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From postnatal to prenatal determinants of development: a shift of a paradigm

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1.1 Abstract

Traditionally, the study of child development has taken birth as its starting point. However, current insight suggests that prenatal influences explain a significant part of variation in later behavior and development. Small variations in the fetal physiological environment induced by internal or external factors can be of critical and long lasting importance, given an increased sensitivity of the rapidly developing brain. This calls for the need of a shift in a paradigm in infant studies from postnatal to prenatal determinants of development.

1.2 Introduction

In 13-16 % of all young children psychosocial adaptation is hampered by mild or severe neurodevelopmental disorders, that range from hyperactivity, learning disabilities, language delays and motor abnormalities to autistic spectrum disorders and cerebral palsy (Kirby & Brewster, 1995; Robert et al., 1998; Thompson et al., 1996). Possible harmful effects on the brain during delivery explain only a proportion of these disorders in children's behavior and development (Goodman & Stevenson, 1989; Gillberg et al., 1983; Uljas et al., 1999; O'Callaghan et al., 1997; Taylor et al., 2000). Moreover, improved obstetric care during the last decades has not been able to reduce the rate of these neurodevelopmental disorders (Casaer, 1993; Hjalmorson et al., 1988; Visser & Narayan, 1996). Animal studies have shown that the prenatal period should not be neglected when one is interested in early determinants of development (Weinstock, 1997). As a result, there is now an increasing recognition of the role played by prenatal factors in the development of subsequent neuropsychiatric impairment, particularly in term born infants.

Interest in prenatal risk factors can be found in various fields of research. First, prenatal influences may affect the general development of the fetus. Food deprivation (Creasy, 1991), alcohol-intake (Faden et al., 1997), smoking (Cnattingius et al., 1999; Eyler et al., 1998) and drugs during pregnancy (Tuthill et al., 1999) may result in adverse birth outcome, such as preterm birth and low birth weight. Internal factors, like elevated prenatal stress, are likewise associated with premature delivery, and low birth weight. (Dunkel-Schetter, 1998; Copper et al., 1996; Wadhwa et al., 1993).

Second, effects of prenatal influences on physical development have been found, which may result in specific illnesses. For instance, food deprivation during pregnancy has been found to have an effect on health status at adult age (Barker, 1995; Ravelli et al, 1998). The Barker hypothesis states that children with low birth weight, possibly as a result of prenatal food deprivation of the pregnant woman and secondary of the fetus, have an increased risk for diabetes, obesity, high blood pressure and cardiovascular disease at adult age. After alcohol-intake in pregnancy disturbances of physical development occur, resulting in heart defects, distortions of the joints and minor physical abnormalities (Day & Richardson, 1991; Sokol & Clarren, 1989). Prenatal smoking is associated with increased susceptibility to emphysema (Maritz et al., 1993) and abnormal early pulmonary maturity (Lieberman et al., 1992). The use of pharmacological agents during pregnancy may result for instance in deformed limbs (thalidomide) or in an increased risk for abnormalities in the structure of the reproductive organs and for the development of cancers in the vagina or cervix (diethylstilbestrol, DES; in: Seifert & Hoffnung, 1987).

Third, variations in the fetal physiological environment, caused by the aforementioned external factors, appear to have effects on brain development, which may lead to neonatal brain disease or psychopathology later in life. In the field of child neurology, etiological factors for cerebral palsy are sought in the prenatal period, because perinatal complications seemed to explain only part of the occurrence of this brain dysfunction in at term born infants (Bottos et al., 1999; Casaer, 1993; Sugimoto et al. , 1995; Truwit et al., 1992).The harmful effects of prenatal exposure to tobacco, alcohol, medication or drugs on human brain development are well established (see for a review: Ferreiro & Dempsey, 1999). In short, gestational alcohol exposure may result in microcephaly and central nervous system

malformations (Sokol & Clarren, 1989; Day & Richardson, 1991), disturb neuronal migration (Day & Richardson, 1991) and reduce neuronal numbers (Kumari & Ticku, 1998; Pantazis et al., 1998). According to these studies, alcohol exerts its effects on a variety of genes and can modify the composition of the postsynaptic membrane (Ferreiro & Dempsey, 1999). Likewise, fetal nicotine exposure results in alterations of cholinergic, noradrenergic and dopaminergic projections in postnatal life and appears to elicit a premature switch from proliferation to differentiation. In addition, fetal cell damage and cell loss is found (Slotkin, 1998). Besides the direct effect of alcohol, nicotine and cocaine on fetal brain development, the prenatal exposure to these substances may further interfere with normal brain processes. This may result in later cognitive dysfunction (Fried et al., 1998; Richardson et al., 1995; Frydman, 1996; Naeye & Peters, 1984), behavioral deficits (Weissman et al., 1999; Eckhardt et al., 1998; Fergusson et al., 1998; Williams et al., 1998; Olson et al., 1997; Sampson et al., 1997; Wakschlag, et al. , 1997; Orlebeke et al., 1997; Milberger et al., 1996) and even mental retardation (Drews et al., 1996). Exposure to high levels of radiation in pregnancy has also been related to mental retardation (Otake & Schull, 1984). Other prenatal factors linked with later compromised development, in particular schizophrenia and major affective disorders, included malnutrition (Hoek et al., 1998; Susser et al., 1998; Geddes, 1999) and influenza (Machon et al., 1997).

The effects of these external prenatal factors generally result in explicit physical pathology, growth retardation or psychopathology. Internal prenatal factors such as maternal stress may lead to a more subtle disruption in normal development besides the obvious effects on general fetal development that resulted in preterm birth and lower birth weight. In humans, prenatal stress has been associated with a smaller head circumference of the neonates (Lou et al., 1994). Severe maternal stress in pregnancy has been linked with an increased risk for schizophrenia at adult age for the infants born of these mothers (Van Os & Selten, 1998). In non-human primates, it was found that prenatal stress had long-term effects on behavioral regulation in the offspring that persist into adolescence (Clarke & Schneider, 1997). Offspring of prenatally stressed rats had stronger and prolonged responses of the Hypothalamic-Pituitary-Adrenal (HPA) axis in stressful situations (Weinstock, 1997). The effects of prenatal stress on animal offspring will be discussed in detail elsewhere in this thesis.

The early effects of stress hormones on the developing brain may account for a part of variation in human brain development. So far, the effects of psychosocial factors, and the direct or mediating effects of stress hormones and gonadal hormones on fetal brain development have received little attention from the field of infant studies until now.

Therefore, this chapter aims to affirm that it is worthwhile to study the influence of prenatal determinants, and in particular of prenatal stress, on infant development. The concepts of early programming and prenatal maternal stress are briefly introduced. Fetal brain development and possible sensitive periods in fetal brain developement are described. The role of prenatal hormones as mediators for the effect on human development is elaborated. Moreover, the importance of longitudinal, prospectively designed studies is endorsed.

1.2.1 Early programming effects on the brain

The study of early 'programming' effects on the brain has the potential of gaining more insight in normal and abnormal neurodevelopmental processes. The term 'programming' has been used to describe the process whereby a stimulus or input during a sensitive period of development has permanent effects on the structure, physiology and metabolism of the body, including the brain (Barker, 1995). From various fields of research, the concept of early programming of the fetal brain and the influence on subsequent development emerges. Small variations in the fetal environment may result in developmental and behavioral problems later in life, as the aforementioned studies have shown.

1.2.2 The concept of prenatal maternal stress

Prenatal maternal stress may induce changes in the metabolic environment of the fetus and account for some of these early programming effects on brain development. A problematic issue of the concept of prenatal maternal stress in human pregnancy is the lack of consensus on the definition and operationalization of prenatal stress. Older studies frequently used single questionnaires to assess an aspect of prenatal stress, such as major life events or general anxiety, whereas more recent studies have focused on prenatal stress as a multidimensional concept. In line with these recent studies, we formulated and tested a multidimensional model of prenatal stress in this thesis. As a theoretical starting point, we used the model of Lazarus and Folkman (1984) which differentiates between stress-provoking, stress-mediating or -moderating, and stress-resulting factors.

It is difficult to compare animal findings with human findings with regard to prenatal stress effects on the offspring. Prenatal stressors in animal studies are well-defined and circumscribed and are externally inflicted upon the animal. Many forms of human stress are linked to the occurrence of life events of daily hassles and are partly attributable to the person and may be interwoven with personality and lifestyle factors. It is therefore of great importance to clearly define prenatal maternal stress in humans. In the present thesis the concept of prenatal maternal stress will be elaborated in detail in normal risk pregnant women.

1.2.3 Fetal brain development

From conception onwards the human brain develops rapidly. During early gestation, the neural tube is formed which will differentiate into diverse sections of the brain. Cells also differentiate into neurons and supportive cells, followed by a period of neuronal migration. If neuronal migration is disrupted, an abnormality in cell position results and neurons are then said to be heterotopic. Behavioral disorders that have been associated with such a disruption include some forms of schizophrenia (Korelman & Scheibel, 1983) and of dyslexia (Sherman et al., 1985). Middle gestation is known as a period during which there is neuroblast proliferation and adult numbers of neurons are virtually achieved by the time it is over (Dobbings & Sands, 1979). The later part of gestation corresponds to the brain growth spurt, a period during which brain weight and developmental processes proceed very quickly, which continues

postnatally, and to early synaptogenesis. The timing of brain development differs from one cell type to another and from region to region, however, resulting in an extremely complex developmental pattern.

1.2.4 Sensitive periods in fetal brain development

It has been suggested that sensitivity to harmful effects of various fetal environmental factors on fetal brain development is increased in specific periods of pregnancy. A sensitive period is defined as a specific time period during central nervous system development in which the effects of experience can alter neuronal connectivity (Bear, 1995). When the fetal brain is confronted during a sensitive period, small variations could therefore result in large and lasting effects on brain functioning. Exposure to a substance during a sensitive period may alter normal development and cause malformations or defects. It could be that a specific lack of a substance essential for fetal brain development or an overdose of a harmful essence during such a sensitive period, would cause a detrimental effect with lasting consequences.

To investigate if an increased vulnerability can be detected for the effects of internal prenatal factors such as elevated prenatal stress hormone levels, Schneider et al. (1999) conducted a study in nonhuman primates. The primate offspring proved to be more vulnerable to stress in early gestation as compared to stress exposure in mid-late gestation. However, no specific sensitive period for prenatal stress was found, because the effects of prenatal stress were leveling off from early to mid-late gestation, without a clear demarcation. Although these findings do suggest that early pregnancy could be a sensitive period for brain development, only limited empirical proof is available as yet. This could be attributed to methodological problems in many studies, and therefore further research on this topic is warranted. In the present thesis, we will explore the possible sensitive periods in human fetal brain development for prenatal maternal stress effects.

1.2.5 Importance of maternal hormones for fetal brain development

Even small variations in the fetal hormonal environment have been shown to exert programming effects on the developing brain. Especially the internal steroid hormones produced by the gonads, the thyroid, and the adrenal glands have been found to exert a great influence on the development of the fetal brain (Collaer & Hines, 1995; Sikich & Todd, 1988). Steroid hormone effects occur at the level of gene transcription, via the actions of intracellular hormone receptors. Other effects occur at the level of the membrane via receptors on the cell surface that produce rapid effects on bioelectrical activity and secondary messenger systems. These hormones are regarded as links between the gene and the environment (McEwen, 1992). Increased or decreased levels of maternal steroid hormones during pregnancy may be the mediating factors in explaining disruptions in development.

First, products of the gonads, such as androgens, estrogens and progesterone have shown to program the development of the brain and to affect social development of the infant. Higher levels of testosterone were associated with timidity in preschool boys (Marcus et al.,

1985) and increased visual-spatial performance in girls at the age of 6 years (Jacklin & Maccoby, 1988). More recent studies (Finegan et al., 1992; Grimshaw et al., 1995) found indications of an effect of gonadal hormones on the cerebral lateralization and of cognitive abilities at 4-year-old girls. Prenatal testosterone levels showed a curvilinear (inverted U-shape) relation to language comprehension and classification abilities, and a linear relation to counting, number facts and block building. Furthermore, girls with higher prenatal testosterone levels were more strongly right-handed and had stronger left-hemisphere speech representation, thus had a greater lateralization of function than girls with lower prenatal testosterone levels.

Second, thyroid hormone levels were found to be critical signals for brain development. The presence of sufficient levels of maternal thyroid hormones during the first 10-12 weeks of gestation is important because only from that period on does the fetus start to produce its own thyroid hormones. It has been shown that subtle and subclinical abnormalities of maternal thyroid status in this early period in pregnancy were associated with a compromised cognitive development at age five years (Pop et al., 1995).

Finally, the adrenal gland produces hormones, like cortisol, that are involved in stress responses. From animal studies we know that prenatally stressed rodents and monkeys showed an abnormal reactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis early and later in life. Also, prenatal exposure to prolonged increased levels of corticosteroids resulted in adverse social and exploratory behavior and motor developmental delays in offspring. Studies of Mary Schneider et al. (1992a,b,c; 1993; 1997; 1999) showed that prenatal stress (daily exposure to unpredictable noise stimuli) in nonhuman primates was associated with slower motor development, less exploration in a novel environment and more disturbed behavior of the offspring, even in the absence of clear effects on physical development.

In short, small variations in maternal hormone levels during gestation may result in developmental problems later in life. Therefore, these variations in maternal hormone levels may be mediating the effect on brain development. In this thesis the focus will be on the potential mediating effects of maternal stress hormones, in particular the HPA axis activity, on postnatal developmental delays and behavioral problems.

1.2.6 Methodological guidelines

Precise analysis of the relationship between prenatal events or elevated stress hormones and disruption of fetal brain development and later deviant development is very difficult, especially in humans. Many factors may confound assignments of causation to specific agents. Increased prenatal stress hormones is often accompanied by exposure to prenatal alcohol or nicotine. Furthermore, intrinsic genetic variation could influence the susceptibility of the mother or fetus to potential harmful hormones, which may further complicate efforts to identify factors that are harmful for the developing brain. In this field of research, retrospectively designed studies are commonly used in order to examine possible prenatal stress influences on later compromised development (Van Os & Selten, 1998; Huttunen et al., 1994; Clements, 1992; Meier, 1985; Stott, 1973; Davids, 1963). Since most of these retrospective studies depend on maternal reports, the effects cannot be attributed to specific forms and amounts of stress and confounding factors cannot be adequately controlled for. Recall bias is

a major disadvantage of such a design. Moreover, it is almost impossible to study the effects of a particular factor in a specific period during pregnancy. Prospective longitudinal studies are therefore needed to collect data throughout pregnancy at several gestational periods and from birth onwards. In the present thesis we therefore used a prospective longitudinal design.

It is important to appreciate that the design of the present studies does not allow to examine the relative contribution of genetic versus environmental versus gene by environmental interactional influences on infant development and temperament. Twin studies in humans have shown that the exposure to stressful life events and daily hassles is not independent of the genetic make-up of the individual (Kendler et al., 1993). Especially, for personal and network dependent stressful life events a significant aetiological role for genetic factors has been found (Kendler et al., 1999). Therefore, any association between stress of the pregnant mother and infant development cannot simply be interpreted as reflecting environmental influences on infant development. Rather, these assocations will be due to a complex interplay between genetic and environmental influences that can be unraveled only by using genetic sensitive designs like twin and (half-)sibling studies.

1.3 Conclusion

The concept of early programming of the development of behavior and cognition with a focus on prenatal instead of postnatal influences offers a new paradigm for researchers interested in infant and child development.

Even small variations in fetal physiological environment in specific periods of time may be mediating the effects on later development. It is still questionable if specific sensitive periods exist for the harmful effects of prenatal exposure to maternal stress hormones. Prospective longitudinal studies will offer the opportunity to investigate the effects on the developing fetal brain more precisely. Researchers in the field of infant studies, should take advantage of the knowledge already available in other fields of research and start studying children from their earliest days, instead of having birth as a starting point of their focus of attention. Since prenatal stress is common in today's and probably tomorrow's society, we strongly recommend research with a focus on the effects of psychosocial factors, such as stress, on development from the earliest stages of human life onwards.

1.4 References

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