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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 20⁵ 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.

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 schizotypal 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, Alphas, & 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,XXXXY and 49,XXXXXY; 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

^aAnomalies:

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 transverse 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 syndactyilia 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 comorbid 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, Mellekjaer, 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-1 β , 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, Gispén-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 dysmorphism 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.