, neural crest development starts around day 20 after fertilization, at the beginning of early organogenesis (Müller & O'Rahilly, 1983, 1985).

Conclusion. There is ample evidence that minor physical anomalies co-occur with schizophrenia, and that many of these anomalies are the result of disturbances during early organogenesis. Moreover, minor anomalies are often an indication of major abnormalities (Leppig, Werler, Cann, Cook, & Holmes, 1987; Marden, Smith, & McDonald, 1964; Mehes, Mestyan, Knoch, & Vinceller, 1973), and, hence, of a disturbance of early organogenesis.

Medical comorbidity

People diagnosed with schizophrenia have increased rates of cormorbid medical disease (e.g., Lambert, Velakoulis, & Pantelis, 2003; Mitchell & Malone, 2006). This is in agreement with our hypothesis that schizophrenia is the result of disturbances during early organogenesis. However, many other factors may contribute to the comorbidity of schizophrenia and medical conditions, such as the use of antipsychotic drugs (e.g., Glassman, 2005) and unhealthy lifestyle (e.g., Compton, Daumit, & Druss, 2006; Hughes, 1986). Eighty-five percent of the people diagnosed with schizophrenia smoke cigarettes, compared to 33% of the general population (Compton et al., 2006; Hughes, 1986), and people diagnosed with schizophrenia are more than 50% more likely to be overweight or obese (Compton et al., 2006). Thus, medical comorbidity in people diagnosed with schizophrenia cannot be regarded as conclusive evidence for our hypothesis, but it is in agreement with it.

Furthermore, people diagnosed with schizophrenia have an excess mortality rate compared to the general population (e.g., Goff et al., 2005a; Harris & Barraclough, 1998). In a meta-analysis, it was found that mortality rate is elevated in people with schizophrenia: among this group there are 189 deaths/10,000 population per year, compared to 151 death/10,000 population per year in the general population (S. Brown, 1997). Eighty percent of the people diagnosed with schizophrenia die from natural causes, compared to 97% of the general population. The most important cause of the excess mortality of people diagnosed with schizophrenia was suicide (28% of the excess deaths), followed by accidents (12%) and homicide (1%). Based on this meta-analysis, around 60% of the excess mortality of people diagnosed with schizophrenia is due to natural causes (i.e., medical problems). The meta-analysis showed that people diagnosed with schizophrenia suffer from the same kinds of diseases as the general population, but suffer from them more often than people in the general population (the same pattern was found by S. Brown, Inskip, and Barraclough, 2000). Interestingly, people diagnosed with schizophrenia appear to have a lower risk of cancer (e.g., Barak et al., 2005; Dalton, Mellemkjaer, Thomassen, Mortensen, & Johansen, 2005) - which may be related to the earlier age of death in people diagnosed with schizophrenia - although they die more often once they get cancer (Mortensen & Juel, 1990). People diagnosed with schizophrenia have an increased risk for the following medical diseases.

Heart disease. There is ample evidence of an increased risk of cardiovascular disease. Hennekens, Hennekens, Hollar, and Casey (2005) reviewed the literature on the relation between schizophrenia and heart diseases. They found that the risk of death due to heart disease is 50 to 75% for people diagnosed with schizophrenia, compared to 33% in the general population. Osborn, Nazareth and King (2006) studied risk for coronary heart disease in 74 people with and 148 without severe mental illness. Of the people with severe mental illness, 66 had a diagnosis of schizophrenia, 6 of schizoaffective disorder, and 2 of chronic or persistent delusional disorder. The Framingham risk score was calculated to assess risk. This score is a function of age, gender, high-density-lipoprotein-cholesterol, total cholesterol level, blood pressure, smoking, and diabetic status. Results revealed that people with severe mental illness were twice as likely to have a raised Framingham risk score as people without severe mental illness. Medication and socio-economic deprivation could not explain this elevated risk score. Goff et al. (2005b) examined 687 people diagnosed with schizophrenia and matched controls and found that coronary heart disease risk was significantly elevated for people diagnosed with schizophrenia, also after controlling for body mass index, smoking, diabetes, HDL cholesterol, and hypertension. It was concluded that the increased risk of a heart disease for people diagnosed with schizophrenia cannot be fully explained by their unhealthy lifestyle. The heart starts to develop during early organogenesis (O'Rahilly, 1971; Moorman & Christoffels, 2003), hence the increased risk of heart disease may be due to disturbances during this embryonic period.

Lung diseases. Sokal et al. (2004) compared medical comorbidity of people diagnosed with schizophrenia (n = 100) with a matched sample from the general population (n = 2705). The schizophrenia sample had significantly more often asthma (16 versus 8%), chronic bronchitis (15 versus 6%), and emphysema (10 versus 2%), while controlling for age, sex, race or ethnicity, body mass index, and smoking behavior. So here again, the increased risk of lung diseases for people diagnosed with schizophrenia cannot be fully explained by their unhealthy lifestyle. The lungs start to develop around 26 days after fertilization, with the appearance of the lung bud, during early organogenesis (O'Rahilly & Boyden, 1973; Sutliff & Hutchins, 1994).

Conclusion. There is considerable evidence that people diagnosed with schizophrenia have an increased risk of heart and lung diseases, even when the effects of an unhealthy lifestyle are statistically removed. Because the lungs

and the heart start to develop during early organogenesis, this increased risk is in agreement with our hypothesis that schizophrenia results from disturbances during early organogenesis.

Prenatal exposure to infections

There are some indications that prenatal infections lead to an increased risk of schizophrenia (for an overview, see A. S. Brown, 2006; A. S. Brown & Susser, 2002). For our hypothesis that schizophrenia is the result of disturbances during early organogenesis, it is important to know the timing of the infection, i.e., whether the infection occurred during early organogenesis. Unfortunately, there is no study available that tested the specific prediction that infections between 20 and 40 days after fertilization lead to an increased risk of schizophrenia. However, there are studies that show the relation between infections during the first trimester of pregnancy and the development of schizophrenia. In this section we review these studies.

Influenza. Many studies have been performed to examine the relationship between prenatal exposure to influenza and schizophrenia. Ebert and Kotler (2005) reviewed the literature and found contradictory results; 11 studies reported a positive relation between influenza and schizophrenia, whereas 8 other studies did not find this association. Most studies were limited because individuals were considered to have been prenatally exposed to influenza when they were in utero during an influenza epidemic, and did not rely on data that they were actually exposed to influenza. A. S. Brown et al. (2004a) overcame this limitation by examining maternal blood samples that were collected during pregnancy of a group of 64 people diagnosed with a schizophrenia spectrum disorder, and comparing them to those of 125 unaffected matched controls. Of most people diagnosed with schizophrenia (n = 63), maternal blood samples collected during the third trimester were available. The difference in infection rate between people diagnosed with schizophrenia and controls was nonsignificant (19% versus 17%). Maternal blood samples collected during the second trimester were also available for 48 of the people diagnosed with schizophrenia. This difference was again nonsignificant (15% versus 13%). Maternal blood samples, collected during the first trimester, were also available for 20 people diagnosed with schizophrenia. Interestingly, this difference in infection rate between people diagnosed with schizophrenia and unaffected controls was marginally significant ($p = 0.08$): 21% versus 9%. These data are consistent with our hypothesis that infections early in pregnancy are

most harmful. However, here caution is called for as the small sample size of the study.

Rubella. A. S. Brown et al. (2001) examined a group of 53 subjects whose mothers had been exposed to a major rubella pandemic during pregnancy in 1964. At the age of 34, 21% of the subjects received the diagnosis of a schizophrenia spectrum disorder. Most mothers (88.9%) of the schizophrenia spectrum subjects were exposed to rubella during the first trimester of their pregnancy, compared to 59.3% of the mothers of subjects without schizophrenia. Buka et al. (2001a) compared 27 people diagnosed with a schizophrenia spectrum disorder with 54 unaffected matched controls on maternal blood samples that were collected when the mother was delivered of the neonate. They did not find a significant difference in IgG antibodies to rubella in the blood samples between the two groups. So far, the evidence provided by A. S. Brown et al. for the relation between first trimester exposure to rubella and the development of schizophrenia is suggestive, but clearly requires replication.

Toxoplasmosis. Wang et al. (2006) tested blood samples of 600 people diagnosed with schizophrenia, 600 people with affective disorders, 200 people with physical disease, and 200 unaffected controls on serum reactivity to Toxoplasmosis. Fourteen percent of the people diagnosed with schizophrenia had antibodies to Toxoplasmosis, compared to 7% of the people with affective disorder, 5% of people with physical disease, and 3% of the unaffected controls. A drawback of this study is that it is not known whether the individuals did get the infection before or after the development of schizophrenia. Mortensen et al. (2007) compared neonatal heel stick blood samples of 71 subjects who developed schizophrenia and 684 control subjects on antibodies for Toxoplasmosis. The association between schizophrenia and Toxoplasmosis was significant. A. S. Brown et al. (2005) compared maternal blood samples obtained during pregnancy of 63 people diagnosed with a schizophrenia spectrum disorder with maternal blood samples of 123 unaffected matched controls. Gestational ages of sera from people diagnosed with schizophrenia and control subjects were similar. Antibodies to toxoplasmosis were found in maternal blood samples of 29% of the people diagnosed with schizophrenia, compared to 18% of the unaffected controls, a significant difference. Buka et al. (2001a) compared 27 people diagnosed with a schizophrenia spectrum disorder with 54 unaffected matched controls on maternal post-partum blood samples. They did not find a significant difference in antibodies to Toxoplasmosis in the

blood samples between the two groups. In sum, there is some evidence for the association between Toxoplasmosis infection and the development of schizophrenia, but the hypothesis that a Toxoplasmosis infection during the first trimester is related to schizophrenia could not be tested with the available data.

Herpes. Buka et al. (2001a) compared 27 people diagnosed with a schizophrenia spectrum disorder with 54 unaffected matched controls on maternal post-partum blood samples. They found significantly more antibodies to herpes simplex virus type 2 (one of 6 known human herpes viruses) in the schizophrenia group, but not significantly more antibodies to the other types of herpes viruses. A. S. Brown, Schaefer, Quesenberry, Shen, and Susser (2006) collected the last maternal serum sample (generally third trimester or perinatal) of 60 people diagnosed with schizophrenia. They found no significant difference between the maternal samples of the people diagnosed with schizophrenia and those of 110 unaffected matched controls on antibody levels of herpes simplex virus type 2 and two other human herpes viruses. Dickerson et al. (2006) compared 88 people diagnosed with deficit schizophrenia with 235 people diagnosed with nondeficit schizophrenia, and found that the former had more antibodies to cytomegalovirus than the latter. Unfortunately, none of these studies specifically tested the hypothesis that first trimester infections lead to an increased risk of schizophrenia.

Cytokines. A. S. Brown et al. (2004b) compared maternal blood samples of 59 people diagnosed with schizophrenia with those of 118 unaffected matched controls on cytokine levels (interleukin-8, interleukin-1β, interleukin-6 and tumor necrosis factor-α). Blood samples were taken from the second and third trimester of pregnancy. It was discovered that interleukin-8 levels, but not the other cytokine levels, were elevated in maternal blood samples of the people diagnosed with schizophrenia compared to those of the unaffected controls. Buka et al. (2001b) found that tumor necrosis factor-α, but not the other cytokine levels, were elevated in maternal blood samples of 27 people diagnosed with schizophrenia compared to those of 50 matched unaffected controls. The blood samples were obtained at the time of delivery. Unfortunately, no data are available about the relation between first trimester cytokines infections and the development of schizophrenia.

Conclusion. There is some evidence for the relation between prenatal infections and the development of schizophrenia, but the results are equivocal.

Studies that specifically test the hypothesis that infections during early pregnancy lead to an increased risk of schizophrenia will be more informative given our hypothesis.

Maternal obstetric complications

Maternal obstetric complications is a broad category which includes several problems associated with pregnancy and delivery. Three meta-analyses revealed that obstetric events are associated with the development of schizophrenia, although the effect sizes are relatively small, with odds ratios around 2 (Cannon, Jones, & Murray, 2002; Geddes & Lawrie, 1995; Verdoux et al., 1997; see also M.C. Clarke, Harley, & Cannon, 2006, for a review). Here we review the evidence for the hypothesis that maternal obstetric complications during early pregnancy lead to an increased risk of schizophrenia.

Nutritional deficiency. Susser and Lin (1992) reported increased rates of schizophrenia after prenatal exposure to famine during the Second World War in The Netherlands. In the famine region, the risk of schizophrenia for women after prenatal first-trimester only exposure was significantly elevated to 2.56%, compared to the expected 1%. Women who suffered the famine during the prenatal first *and* second trimester had a risk that was significantly elevated to 2.29%. However, women who suffered the famine during the prenatal second or third, but *not* the first trimester, had a risk that was not significantly elevated: 1.01% and 1.09%, respectively. No increased risk was found for males who were prenatally exposed to famine.

St Clair et al. (2005) studied the rates of people diagnosed with schizophrenia after prenatal exposure to the Chinese famine from 1959 to 1961. For individuals born before the famine from 1956 to 1959, the risk to develop schizophrenia was around the expected 1%. For individuals born in 1960, the risk was elevated to 2.15%, and for those born in 1961, it was 1.81%. After this year, the risk declined again to normal levels. No distinction was made between first-, second- and third-trimester exposure, so our specific hypothesis about the vulnerability of early organogenesis could not be tested with the Chinese data.

Stress. Van Os and Selten (1998) reported a small but statistically significant increased risk of schizophrenia after exposure to the five-day invasion of the Netherlands in May 1940. The risk was highest when the exposure was during the first trimester of pregnancy. Risk ratio was 1.28 for first trimester exposure,

compared to 1.09 for second trimester exposure, and 1.07 for third trimester exposure. However, in another study, Selten et al. (2003) found no relationship between prenatal exposure to stress and schizophrenia in a study of a birth cohort born nine months after the Six-Day War (1967) and the Yom Kippur War (1973) in Israel, regardless of whether this exposure took place during the first, second, or third trimester of pregnancy. Selten, van der Graaf, van Duursen, Gispen-de Wied, and Kahn (1999) found no elevated risk of schizophrenia in a group that was prenatally exposed, regardless of trimester, to a major flood disaster in The Netherlands in February 1953. Kinney (2001) reported a significantly higher incidence of schizophrenia after prenatal exposure of a tornado that struck Worcester, Massachusetts, on 9 June 53. Data on gestational ages were not given.

Huttunen and Niskanen (1978) reported a relatively high incidence of schizophrenia among people who had lost their fathers prenatally, which presumably caused stress among the mothers. The prenatal loss for these people diagnosed with schizophrenia occurred from the third to the fifth month of fetal development, which is not consistent with our hypothesis. However, the sample was very small (6 people diagnosed with schizophrenia who had lost their fathers prenatally). Myhrmann, Rantakallio, Isohanni, Jones, and Partanen (1996) found evidence for the relation between unwanted pregnancy and the development of schizophrenia. The cumulative incidence of schizophrenia was 0.6% for those born from a wanted pregnancy, 0.5% for those born from a mistimed pregnancy, and 1.5% for those born from an unwanted pregnancy. Data about the wantedness of the pregnancy were collected during the first visit to the perinatal clinic. Herman et al. (2006) did not find an association between unwantedness of pregnancy and the development of schizophrenia spectrum disorders. They collected data about attitude toward pregnancy of 7795 mothers during their first contact with the prenatal clinic. Of the mothers with a favorable attitude towards their pregnancy, 0.64% of the children developed a schizophrenia spectrum disorder, compared to 1.07% of the children of mothers with an ambivalent or negative attitude toward their pregnancy. This difference was not statistically significant.

Khashan et al. (2008) studied a birth cohort of 1.38 million Danish people, and compared the risk of schizophrenia for offspring of mothers who were exposed during pregnancy to the death of a close relative, to the risk of offspring of mothers without a major loss. They found a significantly elevated risk of

schizophrenia in the prenatally exposed group, but only when the exposure occurred during the first trimester of pregnancy. This is consistent with our hypothesis.

Low birth weight. Low birth weight is related to disturbances during early organogenesis (Galis et al., 2006). Rifkin, Lewis, Jones, Toone, and Murray (1994) reported a significantly higher incidence of low birth weight in 100 subjects with schizophrenia, compared to 67 bipolar and depressed people. A birth weight of less than 2500 g occurred in 15% of the people diagnosed with schizophrenia, compared to 2% of the bipolar and depressed people. Willinger, Heiden, Meszaros, Formann, and Aschauer (2001) found a significantly lower birth weight for 36 people diagnosed with schizophrenia or schizoaffective disorder (3,114 g) compared to their same-sex, healthy siblings (3,306 g). Similar results were found by Bersani et al. (2007). Barker (1992, 2007) hypothesized that low birth weight is related to medical problems in later life. Evidence for this hypothesis comes from several studies, e.g., the relation between low birth weight and cardiovascular disease (Barker, 1995; Barker et al., 1993), insulin resistance syndrome (Li, Johnson, & Goran, 2001), autoimmune diseases (Phillips, 2006), and kidney disease (Schreuder & de Waal, 2006). The structures involved in these diseases are established during early organogenesis.

Conclusion. There is some evidence that maternal obstetric complications, including nutritional deficiency, stress during early pregnancy, and low birth weight of the newborn, are related to the development of schizophrenia, which is in agreement with our hypothesis that schizophrenia is the result of disturbances during early organogenesis.

Discussion

We have reviewed the literature to find support for the hypothesis that schizophrenia is the result of disturbances during early organogenesis. We have found support from several lines of research. Schizophrenia co-occurs with neuropathologies, major congenital abnormalities, minor physical anomalies, and other medical problems, which are determined during early organogenesis. Some evidence exists that schizophrenia co-occurs with prenatal infections and maternal obstetric complications during early organogenesis.

Our hypothesis is in agreement with the neurodevelopmental hypothesis of schizophrenia (Weinberger, 1987), which postulates that schizophrenia is the result of a brain defect, caused by a combination of genetic and environmental events. Our hypothesis is also largely in agreement with the lifetime trajectory model of schizophrenia (Waddington et al., 1998, 1999), a model based on the neurodevelopmental hypothesis. This model posits, as we do, that brain development of people diagnosed with schizophrenia is disrupted early during embryogenesis, and that there is a close connection between brain development and craniofacial morphogenesis. A difference between Waddington et al.'s model and our hypothesis lies in the exact timing of the disturbance. Waddington et al. propose that the neurodevelopmental basis of schizophrenia starts from week 9/10 after fertilization. The estimate of this start is based on several findings. Brain and craniofacial development are intimately related and, hence, information on the association of craniofacial dysmorphologies with schizophrenia is informative about the timing of the first disturbance of brain development. The presence of craniofacial dysmorphology in people with schizophrenia has been established (e.g., Hennessy et al., 2004, 2007). Furthermore, Waddington et al. cite evidence that the craniofacial dysmorphogenic events during embryological development act over weeks 9/10 through 14/15 of gestation (Diewert & Lozanoff, 1993a, 1993b; Diewert, Lozanoff, & Choy, 1993). This would be later than predicted from our hypothesis that schizophrenia and accompanied physical anomalies originate during early organogenesis (approximately weeks 3/4/5 after fertilization). However, the determination of morphogenetic events occurs considerably earlier than the observable anatomical effects. For instance, the determination of the presence or absence of a rib on a vertebra occurs very early, even before the appearance/arrival of vertebral precursor cells around the notochord, where they will develop into a vertebra (e.g., Gilbert, 2003). Similarly the number of digits is determined before the actual digits appear (Galis et al., 2001). The induction of a cleft lip and/or palate occurs before the primary palate first appears around 42 days after fertilization (Chai & Maxson, 2006). Furthermore, animal studies have shown that clefting and hypotelorism, i.e., abnormal closeness of the eyes, that appears to be associated with schizophrenia, are induced during early organogenesis. For example, Cordero et al. (2004) showed that disturbing *Sonic hedgehog* (*Shh*) gene activity, which plays a key role in vertebrate organogenesis, only led to clefting and hypotelorism in chickens if it occurred during early organogenesis. This is in agreement with findings on mice (Jeong, Mao, Tenzen, Kottmann, &

McMahon, 2004). Jeong et al. (2004) found that the first genetic effects of disturbing *Shh* during craniofacial (and the associated brain) development occurred during early organogenesis. Similar experiments can naturally not be performed on humans, however, *Shh* signaling in humans during early organogenesis appears to be similar to that in mice and chickens (Odent et al., 1999).

If schizophrenia is induced at a very early stage, would one not expect more serious malformations? Firstly, it is quite probable that a large percentage of individuals with damage that can lead to schizophrenia die early in miscarriages, as this appears to be generally the case with disturbances of early organogenesis (Opitz et al., 1987; Galis et al., 2006). Hence, the actual association of schizophrenia with major abnormalities may be much larger than perceived in adult individuals. Secondly, even though disturbances of early organogenesis are on average more harmful than disturbances of earlier or later stages (Galis & Metz, 2001), this does not imply that such disturbances invariably lead to minor or major abnormalities. For instance, extreme famines and other serious threats that occur during early pregnancies, do not necessarily result in noticeable abnormalities. In addition, minor defects that are known to be induced during early organogenesis are not necessarily accompanied by other, more major defects, such as syndactyly, polydactyly, and cervical ribs.

A remaining question is why the first symptoms of schizophrenia usually appear in the late teens or early twenties, if the cause of schizophrenia lies so early in pregnancy. Here we follow suggestions made by others (for references, see Waddington et al., 1998) that the occurrence of psychoses requires full maturation of certain brain structures (e.g., prefrontal cortex).

Another line of evidence for our hypothesis may be provided by animal studies (e.g., Boksa, 2004). With animals, it is possible to test the relation between disturbances of early organogenesis and brain defects and other physical anomalies experimentally. It is beyond the scope of this chapter to review the literature on animal studies, but one study is worth mentioning. Fatemi, Pearce, Brooks, and Sidwell (2005) exposed pregnant mice during early organogenesis to influenza, resulting in gene changes that caused brain anomalies in the neonate mice that were comparable to brain anomalies in people diagnosed with schizophrenia. This kind of research may elucidate the

mechanism behind disturbances during early organogenesis and the origins of schizophrenia.

CHAPTER 5

THE ASSOCIATION BETWEEN AUTISM AND ERRORS IN EARLY EMBRYOGENESIS: WHAT IS THE CAUSAL MECHANISM?

Abstract

The association between embryonic errors and the development of autism has been recognized in the literature, but the mechanism underlying this association remains unknown. We propose that pleiotropic effects during a very early and specific stage of embryonic development – early organogenesis – can explain this association. In humans early organogenesis is an embryonic stage, spanning day 20 to day 40 after fertilization, which is characterized by intense interactivity among body parts of the embryo. This implies that a single mutation or environmental disturbance can have several phenotypic effects (i.e., pleiotropic effects). Disturbances during early organogenesis can lead to many different anomalies, including limb deformities, craniofacial malformations, brain pathology, and anomalies in other organs. We reviewed the literature and found ample evidence for the hypothesis that autism is associated with errors during early embryogenesis, brain pathologies, major and minor structural anomalies, and various other medical conditions. The proposed mechanism integrates findings from a variety of studies, including neurobiological studies, studies on major and minor anomalies, and studies on prenatal influences on neurodevelopmental outcomes. The implication is that the origin of autism is much earlier in embryological development than has been frequently reported.

Autism is a psychiatric disorder that is characterized by qualitative impairment of social interactions and communication, by restricted patterns of behaviors or interests, and an onset prior to 3 years of age (Volkmar & Pauls, 2003). Its prevalence is considered to be around 7 cases per 10,000 (Williams et al.,

2006), although estimates vary greatly (Newschaffer et al., 2007). Autism spectrum disorders include autism, Asperger's syndrome, childhood disintegrative disorder, Rett syndrome, and PDD-NOS (pervasive developmental disorder – not otherwise specified), and have a prevalence of 20 cases per 10,000 (Williams et al., 2006). It is well-established that autism has a strong polygenic basis (Freitag, 2007; Gupta & State, 2007). Thus, as a polygenic disorder, autism is attributable to the effects of an unknown number of mutations and their possible interaction[6]. However, to understand the genetic etiology of autism, it is useful to take a developmental perspective on how the genetic influences may lead to autism.

Studies have identified a particular stage during embryological development that is very susceptible to both genetic and environmental disturbances (Sander, 1983; Raff, 1994; Galis & Metz, 2001). This stage is called early organogenesis, and occurs in humans from around day 20 to day 40 after fertilization. In this chapter, we present support for the hypothesis that the vulnerability that characterizes this stage, is implicated in the causation of autism. It has been established that autism correlates with conditions due to errors in early embryogenesis (Arndt et al., 2005; Miller et al., 2005), but the underlying mechanism that causes autism remains unknown. We argue that insights from studies in developmental biology reveal a potential underlying mechanism, which allows the meaningful integration of disparate research findings. First, we discuss the results of studies in developmental biology concerning the vulnerability associated with early organogenesis. Second, we review the literature that supports the hypothesis that autism is the result of disturbances during early organogenesis.

The vulnerability of early organogenesis

Early organogenesis is a remarkable embryological stage, because all vertebrates, including humans, look similar during this stage, i.e., the stage displays striking evolutionary conservation. It has been hypothesized that high interactivity among body parts during this stage explains the evolutionary conservation of the stage (Sander, 1983; Raff 1994). Specifically, because of this high interactivity, a change in one part of the body affects other body parts.

[6] This is not to deny the possible role of environmental influences and possible gene-environment interaction.

Such side-effects are called *pleiotropic effects*. For example, changes in number of digits, which start to develop during early organogenesis, are often accompanied by other anomalies (Biesecker, 2002), and the same holds for an extra vertebra (Galis et al., 2006). This implies that a mutation, which affects early organogenesis, is unlikely to be maintained in evolution: any local beneficial effect is likely to be off-set by pervasive pleiotropic effects, which are likely to be negative. It is assumed that because of the strong selection against new variants during the stage of early organogenesis, all vertebrates look very similar during this stage.

The interactivity of the stage of early organogenesis also leads to a high vulnerability for environmental disturbances, which can induce the same effects as genetic mutations (West-Eberhard, 2003). A review of the literature showed that in several species the incidence of anomalies and mortality as a result from teratological treatments (e.g., the administration of methanol) is greatest if the treatment is administered during early organogenesis (Galis & Metz, 2001). Importantly it is the timing of the disturbance, not necessarily its nature that determines the incidence of mortality and anomalies (DeSesso & Harris, 1996; Wilson, 1965).

Many body parts undergo their first development during early organogenesis, as shown in Table 5.1. The very low threshold of pleiotropic effects during early organogenesis makes the early development of these body parts susceptible to disturbances. As the brain starts to develop during early organogenesis, it is likely that a disturbance in brain development, which is either genetic or environmental in origin, will also affect other body parts, and vice versa. For example a mutation that results in the development of an extra digit, may also induce a neurodevelopmental disorder. We propose that the presence of such pleiotropic effects during early organogenesis provides a plausible explanatory mechanism for the development of autism due to errors during early embryogenesis. Support for this hypothesis comes from studies that show the co-occurrence of autism and physical abnormalities that originate in early organogenesis. We review the evidence for five categories of abnormalities: prenatal complications, neuropathology, major structural anomalies, minor physical anomalies, and other medical comorbidities. For our present purposes, it is of minor importance whether the studies considered specific autism or the broader category of autism spectrum disorders, because we propose that early disturbance of development plays a role in all these disorders.

Table 5.1 Body parts that first appear during the stage of early organogenesis from day 20 to 40 after fertilization

Body part		**First appearance of body part in days after fertilization**	**References**
Brain	Brain stem (including the cranial nerves)	29	Larsen, 2001; ten Donkelaar et al., 2006
	Cerebellum	32	Müller & O'Rahilly, 1988a; O'Rahilly & Müller, 2006
	Limbic structures	33	Müller & O'Rahilly, 2006; O'Rahilly & Müller, 2006
	Cerebral hemispheres	33	Müller & O'Rahilly, 1988b; O'Rahilly & Müller, 2006
Limbs		31	O'Rahilly & Gardner, 1975
Heart		23	O'Rahilly, 1971
Kidney		33	O'Rahilly & Muecke, 1972; Larsen, 2001
Lung		31	O'Rahilly & Boyden, 1973
Gastrointestinal tract		23	O'Rahilly, 1978
Skin		23	Larsen, 2001; Holbrook et al., 1975
Eye		29	O'Rahilly, 1983a
Ear		29	O'Rahilly, 1983a
Head		25	Larsen, 2001; ten Donkelaar & Vermeij-Keers, 2006
External genitalia		37	O'Rahilly, 1983b

Comment: The embryonic period is subdivided into 23 stages, termed Carnegie stages, based on morphological criteria. Neurulation starts at stage 8, which is generally listed as 18 days after fertilization, but has recently been corrected to 23 days after fertilization (O'Rahilly & Müller, 2006). All postfertilization days in this Table are adapted to the new classifcation of O'Rahilly & Müller (2006).

Autism and prenatal complications

The association between early prenatal complications and autism has been recognized in the literature (Arndt et al., 2005; Miller et al., 2005). Here we review the main findings and explain why these findings provide support for our hypothesis.

Thalidomide. Thalidomide was prescribed in the treatment of anxiety, insomnia, tension, gastritis, and pregnancy sickness (Miller & Strömland, 1999). In the 1960s, many pregnant women took thalidomide. Sadly, it turned out that thalidomide use during pregnancy produced a variety of congenital malformations in the newborns. These included limb and craniofacial anomalies, and kidney, cardiovascular, genital, and lung malformations. Because most women knew the date they took the drug, time tables could be reconstructed that showed that thalidomide was teratogenic between 20 and 36 days after fertilization (Lenz & Knapp, 1962), i.e., during early organogenesis. Four percent Swedish individuals, whose mothers took thalidomide in this period, developed autism (Miller et al., 2005; Strömland et al., 1994). This is significantly greater than the 0,1 percent in the general population. The studies of thalidomide defects confirm that early organogenesis is a vulnerable stage of embryological development, leading to many different anomalies. The large variety in effects (i.e., the apparent pleiotropy) is caused by the high interactivity among different body parts that characterize the stage. One of the hypothesized negative effects of this interactivity is a disturbance of normal brain development, eventually leading to the development of autism.

Rubella. A rubella infection suffered during early pregnancy leads to serious malformations in the newborn. The 1964 rubella epidemic in the United States, resulted in 20,000 to 30,000 neonates born with congenital malformations (Desmond et al., 1967). These included heart defects, deafness, eye defects (e.g., cataracts, retinopathy), and neurological impairment. Another study showed that 90 percent of infants infected with the rubella virus during the first ten weeks of pregnancy developed a defect, mostly heart defects and deafness. In constrast, the percentage is much lower in children infected after week 10 of pregnancy: 33% (week 11 to 12), 11% (week 13 to 14), 24% (week 15 to 16), and, finally, zero % (any time after week 16) (Miller et al., 1982). Thus, prenatal exposure to the rubella virus during early organogenesis results in more different defects than later in pregnancy (Ueda et al., 1979). In a study on

243 children with prenatal exposure to rubella, it was found that 10 of them (4.1%) met the criteria of autism (Chess, 1971). In a follow-up with the same sample, four more individuals met the criteria of autism (Chess, 1977). Thus, about 6% percent of the rubella infected children developed autism. These two studies did not provide data on the exact timing of the rubella exposure, but the association with physical anomalies suggest that negative pleiotropic effects during early organogenesis played a role in the development of autism.

Anticonvulsants. Anticonvulsants are prescribed, inter alia, to prevent seizures in epileptics. Women with epilepsy who take anticonvulsants during first trimester of pregnancy have an increased risk of delivering a child with major congenital malformations compared to women with epilepsy who do not take anticonvulsants (3.4 percent versus 1 percent) (Jick & Terris, 1997). Another study showed that among 57 children with fetal anticonvulsant syndromes (characterized by facial dysmorphic features and cardiac malformations), four were diagnosed with autism and another two with Asperger syndrome. Eighty-one percent showed autistic type behaviors, such as poor social interaction and communication skills (Moore et al., 2000). The co-occurrence of autism and congenital malformations is consistent with the hypothesis that pleiotropic effects during early organogenesis resulted in the development of autism.

Misoprostol. Misoprostol is prescribed in the treatment of gastric ulcers, but it is in some countries also used to induce abortions (Norman et al., 1991). Children born after use of misoprostol in the first trimester of pregnancy have several congenital malformations. In a review of 69 case reports of congenital defects associated with misoprostol use during pregnancy, it was found that 83% of the children had lower limb defects, 55% had central nervous system defects involved in the cranial nerves, and 46% had upper limb anomalies (Population Council, 2003). The majority of pregnant women took misoprostol between the third and sixth week after fertilization. Another remarkable consequence of misoprostol use during early pregnancy is the presence of Möbius sequence in children (Bandim et al., 2003). Möbius sequence is a congenital syndrome characterized by facial paralyses, i.e., the disability to smile or frown, being the result of the absence of or underdeveloped sixth and seventh cranial nerves. Other characteristics are malformations of orofacial structures, limb anomalies, and defects of the chestwall (Sudarshan et al., 1985). A study found that 50 percent of 23 children with Möbius sequence had been prenatally exposed to misoprostol. Five of the 23 children met the criteria for autism, and two other children showed autistic-like behavior. Of those

seven children, four had been prenatally exposed to misoprostol (Bandim et al., 2003), suggesting that disturbances during early organogenesis influenced the development of autism.

Prematurity and low birth weight. A study showed that 26 percent of 91 ex-preterm infants with a birth weight lower than 1500 g showed autistic traits at the age of 21 months (Limperopoulos et al., 2008). A review of the literature revealed a substantial association between low birth weight and autism (Kolevzon et al., 2007), and a large population-based study revealed a significant association between prematurity and autism (Larsson et al., 2005). There is substantial evidence for the hypothesis that prematurity and low birth weight are often caused by disturbances during early organogenesis (e.g., Barker, 2007). For example, there is a positive correlation between low birth weight and later cardiovascular (Barker, 1995) and kidney (Schreuder & de Waal, 2006) disease. The structures involved in these diseases are established during early organogenesis (see Table 5.1).

Neuropathologies associated with autism

A recent review on the neuropathology of autism (Schmitz & Rezaie, 2008) summarized the evidence that people diagnosed with autism often have subtle abnormalities in the development of several brain structures, including the cerebellum, limbic structures, brainstem, and cerebral cortex. The prenatal brain starts to develop with neurulation, which marks the start of early organogenesis. Neurulation starts when the neural plate is formed. Around day 23 after fertilization, the neural plate starts to fold, resulting in the neural groove (O'Rahilly & Müller, 2006). Around day 26 after fertilization, the three major divisions (prosencephalon, mesencephalon, and rhombencephalon) of the brain are visible on the folds of the open neural groove. The neural crest, a temporary embryological structure that gives rise to a variety of body structures, starts to develop on the same day.

Around day 29 after fertilization, the neural folds start to fuse, resulting in the neural tube. The brain stem first appears, with distinguishable cranial nerve motor nuclei (Larsen, 2001). Failure of neural tube closure results in an incomplete spinal cord, which leads to defects such as spina bifida and anencephaly (Botto et al., 1999). Around day 32 after fertilization, the cerebellum first appears, and one day later the future cerebral hemispheres and the future amygdaloid region become visible (O'Rahilly & Müller, 2006;

Müller & O'Rahilly, 2006). Thus, the brain structures that are commonly disturbed in people diagnosed with autism, have their origin in early organogenesis. The co-occurrence of deviant brain structures and other physical anomalies suggests that pleiotropic effects play a major role in the development of autism. In addition, studies have shown that pregnant mice infected during early organogenesis have offspring with similar brain deviations as people with autism (Fatemi et al., 2005).

Major structural anomalies

Congenital anomalies were found in 11 percent of 45 children diagnosed with an autism spectrum disorder, compared to 6 percent of 128 children without this diagnosis (Wier et al., 2006). This difference remained statistically significant after correcting for gestational age, plurality, birth order, maternal age, maternal ethnicity, and maternal education. The congenital anomalies included anomalies of the central nervous system, the eye, ear, face, and neck, the heart, the respiratory system, the gastrointestinal system, the genito-urinary system, the musculoskeletal system, and the integumentary system. Especially anomalies of the gastrointestinal system were more frequent in children diagnosed with an autism spectrum disorder.

A recent review (Zafeiriou et al., 2007) showed that autism or autistic features are often observed in children with genetic syndromes, such as tuberous sclerosis complex (Wiznitzer, 2004), fragile X syndrome (Clifford et al., 2007), Down syndrome (Lowenthal et al., 2007), and neurofibromatosis type 1 (Williams & Hersh, 1998). Tuberous sclerosis complex is a disorder characterized by anomalies of the integumentary system, brain, retina, heart, kidney, and/or lungs (Crino et al., 2006). Autism spectrum disorders are present in 25 to 50 percent of people with this syndrome, and the prevalence of the syndrome in people diagnosed with autism spectrum disorder is 1 to 4 percent (Wiznitzer, 2004).

Fragile X is a syndrome that is characterized by mental retardation, and several physical features, including macrocephaly, prominent forehead, loose joints, soft skin, prominent ears, high arched palate, and, in males, large testicles (Visootsak et al., 2005). In a group with 33 males and 31 females with full mutation fragile X, 67 percent of the males and 23 percent of the females met the criteria for autism spectrum disorder (Clifford et al., 2007). In a group of

316 people with autism spectrum disorder, 2.2% had fragile X mutations (Reddy, 2005).

The phenotypic features of Down syndrome are mental retardation, brachycephaly, hand and foot anomalies, duodenal atresia, epicanthal folds, flat nasal bridge, and hypotonia (Roizen & Patterson, 2003). In addition, about fifty percent of the children born with Down syndrome have congenital heart disease, hearing loss, and ophthalmological disorders. Autism spectrum disorders are present in 16 percent of children with Down syndrome (Lowenthal et al., 2007).

Neurofibromatosis type 1 is characterized by six or more café-au-lait spots on the skin, and two or more neurofibromas, a type of nerve sheath tumor, usually in the gastrointestinal tract (Reynolds et al., 2003). Four percent of individuals with neurofibromatosis type 1 was diagnosed with autism (Williams & Hersh, 1998). As can be seen in Table 5.1, all body structures involved in these syndromes are established during early organogenesis. The co-occurrence of several anomalies implies that pleiotropic effects, including the development of autism, played a role in the development of the syndromes.

Minor physical anomalies

Minor physical anomalies are morphological abnormalities that can be detected quite easily, but have no serious medical or cosmetic consequences for the individual. Although minor physical anomalies are not life-threatening themselves, it is well-established that they are associated with major anomalies (Marden et al., 1964; Leppig et al., 1987; Mehes, 1985). The relation between autism and minor physical anomalies has been observed frequently (Miles & Hillman, 2000; Walker, 1977; Rodier et al., 1997; Hardan et al., 2006). Most studies used the Waldrop Physical Anomaly Scale, which assesses 18 anomalies in six body regions: head, eyes, ears, mouth, hands, and feet (Waldrop & Halverson, 1971).

Of the three studies concerning the incidence of individual anomalies, the first reported an average of 5.76 physical anomalies in children diagnosed with autism, compared to 3.53 anomalies in matched controls (Walker, 1977). The anomaly with the highest frequency in autism was low-seated ears (14.3% of the children with autism, compared to 4.5% of the healthy controls). In addition, children with autism more often had hypertelorism (i.e., a large

interpupillary distance) and syndactylia of toes (i.e., partially fused toes) compared to healthy controls. The second study showed that children diagnosed with autism had a significant posterior rotation of the ears, compared to healthy controls (Rodier et al., 1997). In the same study it was found that children with autism had hypotelorism (i.e., a short interpupillary distance), smaller feet, and an increased total hand length compared to healthy controls. In a recent study in which MRI was used to scan minor physical anomalies, no significant differences were found between non-mentally retarded people diagnosed with autism and healthy controls (Hardan et al., 2006). When only lower functioning individuals (IQ < 103) were analyzed, significant differences in hypotelorism were found; people diagnosed with autism had smaller interorbit distances and a lower interorbit/orbit skull ratio.

Another physical feature that is frequently observed in children with autism is macrocephaly (i.e., a head circumference that is two or more standard deviations above the mean), with an average reported rate of 20 percent (Lainhart et al., 2006). All minor physical anomalies observed in people diagnosed with autism are established during early organogenesis (see Table 5.1).

Medical comorbidities

In a case-control study, 12 percent of people diagnosed with autism were given one or more diagnoses of medical disorders, including congenital malformations of the cardiovascular system, the urinary system, the skeletal system, and the eyes (Lauritsen et al., 2002). Another study found that children diagnosed with autism had significantly more ear infections, more use of antibiotics, and more gastrointestinal problems before the age of 2 years, compared to healthy controls (Niehus & Lord, 2006). Specific medical problems that are found significantly more often in people diagnosed with autism compared to controls are epilepsy (Canitano, 2007), visual impairment, including blindness (Mukaddes et al., 2007), abnormal metabolism (Manzi et al., 2008), vascular changes (Yao et al., 2006), and gastrointestinal problems (Galli-Carminati et al., 2006), which are possibly related to general failure of the immune system (Cohly & Panja, 2005). All these comorbidities involve body structures that are established during early organogenesis.

In addition, the comorbidity of autism with other psychiatric disorders is high: more than 70 percent of the children with autism also meet the criteria of one

or more other psychiatric disorders (Leyfer et al., 2006). Forty-four percent meet the diagnostic criteria of specific phobia, 37 percent those of obsessive compulsive disorders, 31 percent those of ADHD and 10 percent those of major depression. This shows that the psychological/behavioral phenotype of people diagnosed with autism, like their physical phenotype, displays considerable variation. This suggests that pleiotropic effects during early organogenesis result in a diverse array of physical anomalies, including subtle brain anomalies that lead to a diverse pattern of psychological/behavioral problems.

Discussion

Our present review of the literature has shown that autism is associated with

1. errors during early embryogenesis;
2. neuropathologies;
3. major structural anomalies;
4. minor physical anomalies; and
5. several other medical conditions.

So far most studies on the association between autism and physical anomalies were focused on only one of these topics, although a few researchers have recognized the combination of autism, errors during embryogenesis, neuropathologies, and physical malformations (Miller et al., 2005; Rodier, 2002). However, so far no hypothesis has been advanced to explain and integrate all these different research findings. We argued that developmental biology provides this hypothesis. We hypothesized that autism, and the associated physical anomalies, are the result of disturbances during early organogenesis, the embryonic stage from day 20 to day 40 after fertilization. During this stage, high interactivity among body parts renders the organism highly susceptible to pervasive effects of developmental disturbances. Consequently, a single mutation or environmental disturbance can have many different, often deleterious, pleiotropic effects. We proposed that the abundance of pleiotropic effects during early organogenesis is the mechanism that explains why disturbances during embryogenesis can have severe effects such as the development of autism.

A remaining question is whether the cause of autism is limited to disturbances during early organogenesis, or whether disturbances later in development can also cause autism. Studies on the age of onset of autism may provide insight into this issue. On average, parents begin to recognize the first signs of autism

at around 19 months, with 30 percent noticing first abnormalities (e.g., lack of eye contact and smiling) prior to the first birthday (De Giacomo & Fombonne, 1998). However, there is a group of children diagnosed with autism, which first appeared to develop normally, but show regression (e.g., speech loss) between 12 and 42 months. Prevalence rates of regression among children with autism vary from 20% to 49%, and the developmental outcomes of regressed autistic children appear to be worse than those of non-regressed autistic children (Bernabei et al., 2007).

It has been hypothesized that there is an association between regression and vaccinations, but studies could not confirm this association (Fombonne & Chakrabarti, 2001; Taylor et al., 2002). In the literature cases are described of late-onset autism after a herpes infection (Ghaziuddin et al., 2002), so it is possible to develop autism after an environmental insult later in life, but these few cases cannot fully explain the origin of late-onset autism. A recent study revealed that regressed autistic children have a higher incidence of circadian rhythm disorders, and a higher incidence of epilepsy and epileptiform EEG abnormalities, compared to nonregressed autistic children (Giannotti et al., in press). However, epilepsy is not considered a causal factor in autism, but rather as part of brain dysfunction that is implicated in both the development of autism and epilepsy (Gurrieri et al., 1999). The origin of the brain dysfunction still has to be explained.

Late-onset autism does not necessarily imply a later cause of autism (i.e., originating in a stage of development later than early organogenesis). An early developmental disturbance may result in a cascade of effects, which may only be detected relatively later in life (Rice & Barbon, 2000; Meyer et al., 2007). It is possible that there are other vulnerable prenatal periods after the stage of early organogenesis (Kinney et al., 2008), but it cannot be excluded that the later vulnerability was associated with disturbances during early organogenesis.

This may imply that our hypothesis is hardly falsifiable. However, there are two ways to deal with the falsifiability problem. The first way is to perform animal studies in which our hypothesis can be tested experimentally. There are already several animal studies indicating that the stage of early organogenesis is extremely vulnerable for disturbances (Galis & Metz, 2001), and that first trimester rather than second trimester disturbances result in negative neurodevelopmental outcomes (Meyer et al., 2007). In the future, animal studies can be performed in which pregnant animals are subjected to

disturbances at various periods during pregnancy (including early organogenesis). Neurodevelopmental and other physical outcomes then can be related to the specific timing of the disturbance. Studies by Fatemi and colleagues already showed that brain anomalies of newborn mice after prenatal exposure to the influenza virus during early organogenesis, are similar to those in people with autism (Fatemi et al., 2005). A second way to test our hypothesis is to examine a large sample of people diagnosed with autism with respect to a variety of physical deviations. It follows from our hypothesis that disturbances during early organogenesis result in several anomalies, so all possible anomalies associated with body parts that start to develop during this embryonic stage (see Table 5.1) should be examined. It is our expectation that a majority of people diagnosed with autism will show a diverse pattern of anomalies, due to pleiotropic effects that only occur during early organogenesis.

CHAPTER 6

SUMMARY AND DISCUSSION

The main aim of this dissertation was to show that evolutionary psychology can serve as a metatheory for psychology, but only if its scope is broadened to include theories and findings from evolutionary developmental biology. Evolutionary psychology is defined as 'simply psychology that is informed by the additional knowledge that evolutionary biology has to offer, in the expectation that understanding the process that designed the human mind will advance the discovery of its architecture' (Cosmides, Tooby, & Barkow, 1992, p. 3). It is claimed to be a metatheory for psychology, i.e., a theory that unites the different branches and minitheories in psychology (Buss, 1995). The main tenet of evolutionary psychology is that the human mind consists of a multitude of evolved domain-specific psychological mechanisms, also called modules. These modules arose through natural selection because they could solve recurrent survival- and reproduction-related problems in ancestral times (Tooby & Cosmides, 1992; Buss, 1995). This tenet has been called the *massive modularity thesis* (Sperber, 1994), and is part of the *Integrated Causal Model* (Tooby & Cosmides, 1992). Evolutionary psychology is based on neo-Darwinian evolutionary theory, which states that evolution can be explained by small genetic changes that lead to variation upon which natural selection can act.

Evolutionary developmental (evo-devo) biology is an approach that forges a synthesis between processes active during individual development and processes active on an evolutionary time scale. It tries to explain both *that* evolution occurs, and *how* it occurs. In order to know how evolution occurs, one has to study the origin of traits, which implies studying the development of traits (Hall & Olson, 2003; S.B. Carroll, 2005).

In chapter 2 I proclaimed that evolutionary psychology is a useful framework to derive new hypotheses and novel interpretations of data, but that this is not enough to ascribe to evolutionary psychology the status of a metatheory. Such a metatheory should contribute to the major issues in the field of psychology. These include the modularity of the mind, the nature-nurture debate, the question whether development occurs gradually or in stages, and the question how individual differences arise. In chapter 2, each of these issues was considered from the perspectives of evolutionary psychology and evo-devo

biology. It was concluded that the view of evolutionary psychology is quite limited in addressing the major issues, whereas models and empirical findings of evo-devo biology provide new insights in these issues.

This chapter was published in *Psychological Inquiry* (Ploeger, van der Maas, & Raijmakers, 2008a), a journal that invites commentaries to target articles. Consequently, this chapter elicited several interesting reactions. A first issue that had to be considered was the definition of evolutionary psychology. Duntley and Buss (2008) argued that evolutionary psychology is a very broad field, and that it should not be equated with the *Integrated Causal Model* as advocated by Tooby and Cosmides (1992). We argue that evolutionary psychology in general is more a collection of point of views, rather than a coherent theory (see Ploeger, van der Maas, & Raijmakers, 2008b, for an extensive reply to the commentaries that appeared in *Psychological Inquiry*). The *Integrated Causal Model* is a coherent theory, and its tenets can be judged on their metatheoretical status. Evolutionary psychology in general can not be judged in that way, because the field is too diverse.

The main issue was, of course, whether evolutionary psychology can serve as a metatheory for psychology. Unsurprisingly, Duntley and Buss (2008) did not agree with our conclusion that evolutionary psychology is limited as a metatheory (Buss (1995) was among the first to introduce evolutionary psychology as a metatheory). Duntley and Buss argued that evolutionary psychology unites the field of psychology with all the other life sciences, including biology, economics, political science, history, legal scholarship, and medicine. We agree with this, but this does not weaken our conclusion that evolutionary psychology is limited as a metatheory *for psychology*, as it does not contribute substantially to the major issues in psychology. Barrett (2008) argued that evolutionary psychology is a way of thinking, a set of heuristics for generating hypotheses to be tested empirically. We also agree with this, but we note that a heuristic is not the same as a metatheory; a metatheory can contribute to the major issues in a field, while a heuristic does not necessarily do so.

Another issue raised was whether evo-devo biology constitutes a paradigm shift (Barrett, 2008; Duntley & Buss, 2008). Is evo-devo biology really something new, compared to neo-Darwinian theory? As we argued in chapter 2, the evo-devo and the neo-Darwinian approach are complementary rather than antagonistic, so the term 'paradigm shift' is not a good description of the

novelty of the evo-devo approach. The main difference between the two approaches is that the neo-Darwinian approach emphasizes the process of natural selection, and the evo-devo approach the mechanism of generating new variation. So the difference lies in emphases, not in different views or inconsistent empirical findings. Evo-devo biologists consider themselves as neo-Darwinians, and neo-Darwinians easily accept the research findings of evo-devo biologists.

Another issue was the tenability of the massive modularity thesis. This thesis has evoked a large debate in the literature (for a review, see Barrett & Kurzban, 2006). Buunk and Park (2008) argued that not massive, but messy modularity is a better account of the human mind: 'natural selection does not strive to "design" efficient solutions - it merely sifts out the most adequate (or the least bad) alternative, all the while tinkering with existing features' (p. 23), and 'the human mind is better conceptualized as a mixed bag of mutually linked mechanisms and traits that reflect compromise and imperfection' (p. 25-26). Although we agree we this, evo-devo research has shown that we can predict the likelihood of more domain-specific or domain-general mechanisms, based on certain conditions in our environment (Griswold, 2006; Kauffman, 1993). Barrett (2008) argued that the massive modularity thesis does not exclude the possibility of the existence of domain-general mechanisms. However, evolutionary psychology as advocated by Tooby and Cosmides (1992) does not offer a theory that explains the existence of domain-general mechanisms. Evo-devo biology does offer this theory (Hansen, 2003; Hansen et al., 2003: Griswold, 2006; Kauffman, 1993).

A final issue was whether evo-devo biology generates new, empirically testable, hypotheses. In chapter 3, 4, and 5 I have shown that this is the case. In chapter 3 we proposed the hypothesis that the savant syndrome did not spread in the population because of a developmental constraint. A developmental constraint is a mechanism that limits the possibility of a phenotype to evolve. Biologists have shown that there exist developmental constraints as the result of the high interactivity among body parts in an early stage in embryological development, namely early organogenesis or the phylotypic stage. The interactivity during this stage involves all components of the embryo, and as a result mutations that affect one part of the embryo also affect other parts. We hypothesized that a mutation, which gives rise to the development of the positive aspects of the savant syndrome (e.g., an impressive memory capacity), will virtually always have a deleterious effect on the development of other phenotypic traits, (e.g.,

resulting in autism and/or impaired motor coordination). Thus, our hypothesis stated that the savant syndrome did not spread in the population, because of this developmental constraint. The finding that children with savant syndrome often have autism and physical anomalies, which are known to be established during early organogenesis, supports our hypothesis.

In chapter 4 we proposed the hypothesis that schizophrenia is the result of disturbances during early organogenesis. Evidence has shown that there is a significant association between the development of schizophrenia and brain defects, major and minor congenital anomalies, other medical comorbidities, prenatal infections, and maternal obstetric complications. These abnormalities are usually established during early organogenesis, suggesting that schizophrenia has its origins very early in embryological development.

In chapter 5 we showed that the same hypothesis can be applied to the development of autism. We reviewed the literature and found ample evidence for the hypothesis that autism is associated with errors during early embryogenesis, brain pathologies, major and minor structural anomalies, and various other medical conditions. In these chapters we have shown that insights from evolutionary developmental biology lead to new hypotheses for psychology.

I have written this dissertation with great pleasure. The broad field of evolutionary developmental biology has opened my eyes; evolutionary research has so much more to offer than the easily comprehensible theory of evolution by natural selection. In the future I hope to expand the evolutionary developmental biology framework for psychology. It is my greatest ambition to make theories and research findings of evolutionary developmental biology accessible to psychologists.

CHAPTER 7

DUTCH SUMMARY

Het was in 1996 toen ik voor het eerst kennis maakte met de evolutionaire psychologie. Ik studeerde toen een half jaar aan de Florida Atlantic University in de Verenigde Staten, met name om te werken aan mijn afstudeerproject voor mijn studie psychologie. Ik ontmoette daar professor David Bjorklund die een cursus gaf over evolutionaire psychologie. Deze cursus heeft mij meer beïnvloed in mijn wetenschappelijk denken dan welke andere cursus ook. Dit was verrassend, want als gymnasium-alpha leerling, zonder biologie in mijn vakkenpakket, was mijn kennis over de evolutietheorie zeer beperkt. Voor de cursus lazen we het boek *The Adapted Mind: Evolutionary Psychology and the Generation of Culture*, geredigeerd door Barkow, Cosmides en Tooby (1992). Van begin tot eind vond ik het boek zeer fascinerend, en ik was overweldigd door de nieuwe inzichten en nieuwe experimenten geïnspireerd door de evolutietheorie. Zoals veel psychologiestudenten was ik verbaasd over de versnippering van het onderzoek in de psychologie: er worden veel interessante experimenten uitgevoerd, maar de meeste onderzoekers werken op hun eigen eilandje zonder een overkoepelende theorie over de werking van de menselijke psyche. Evolutionair psychologen proberen te werken vanuit een overkoepelende theorie, een metatheorie, die de versnippering van het onderzoek in de psychologie kan tegengaan.

De evolutionaire psychologie laat zich informeren door de kennis van de evolutiebiologie met de verwachting dat kennis over de evolutie van de mens kan bijdragen aan het begrijpen van de werking van de menselijke psyche. Net zoals het menselijk lichaam is geëvolueerd door middel van natuurlijke selectie, zo is ook de menselijke psyche geëvolueerd. Dit betekent dat de menselijke psyche bestaat uit een aantal mechanismen dat bijdraagt aan de overleving dan wel de voortplanting van het individu. Voorbeelden van dergelijke mechanismen zijn emoties, ruimtelijk inzicht, sociale uitwisseling, partnervoorkeuren en taal. De evolutionaire psychologie heeft geleid tot nieuwe hypothesen voor de sociale psychologie, ontwikkelingspsychologie, klinische psychologie, en organisatiepsychologie, als ook voor de sociologie, antropologie, rechtsgeleerdheid, economie, politicologie en geneeskunde. Op basis hiervan beweren verschillende evolutionair psychologen dat hun theorie

een metatheorie is die verschillende onderzoeksgebieden met elkaar kan verbinden.

In hoofdstuk 2 beargumenteer ik dat de evolutionaire psychologie een nuttig denkkader is voor het afleiden van nieuwe hypothesen en het opnieuw interpreteren van bestaande data, maar dat dit niet genoeg is om te dienen als metatheorie voor de psychologie. Een metatheorie zou moeten bijdragen aan de grote vraagstukken in de psychologie, bijvoorbeeld de vraag in hoeverre de menselijke psyche modulair is, het nature-nurture debat, de vraag of ontwikkeling in sprongen of geleidelijk verloopt, en de vraag hoe individuele verschillen ontstaan. In hoofdstuk 2 laat ik zien dat de bijdrage van de evolutionaire psychologie aan deze vraagstukken beperkt is. Dit betekent echter niet dat de evolutionaire psychologie als metatheorie naar de prullenmand mag worden verwezen. Ik stel een uitbreiding van het denkkader voor waardoor het mogelijk wordt wel een nuttige bijdrage te leveren aan de belangrijke issues in de psychologie.

Het denkkader van de evolutionaire psychologie is gebaseerd op de neo-Darwiniaanse evolutietheorie, hetgeen inhoudt dat evolutie wordt verklaard door kleine genetische veranderingen die leiden tot variatie waarop selectie plaatsvindt. De uitbreiding die ik voorstel komt van de evolutionaire ontwikkelingsbiologie, een benadering die een synthese probeert te bereiken tussen processen die tijdens individuele ontwikkeling plaatsvinden en processen die op evolutionaire schaal plaatsvinden. Deze benadering poogt niet alleen te laten zien dat evolutie plaatsvindt, maar probeert ook te begrijpen hoe dit gebeurt. Daarbij staan vragen centraal die ook in de psychologie centraal staan: Hoe ontstaat nieuwe variatie? Welke rol speelt modulariteit in ontwikkeling en evolutie? Op welke manier interacteren genetische en omgevingsprocessen met elkaar? In hoeverre gaan evolutie en plasticiteit samen? Is evolutie een gradueel of een sprongsgewijs proces? De theorieën, modellen en empirische bevindingen naar aanleiding van onderzoek naar deze vragen zijn van nut voor dezelfde vragen in de psychologie.

In hoofdstuk 3, 4 en 5 geef ik een beschrijving van toetsbare hypothesen, afgeleid van onderzoek in de evolutionaire ontwikkelingsbiologie, die relevant zijn voor de psychologie. In hoofdstuk 3 beschrijf ik de hypothese dat het savant-syndroom zich niet verspreid in de populatie door restricties tijdens de ontwikkeling die de mogelijkheden van een kenmerk om te evolueren inperken. Het savantsyndroom is een combinatie van een serieuze beperking,

zoals mentale retardatie of autisme, die samengaat met een spectaculaire vaardigheid die in sterk contrast staat met de beperking. Mensen die dit syndroom hebben worden ook wel 'idiot savants' genoemd. De spectaculaire vaardigheid is bijzonder ontwikkeld op een gespecialiseerd gebied, zoals muziek, kunst, kalender rekenen, wiskunde, of mechanische of ruimtelijke vaardigheden, gekoppeld aan een fenomenaal geheugen op het gebied van de vaardigheid zelf. De vaardigheden zelf kunnen voordelig zijn met betrekking tot overleving of reproductie, en zouden dus door natuurlijke selectie kunnen worden geselecteerd. Echter omdat deze vaardigheden samengaan met een beperking worden ze niet geselecteerd. Er is dus een restrictie die het onmogelijk maakt dat deze vaardigheden evolueren.

Waarom gaan de positieve aspecten van het savantsyndroom samen met de negatieve aspecten, en kunnen die negatieve aspecten een restrictie vormen voor het evolueren van de positieve aspecten? Ik verdedig de hypothese dat deze restrictie het resultaat is van de hoge interactiviteit tussen lichaamsdelen tijdens een vroege periode in embryologische ontwikkeling, genaamd vroege organogenese of het fylotypisch stadium. Deze periode ligt bij mensen tussen de twintigste en de veertigste dag na de bevruchting. De interactiviteit tijdens deze periode omvat alle lichaamsdelen van het embryo, inclusief het brein, waardoor een mutatie die tot expressie komt tijdens deze periode, de ontwikkeling van verschillende lichaamsdelen beïnvloedt en niet alleen de ontwikkeling van een specifiek lichaamsdeel. Wat betreft het savantsyndroom impliceert dit dat een mutatie die de positieve aspecten van het syndroom (bijvoorbeeld een indrukwekkend geheugen) veroorzaakt, bijna altijd een negatief effect heeft op de ontwikkeling van andere onderdelen (met als resultaat bijvoorbeeld autisme of mentale retardatie). Extra ondersteuning voor deze hypothese is de bevinding dat mensen met het savantsyndroom vaak ook allerlei fysieke afwijkingen hebben, die zijn ontstaan tijdens de vroege organogenese.

In hoofdstuk 4 verdedig ik de hypothese dat schizofrenie het gevolg is van genetische of omgevingsverstoringen tijdens de vroege organogenese. Schizofrenie is een psychiatrische stoornis gekarakteriseerd door wanen, hallucinaties, ongeorganiseerde spraak en/of motoriek, weinig emotie en/of motivatie. Deze stoornis komt voor bij één procent van de bevolking en ontstaat meestal in de late adolescentie of vroege volwassenheid. Het is bekend dat er verschillende genen ten grondslag liggen aan deze stoornis, wat inhoudt dat om schizofrenie te begrijpen de interactie tussen de effecten van deze

verschillende genen tijdens de ontwikkeling moet worden bestudeerd. Evidentie voor de hypothese dat schizofrenie het resultaat is van verstoringen tijdens de vroege organogenese komt van studies die een associatie laten zien tussen schizofrenie en hersenafwijkingen, andere grote en kleine fysieke afwijkingen en andere medische aandoeningen in lichaamsdelen die beginnen te ontwikkelen tijdens de vroege organogenese. Daarnaast hangt schizofrenie samen met prenatale infecties en zwangerschapscomplicaties tijdens de vroege embryonale ontwikkeling. In hoofdstuk 5 laat ik zien dat dezelfde associaties worden gevonden bij autisme. Dus ook autisme is het gevolg van verstoringen tijdens de vroege organogenese.

Ik heb dit proefschrift met veel plezier geschreven. Het brede onderzoeksgebied van de evolutionaire ontwikkelingsbiologie heeft mijn ogen geopend; evolutionair onderzoek heeft zo veel meer te bieden dan de gemakkelijk te begrijpen theorie over evolutie door middel van natuurlijke selectie. In de toekomst hoop ik het denkkader dat de evolutionaire ontwikkelingsbiologie de psychologie kan bieden, uit te breiden. Mijn ambitie is de theorieën en onderzoeksbevindingen uit de evolutionaire ontwikkelingsbiologie toegankelijk te maken voor psychologen.

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