

Annual Research Review: Prenatal stress and the origins of psychopathology: an evolutionary perspective

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If a mother is stressed or anxious while pregnant her child is more likely to show a range of symptoms such as those of attention deficit hyperactivity disorder, conduct disorder, aggression or anxiety. While there remains some debate about what proportion of these effects are due to the prenatal or the postnatal environment, and the role of genetics, there is good evidence that prenatal stress exposure can increase the risk for later psychopathology. Why should this be? In our evolutionary history it is possible that some increase in these characteristics in some individuals was adaptive in a stressful environment, and that this type of fetal programming prepared the child or group for the environment in which they were going to find themselves. Anxiety may have been associated with increased vigilance, distractible attention with more perception of danger, impulsivity with more exploration, conduct disorder with a willingness to break rules, and aggression with the ability to fight intruders or predators. This adaptation for a future dangerous environment may explain why stress and anxiety, rather than depression, seem to have these programming effects; why there is a dose–response relationship with prenatal stress from moderate to severe and it is not only toxic stress that has consequences; why not all children are affected and why individual children are affected in different ways; and why the outcomes affected can depend on the sex of the offspring. An evolutionary perspective may give a different understanding of children in our society with these symptoms, and suggest new directions for research. For example, there is some evidence that the type of cognitive deficits observed after prenatal stress have specific characteristics; these may be those which were adaptive in a past environment. **Keywords:** Prenatal, stress, anxiety, evolution, child development, psychopathology.

In this paper I will review some of the more recent papers relevant to the effects of prenatal stress on child psychopathology, and discuss how thinking from an evolutionary perspective can give an added understanding of these effects. It is now well established in animal models, and increasingly in humans, that stress experienced by the mother during pregnancy has many long-term effects on the child (Van den Bergh et al., 2005; Talge, Neal, & Glover, 2007; Beydoun & Saftlas, 2008; Wadhwa, Buss, Entringer, & Swanson, 2009). Even though both prenatal and postnatal stress may have continuing consequences, it can be established in rodent models, using cross-fostering, that there is a definite prenatal component with permanent effects on brain structure and function (Del Cerro et al., 2010). Such brain changes in the offspring can often be mimicked by giving the stress hormone corticosterone to the pregnant animal (Afadlal, Polaboon, Surakul, Govitrapong, & Jutapakdeegul, 2010). In monkeys the offspring of prenatally stressed mothers have been shown to have both increased anxiety and reduced attention span (Schneider, Moore, Kraemer, Roberts, & DeJesus, 2002), as well as changes in brain structure, including reduced hippocampal volume (Coe et al., 2003) and altered size of the cor-

pus callosum (Coe, Lubach, & Schneider, 2002). The mechanisms underlying the transmission of such effects from the mother, including stress- or anxiety-induced changes in placental function, are starting to be uncovered (Mairesse et al., 2007; Mueller & Bale, 2008; O'Donnell, O'Connor, & Glover, 2009).

In the human studies a wide range of prenatal exposures which cause distress to the mother have been studied, including acute and chronic stressors, anxiety and depression. These are all different but related concepts. Stress is the widest and most generic term, which is often used to include both anxiety and depression. As will be discussed in more detail below, all these have been found to be associated with effects on the fetus and the child (e.g., O'Connor, Heron, Golding, Beveridge, & Glover, 2002; Field et al., 2003; Hay, Pawlby, Waters, & Sharp, 2008; Laplante, Brunet, Schmitz, Ciampi, & King, 2008). Many different studies have shown that the child of a mother experiencing stress during pregnancy is at increased risk of anxiety (O'Connor, Heron, Golding, & Glover, 2003; Van Den Bergh & Marcoen, 2004), attention deficit/hyperactivity disorder (ADHD) (O'Connor et al., 2003; Huizink et al., 2007) and conduct disorder (O'Connor et al., 2003; Barker & Maughan, 2009) as well as altered function of the HPA axis (for review see Glover, O'Connor, & O'Donnell, 2009; Table 1). Cognitive

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Table 1 Variety of effects of prenatal stress observed in children, and their possible evolutionary value

Effect	Reference	Evolutionary value
Increased anxiety	O'Connor, Heron, & Glover, 2002; Van Den Bergh & Marcoen, 2004; Bergman et al., 2007; de Bruijn et al., 2009	Greater vigilance and alertness to danger
Increased ADHD <i>More readily distracted attention</i> <i>Increased impulsivity</i>	O'Connor, Heron, Golding et al., 2002; Obel, Henriksen et al., 2003; Huizink et al., 2002; Rodriguez & Bohlin, 2005; Van Den Bergh & Marcoen, 2004	Greater sensitivity to dangerous signals More readiness to explore and find new environments
Increased conduct disorder <i>Breaking rules</i> <i>Increased aggression</i>	O'Connor, Heron, & Glover, 2002; Van Den Bergh & Marcoen, 2004; de Bruijn et al., 2009; Rice et al., 2010; E. D. Barker & Maughan, 2009	More willingness to explore and find new environments More likely to fight off predators or other threats
Lower cognitive performance	Bergman et al., 2007; Laplante et al., 2008; Mennes et al., 2006; Huizink et al., 2003)	May be associated with more readily distracted attention Different ways of thinking which can be adaptive
More mixed handedness	Obel, Hedegaard et al., 2003; Glover et al., 2004; Rodriguez & Waldenstrom, 2008	Side effect of altered neurodevelopment linked with increased ADHD etc.
Altered function of the HPA axis	O'Connor et al., 2005; Yehuda et al., 2005; Gutteling et al., 2005; Huizink et al., 2008; Van den Bergh et al., 2008; Entringer, Kumsta et al., 2009	Altered basal diurnal output, and response to new stressor
Fewer male offspring	Peterka et al., 2004; Obel et al., 2007	Mother invests more in female offspring

deficits (Bergman, Sarkar, O'Connor, Modi, & Glover, 2007; Entringer, Buss et al., 2009; Laplante et al., 2008), increased levels of mixed handedness (Glover, O'Connor, Heron, & Golding, 2004; Obel, Hedegaard, Henriksen, Secher, & Olsen, 2003; Rodriguez & Waldenstrom, 2008), dermatoglyphic asymmetry (King et al., 2009) and a lower male to female ratio at birth (Obel, Henriksen, Secher, Eskenazi, & Hedegaard, 2007) have also been reported. Severe stress in the first trimester has been associated with an increased risk of schizophrenia (Khashan et al., 2008). Stress later in pregnancy has been reported to be associated with increased risk of autism in one study (Kinney, Miller, Crowley, Huang, & Gerber, 2008), but not another (Li et al., 2009). In many of these studies, although not all, possible confounding factors such as prenatal maternal smoking or alcohol consumption, maternal education, birthweight, gestational age, and postnatal maternal mood have been controlled for. Effects of prenatal stress are often different in the two sexes (Weinstock, 2007; de Bruijn, van Bakel, & van Baar, 2009). A recent paper has shown, using structural magnetic resonance imaging (MRI), decreased grey matter in several brain regions in children of mothers with pregnancy anxiety (Buss, Davis, Muftuler, Head, & Sandman, 2009). There are many apparent puzzles about these associations. Why should prenatal stress be associated with more developmental psychopathology?

Insight into this comes from two related concepts, fetal programming and the predictive adaptive response. Fetal programming (the phenomenon whereby changes in the fetal environment, during sensitive periods of development, can cause long-lasting changes in structure and function) has been particularly explored in relation to low birthweight.

It is now clear from many epidemiological studies that babies that have grown less well in utero are at risk for a range of problems much later in life, such as cardiovascular disorder, diabetes and obesity (Barker, 2003). Hales and Barker have discussed how a thrifty phenotype may be adaptive in times of poor nutritional resources postnatally (Hales & Barker, 2001), but be maladaptive in the conditions of plenty in the modern world. Reduced growth in utero has many risk factors, one of which is maternal stress or anxiety while pregnant (e.g., Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993; Hosseini et al., 2009; Rice et al., 2010). Low birthweight babies are at risk for a range of later mental health and behavioural problems too (Schlotz & Phillips, 2009).

The phrase 'predictive adaptive response' has been used to encompass the idea that fetal development is altered in a way that adapts the future child to the world in which it will find itself (Gluckman, Hanson, & Spencer, 2005; Gluckman, Hanson, & Beedle, 2007). These authors argue that such early adaptations have had an important role in human evolution. They particularly focus on fetal growth and nutrition. But it seems likely that the effects of prenatal stress on fetal neurodevelopment also had a predictive role in helping the offspring succeed in a stressful environment. Variation in the stress of the environment, like variation in the availability of food, is a basic parameter, which systems in the body such as the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic system have evolved to respond to.

Thus some of the altered outcomes observed after prenatal stress may well, in their milder forms, have been adaptive in more primitive conditions. Others may be non-adaptive side effects, or the non-adaptive effects of being at an extreme end of an adaptive

spectrum. It is possible, for example, that the mechanism which increases an adaptive increase in vigilance in offspring becomes maladaptive when it causes a disabling level of phobia in some individuals. In the light of findings that genetic changes in many different loci appear to contribute to the risk of schizophrenia, it may be that such traits generally improve cognitive fitness, but at some point reach a cliff-edge and failure (Nesse & Ellsworth, 2009). This discussion is currently speculative, and others may offer different interpretations or explanations for the findings. However, many features of the effects of prenatal stress, and of fetal programming, become more understandable in this context. Why is it anxiety rather than depression that appears to have the greater effect (O'Connor, Heron, Golding et al., 2002; Obel, Hedegaard et al., 2003; Field et al., 2003)? Why do these effects occur across the range of stress, from moderate to extreme, and are not just an effect of toxic stress (O'Connor, Heron, Golding et al., 2002)? Why are increased anxiety and symptoms of ADHD such commonly observed outcomes? Why are different children affected in different ways (Bergman et al., 2007)? Why are males affected in different ways from females (Weinstock, 2007; de Bruijn et al., 2009)? An evolutionary perspective sheds light on all of this.

Evolution and psychopathology

Essential to the theory of evolution are the concepts of variation in the genetic endowment of individuals, and the selection in differing environments, of those individuals most fit to survive and reproduce (Gluckman, Beedle, & Hanson, 2009). Biological fitness for humans is achieved by a strategy of supporting a small number of children who grow successfully to adulthood, and then in their turn, reproduce successfully.

Darwin emphasised the importance of variation within a single species as the raw material for selective success in changeable environments. It helps the survival of the group if not all individuals are the same. This variation has historically been attributed to mutations causing sequence variations in the genome, such as single nucleotide polymorphisms (or SNPs) as have been described for the glucocorticoid receptor (Wust et al., 2004). These have the potential to control the nature of the mRNA and protein expressed. There can also be other important variations in the nature of the DNA sequence, which can control the amount or the stability of the protein expressed.

Epigenetic changes (functionally relevant modifications to the genome that do not involve a change in nucleotide sequence) are also relevant, in addition to these basic mechanisms of evolution. Epigenetic changes, which involve reversible changes to the structure of DNA, such as the addition of a methyl

group, control the amount of mRNA and protein produced. Such epigenetic changes can be induced by the environment and may underlie many of the processes of fetal programming. Waddington (who coined the term epigenetics in 1942, meaning 'on top of genetics') showed that the environment can not only affect the phenotype of the exposed organism, but that of subsequent generations. When he exposed fruit fly larvae to heat some flies showed alterations in the wing vein pattern, and so did the offspring, and further generations of these particular flies, even when not exposed to heat. There is some evidence that environmentally induced, presumably epigenetic, changes can last up to two generations in mammals also (Drake, Walker, & Seckl, 2004; Matthews & Phillips, 2010).

Thus a single genotype can produce a wide range of phenotypes due to epigenetic and other changes. Mammals have developed the capacity to respond in an appropriate way in utero, presumably to improve fitness, and be better prepared for the environment in which they would find themselves after birth (Gluckman et al., 2007). The fetus obtains its information about the environment from its mother, by variation in the nutrients, hormones or other chemicals which cross the placenta from the mother.

The particular effects of prenatal stress, or any other environmental factor, may depend on when in pregnancy it occurs, although much more work needs to be done on this. The association with schizophrenia has been found in the first trimester (Khashan et al., 2008), whereas that with behavioural and emotional problems has been found later in pregnancy (O'Connor, Heron, Golding et al., 2002). Developmental plasticity is characterised by critical windows, when particular organs or systems are being formed. For example the effects of thalidomide on arm and leg formation are limited to the first trimester, as that is when these limbs are being formed, although this example is one of teratology, rather than a predictive adaptive response. However, synaptic formation and receptors in the brain are being formed throughout the second half of gestation as well as after birth. Long-lasting changes caused by the early environment in humans, related to this prolonged neurodevelopmental window, have recently been shown by McGowan et al. (2009). These authors found that early child abuse was associated with epigenetic changes in the hippocampal glucocorticoid receptor in adult post-mortem brains.

It is not at first obvious why emotional, behavioural and cognitive problems have arisen. Some, although not all, of the genes that have been found to be associated with these disorders are common, and are therefore likely to have been adaptive in some way. Our emotions and behaviours have been shaped by natural selection (Nesse & Ellsworth, 2009). Attacks by predators, exclusion from the group, and opportunities for mating were sufficiently important and frequent to have shaped special

patterns of behaviour. Several authors have discussed how psychopathology may be viewed from an evolutionary perspective (e.g., Lilienfeld & Marino, 1995; Wisniewski, Windmann, Juckel, & Brune, 2009).

For example, it has been suggested that because depression is common, and mood is carefully regulated, it is likely to be an evolved response of adaptive value, although the adaptive value of symptoms of depression may differ from those of anxiety. Sadness and emotional withdrawal, like pain, may lead to avoidance of potentially harmful actions. Crying may elicit support by others. Fatigue, especially in winter, as in seasonal affective disorder, may help save energy. Depression may be common in our modern urban societies partly because many feel lack of social support, and are socially isolated. It is thought that our ancestors lived in groups of about 150. This may be the size of community which can result in a well-bonded social group and which our brain has adapted to in order to promote fitness within this environment (Gluckman et al., 2009).

A mismatch between what was adaptive in an earlier environment and the world in which we now live can lead to pathology. Thus the outcomes which can be increased by prenatal stress or anxiety and their potential adaptive value in our ancestral environment, as discussed in more detail below, can be quite maladaptive in our modern environment. For example, we are not usually exposed to the type of danger for which extra vigilance (anxiety) or readily distracted attention (ADHD) would be helpful, and these symptoms can both be distressing and impede formal learning.

Gluckman et al. (2009) make the case that concepts of health and disease are altered by taking an evolutionary perspective. Our understanding of an individual's health may depend on knowledge of their evolutionary origin and how that interacts with the modern world.

Types of prenatal stress associated with altered child outcome

The prenatal stress literature has linked a wide variety of stressors, both acute and chronic, with altered child outcome. The effects of acute disasters such as 9/11 (Yehuda et al., 2005), Chernobyl (Huizink et al., 2007), and a Canadian ice storm (Laplante et al., 2008) have been studied. Others have found associations with much milder stress, such as daily hassles, or pregnancy-specific anxiety (Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003). It is clear that associations with an altered child outcome do not require extreme or toxic stress. There is some evidence for a dose-response effect, across the range (O'Connor, Heron, Golding et al., 2002). However, it may be that some outcomes, such as an increased risk of schizophrenia, do

require more extreme stress, such as the death of a close relative (Khashan et al., 2008). It has also been suggested that a mild degree of prenatal stress may alter the outcome in the opposite direction, actually increasing mental and motor development (DiPietro, Novak, Costigan, Atella, & Reusing, 2006). These authors suggest that mild to moderate levels of psychological distress may enhance fetal maturation in healthy populations, and that the dose-response curve may be an inverted U shape, with optimal outcome in our society associated with mild or moderate prenatal stress, rather than too little or too much. It is also possible that different outcomes are affected in different ways, and that it is not appropriate to think of outcomes as 'good' or 'bad'. It might be of evolutionary benefit to increase both vigilance (anxiety) and the rate of physical maturation (motor development) in times of stress.

Even though there is often a correlation between anxiety and depression, there is some (although not conclusive) evidence that it is prenatal stress and anxiety, rather than the co-morbid depression, that affects fetal and child outcomes in the ways discussed here (O'Connor, Heron, & Glover, 2002; Obel, Hedegaard et al., 2003; Field et al., 2003). The animal studies have all used models with various types of prenatal stress (Weinstock, 2001). Although depression is also a stress-related disorder, it may have a different evolutionary role, possibly to do with conserving energy or eliciting immediate support. It may not have the same role in causing predictive adaptations in the child. Maternal prenatal stress and anxiety may, in contrast, program the offspring to deal with a future dangerous or stressful environment, in order to survive. The programming effects may not be specifically associated with a particular clinical diagnosis or depression in the mother, but the original range of conditions or life events which made her feel generally stressed.

Outcomes increased by prenatal stress and their possible adaptive value

In humans there is evidence that fetal behaviour can be related to the pregnant mother's current emotional state (DiPietro, Hilton, Hawkins, Costigan, & Pressman, 2002; Kinsella & Monk, 2009), and also that there is continuity between fetal and infant behaviour (DiPietro, Bornstein, Hahn, Costigan, & Achy-Brou, 2007). There is also clear evidence from many studies that maternal stress in pregnancy is associated with a range of altered outcomes for the child, independently of any effect on birthweight (e.g., O'Connor, Heron, Golding et al., 2002; Bergman et al., 2007).

ADHD

An increase in symptoms of ADHD is one of the outcomes most commonly found to be associated

with prenatal stress (O'Connor, Heron, Golding et al., 2002; O'Connor et al., 2003; Obel, Henriksen et al., 2003; Huizink, de Medina, Mulder, Visser, & Buitelaar, 2002; Rodriguez & Bohlin, 2005; Van Den Bergh & Marcoen, 2004). It has been suggested that ADHD, from the perspective of evolutionary biology, may reflect the optimisation of brain function to some environments at the cost of poorer response to the demands of others (Jensen et al., 1997). One may speculate that readily distracted attention may be adaptive in a dangerous environment, which the pregnant mother has experienced as stressful. Sensitivity to small signals, such as a new sound, may alert one to the approaching presence of a predator or a hostile human.

An increase in symptoms of hyperactivity, independently of attention problems, has also been found to be associated with increased prenatal anxiety and depression (Harvey, Friedman-Weieneth, Goldstein, & Sherman, 2007). An interesting paper by Williams and Taylor (2006) considers the evolution of hyperactivity, impulsivity and cognitive diversity. They discuss both the value of unpredictable behaviour in changing environments and the value of confining such unpredictable behaviour to a minority. They especially focus on the hyperactive/impulsive dimension, and suggest that novelty seeking, risk taking and seeking maternal attention, as well as increased sexual activity, all may have been adaptive. Novelty seeking and increased exploration could propel migration, which could be important in a stressful environment. Exploration does not always have to be well organised. Random search strategies can be beneficial too.

A greater ability for babies and young children to elicit maternal attention may also be relevant in harsh conditions. Being 'difficult' has been suggested to improve survival of infants during drought among the Masai in East Africa (deVries, 1984). This may possibly also be an adaptive value of a more difficult infant temperament, which has also been found to be associated with both prenatal depression and anxiety (Werner et al., 2007; Davis et al., 2007). There may be a sex difference in this. Befera and Barkley (1985) showed that while hyperactive boys received more direction and praise, and had greater maternal concern about their adjustment than normal children, this was not true for hyperactive girls.

Williams and Taylor (2006) also discuss the advantage for the group in having a proportion of impulsive individuals who do things they should not, such as eating poisonous berries. Though the individual may suffer, the group could benefit by the knowledge gained. They use a statistical model to demonstrate the benefit of a mixed society, and show that a group with 5% of unpredictable individuals survives best. This corresponds, in some measures, to the level of children with symptoms of ADHD in our society. In our own study of the large ALSPAC

population cohort, we found that in children of the most anxious mothers (the top 15%) the level of symptoms of ADHD doubled from 5% to 10% (O'Connor, Heron, Golding et al., 2002). It may be that in a more stressful environment it is adaptive to have a higher proportion of impulsive individuals.

In general it is thought that natural selection acts at the level of the individual or 'selfish' gene. But in some circumstances it has been argued that it may act at the level of the group, such as a change in behaviour whereby some individuals reduce their apparent level of fitness by acting as sentinels to, for example, warn the group of the presence of a predator (Clutton-Brock et al., 1999). There may be an evolutionary benefit in an individual helping their relatives and in developing social behaviour, or even limited self-sacrifice, which enhances the survival of the group and their specific genes (Hamilton, 1964; Pfennig & Sherman, 1995).

Anxiety

Several studies have found that prenatal stress or anxiety is associated with increased levels of anxiety (O'Connor, Heron, & Glover, 2002; Van Den Bergh & Marcoen, 2004; Bergman et al., 2007) or internalising problems (de Bruijn et al., 2009) in the child. Marks and Nesse (1994) have discussed the evolutionary significance of anxiety disorders. They suggest that normal anxiety is an emotion that helps organisms defend themselves against a wide variety of threats. This evolutionary perspective on anxiety explains why we are more likely to develop phobias to archaic dangers like snakes or spiders, and not to modern dangers, such as cars. It is easy to see how extra vigilance may be more necessary and adaptive in a more stressful environment. A mild threat causes a general increase in anxiety that helps to locate the source and type of danger and to plan possible ways to deal with it. Circulation patterns change so that less blood goes to the skin and gut, and more to the muscles; hyperventilation gives more oxygen, and sweating causes the skin to become slippery. All this prepares the body for a direct confrontation of danger. Marks and Nesse (1994) also discuss how subtypes of anxiety protect against particular types of threat. The features of anxiety subtypes largely correspond to dangers that humans have faced during their evolution. A fear of heights induces freezing, making one less likely to fall. Traumas are followed by fear and avoidance of anything reminiscent of the original trauma. Separation anxiety can help promote the attachment of the child to the mother. Social threats evoke responses that promote social cohesion. It is not yet known whether the anxiety in the child following prenatal stress is more likely to be of any particular subtype, or whether it corresponds to the type of anxiety or stress experienced by the pregnant mother.

Conduct disorder

Externalising problems (Van Den Bergh & Marcoen, 2004; de Bruijn et al., 2009) and conduct disorder have been shown to be associated with prenatal stress or anxiety, independent of postnatal maternal mood (O'Connor, Heron, & Glover, 2002; Rice et al., 2010; Barker & Maughan, 2009) or genetic factors (Rice et al., 2010). Barker and Maughan (2009) found that prenatal anxiety was especially associated with conduct disorder that persists into adolescence, as opposed to that limited to childhood. Oppositional defiant behaviour, associated with hyperactivity, has also been shown to be increased in children of mothers who were anxious or depressed in pregnancy (Harvey et al., 2007).

It is easy to understand how more aggressive behaviour may be adaptive in a stressful environment in which there is a shortage of resources, or more danger from outsiders (Archer, 2009). Our early human ancestors could have been at risk from carnivorous predators and also from other humans, such as neighbouring tribes. An ability to react quickly, and to be aggressive, as well as to mount stress responses, may have been helpful to escape or to fight back. There are many examples of organisms that live in threatening or stressful environments making developmental shifts in phenotype on order to handle the potential threat. Other aspects of conduct disorder may be adaptive in such circumstances too. For example, breaking the rules, or behaving in a way different from the group, may aid the discovery of new environments or new strategies. In times of stress or difficulty, those with these dispositions may be the ones who try out new things or literally explore new areas.

Cognitive function

Several studies have found an association between prenatal stress and children performing less well in cognitive tests. The prenatal stresses studied include life events (Bergman et al., 2007), exposure to a Canadian ice storm (Laplante et al., 2008), increased state anxiety (Mennes, Stiers, Lagae, & Van den Bergh, 2006) and exposure to pregnancy-specific anxiety and increased daily hassles (Huizink et al., 2003).

We do not know to what extent the cognitive impairment detected after prenatal stress is a side effect of readily distracted attention, or other behavioural changes. However, in having cognitive variation in a population there may be advantages, similar to the possible benefits of impulsivity discussed above. Individuals who learn, understand and interpret things in different ways may also have had adaptive advantage under varying conditions in an earlier society, although not in our own. In our society symptoms of ADHD are associated with

impaired scholastic achievement (Rodriguez et al., 2007).

There is some evidence for an association between prenatal stress and autism (Kinney et al., 2008). Although autism is primarily a social disorder, individuals with milder autistic features can also have special cognitive abilities. Again there may be some benefit in having more of them in a stressful environment, to seek out new ways of dealing with problems.

Mixed-handedness

The incidence of mixed-handedness, or non-right-handedness, has been found to be increased after prenatal stress or anxiety in three large independent cohorts (Obel, Hedegaard et al., 2003; Glover et al., 2004; Rodriguez & Waldenstrom, 2008). While mixed-handedness may not be adaptive in itself, it may reflect an altered pattern in the development of brain laterality, which is adaptive. In the study of Rodriguez & Waldenstrom (2008), non-right and mixed-handedness were associated with increased risk of language difficulties and particularly with ADHD symptoms, after adjustment for current parental ADHD symptoms, current maternal depressive symptoms, birth outcomes, smoking during pregnancy, depressive symptoms and critical life events. In general there is more mixed-handedness in boys than in girls, and it is associated with increased rates of ADHD, language and scholastic difficulties and mental health problems (Rodriguez et al., 2010). From an evolutionary perspective it is possible that prenatal stress alters brain development in a way that increases the likelihood of the range of outcomes that are adaptive in a stressful environment, as discussed above. Animal studies have established that prenatal stress reduces cerebral asymmetry and can cause anomalies in brain morphology (Weinstock, 2001). It is thus unlikely that mixed-handedness reflects the postnatal environment. This finding gives added support to a prenatal stress environmental component having a causal role in developmental psychopathology.

Altered function of HPA axis

The HPA axis is one of the two major stress response systems in the body. It is thus not surprising that its basal function and reactive responses should be reprogrammed in response to the degree and type of stress experienced in pregnancy. The more stressful the predicted environment, the greater the need for a reactive system. It has been suggested that cortisol, the end product of the HPA axis, has a crucial role in resource partitioning. It helps control the activity of many systems, including metabolism, reproduction and immune function (Worthman & Kuzara, 2005).

Animal studies have shown that prenatal stress, as well as affecting behaviour, can also reprogram the function of the HPA axis in the offspring (Glover et al., 2009). However, the effects on the HPA axis vary greatly with the kind of stress, its timing in gestation, the genetic strain of the animal, the sex and age of the offspring and whether basal or stimulated HPA axis responses are studied. Although in several studies the HPA axis response to a novel stressor is heightened, this is not always the case (Weinstock, 2005, 2008).

Some studies in humans show long-term associations between prenatal stress and altered basal cortisol levels, or cortisol responses to stress (O'Connor et al., 2005; Yehuda et al., 2005; Gutteling, de Weerth, & Buitelaar, 2005; Huizink et al., 2008; Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008; Entringer, Kumsta, Hellhammer, Wadhwa, & Wust, 2009). The designs of these studies differ considerably and the effects on outcome are also varied. The variability in reprogramming the diurnal output and response of the HPA axis suggests that any evolutionary benefit is finely tuned to the particular nature of the environment during gestation.

Reproductive behaviour and sex ratio

In animal models it has been shown that prenatal stress alters reproductive behaviour in both male and female offspring. Females become less maternal (Del Cerro et al., 2010) and males show less masculine behaviour (Ward & Stehm, 1991). Del Cerro et al. (2010) have shown that pregnant rats, stressed during the last week of gestation, also show less nurturing mothering behaviour themselves. In an elegant cross-fostering design, which included studying stressed offspring reared by non-stressed dams and non-stressed offspring reared by stressed dams, they showed that maternal care by a non-stressed mother could counteract the effects of the prenatal stress on the later mothering behaviour of the female offspring, although not the hormonal and neurological morphological alterations. They conclude that both prenatal stress and early mothering are important for the later behaviour and functioning of the female offspring, although the contribution of each differs with outcome.

In mice, prenatally stressed males have been shown to prefer sexually active males to females (Meek, Schulz, & Keith, 2006). It has been suggested that this may be a model for homosexual behaviour in humans. However, there is little good evidence yet linking prenatal stress with altered reproductive behaviour in humans, either male or female (Beydoun & Saftlas, 2008). It is a subject it would be of interest to study further.

In evolutionary terms homosexual behaviour is puzzling. It has been suggested that it may maintain social ties within a group, and this may be especially

valuable in times of stress (Gluckman et al., 2009). Also, in times of stress it may be adaptive for mothers to invest less in raising males. In terms of survival it may help to maximise the future population number by having a lower ratio of males to females, with males mating with more than one female. It is of interest that prenatal stress (both extreme and more moderate) has been shown, in human populations, to be associated with a lower male to female sex ratio at birth (Peterka, Peterkova, & Likovsky, 2004; Obel et al., 2007). Obel et al. (2007) suggest that prenatal stress may be involved in the decreasing sex ratio observed in many countries.

The concept of life history (the particular pattern of growth, development and reproduction a particular species or individual may have) can be helpful in understanding the adaptive reproductive responses that may be shaped in utero (Worthman & Kuzara, 2005). Meaney (2007) describes the evolutionary value of female variety in reproductive strategy, allowing a range of responses to different environments. In times of stress there is evidence that female rodents reach earlier sexual maturity and reproduce earlier, but invest less care in each offspring. In humans there is evidence that a harsh early environment leads to earlier puberty. In a harsh non-nurturing environment it may be adaptive to have more children, and invest less in each one, before the external threats become life threatening.

Prenatal versus postnatal effects

Animal studies using cross-fostering (e.g., Del Cerro et al., 2010) can disentangle long-term prenatal and postnatal effects. In humans disentangling them is harder. Mothers who are stressed while pregnant are likely to be stressed later. However, in several studies attempts have been made to covary out postnatal effects, and the signal from the prenatal period remained strong (e.g., O'Connor, Heron, & Glover, 2002; O'Connor, Heron, Golding et al., 2002; Bergman et al., 2007; Van Den Bergh & Marcoen, 2004). Rice et al. (2010) found that, although the association between prenatal stress and child conduct disorder was maintained when current maternal mood was taken into account, that with child anxiety did not. However, other studies have found that the association between prenatal maternal anxiety and child anxiety was independent of postnatal maternal mood (O'Connor, Heron, & Glover, 2002; O'Connor, Heron, Golding et al., 2002; Bergman et al., 2007; Van Den Bergh & Marcoen, 2004).

There clearly are early postnatal effects also. The quality of early mothering can either attenuate the effects of prenatal stress (Kaplan, Evans, & Monk, 2008) or else exacerbate them (Bergman, Sarkar, Glover, & O'Connor, 2008). A secure attachment also attenuates the association between in utero cortisol exposure and infant cognitive development (Bergman,

Sarkar, Glover, & O'Connor, 2010). The lifetime cumulative effect of maternal mood may also be important (Pawlby, Hay, Sharp, Waters, & O'Keane, 2009). Differential effects of antenatal and postpartum depression on child outcomes have also been reported (Hay et al., 2008).

More research is needed to disentangle the proportion of effects (probably different in relation to different outcomes) of the prenatal as opposed to the postnatal mood of the mother, or of the kind of postnatal care.

Thus there is evidence in humans, as well as in animal models, that prenatal stress does have a role in determining later psychopathology, independent of postnatal factors. It seems probable that evolutionary pressure has developed mechanisms to prepare the infant for the environment into which it would be born, together with the developmental plasticity enabling a flexible response to variations in that environment.

Variety of outcome

Not all children are affected in the same way by prenatal stress (Bergman et al., 2007), and most are not affected at all (O'Connor, Heron, Golding et al., 2002; Talge et al., 2007). It is highly likely that there is a gene-environment interaction (Kim-Cohen et al., 2006; Rutter & Silberg, 2002; Caspi et al., 2003), and also likely that whether there is any effect at all, and if so of what type, depends on the specific genetic makeup of the child and of the mother. Some may be more vulnerable to the effects of stress, some more resilient, and some children may be more vulnerable to specific outcomes. This is predicted by the Darwinian concept of genetic variation as the basis for the action of natural selection.

Some have raised the question as to whether the associations found between prenatal stress and child outcome may be all due to genetic continuity. There may well be a contribution from genetics, but the repeated finding of effects of prenatal stress, independent of postnatal stress, make it unlikely to be the whole story (e.g., O'Connor, Heron, Golding et al., 2002; Bergman et al., 2007). In an elegant design, Rice and co-workers compared, in children born after *in vitro* fertilisation, the association between prenatal stress and child outcome in those who were genetically related to the mother with those who were not (Rice et al., 2010). They showed that there was an association between maternal stress in pregnancy and child symptoms of ADHD, anxiety and conduct disorder, and that the association with anxiety and conduct disorder was apparent in the unrelated mothers. However, the fact that the increase in symptoms of ADHD was apparent only in those with related mothers does not conclusively rule out a prenatal environmental component. There may be a gene-environment interaction, as has been

described for the occurrence of violent behaviour after early maltreatment of the child. Maltreated children with a genotype conferring high levels of MAOA expression were less likely to develop antisocial problems (Caspi et al., 2002). Thus there is evidence that genotypes can moderate children's sensitivity to environmental insults. Prenatal stress may only have the effect of increasing symptoms of ADHD in the genetically vulnerable mother and child pairs. More research is needed to disentangle the role of genetic factors.

Implications for future research

Thinking about the evolutionary significance of the effects of prenatal stress may raise new questions about the exact nature of the outcomes observed, and even have implications for treatment. For example, if the function of the increase in anxiety is to be protective, then it may be that the nature of the anxiety is especially associated with an increase in vigilance. The term anxiety covers many phenotypes and it would be interesting to understand more about its particular nature in children or adults subjected to prenatal stress. Similarly, if the increase in ADHD is associated with the protective nature of readily distracted attention, or impulsivity, it would be of interest to understand more about the exact nature of the condition in people who have experienced prenatal stress. This is also true of the effects on cognition. Studies, including our own (Bergman et al., 2007), which have used the Bayley's Mental Developmental Index, provide only a very crude index of what is altered. We do not know to what extent impaired cognitive development is due to associated problems with attention.

Van den Bergh and her colleagues have started to try to understand more about the changes in memory or cognition following prenatal anxiety. Adolescents of mothers with high levels of anxiety during their pregnancy performed significantly worse in tasks which required integration and control of different task parameters. This suggests the involvement of the orbitofrontal cortex (Mennes et al., 2006). Mennes, Van den Bergh, Lagae, and Stiers (2009) showed in a Gambling paradigm that adolescent children of highly anxious pregnant women made less efficient decisions than those whose mothers had been less anxious. Moreover, they identified specific differences in the event-related potential, with the high anxiety group showing an enlarged early frontal P2a component. Another recent study has shown that perinatal anxiety in the mother is associated with altered auditory evoked responses in neonates (Harvison, Molfese, Woodruff-Borden, & Weigel, 2009). Those whose mothers had low anxiety showed more negative frontal slow wave amplitudes in response to their mother's voice as opposed to that of a stranger. Those whose mothers

had high anxiety showed the opposite response. The authors suggest that this may indicate a specific neurophysiologically based alteration in attentional allocation. Entringer and colleagues (Entringer, Buss et al., 2009) have shown that prenatal psychosocial stress was associated with impaired subsequent prefrontal cortex-dependent working memory performance in human adults, after hydrocortisone (cortisol) administration, but not under placebo conditions. Further detailed studies on effects on verbal or visual memory and recall, and functional magnetic resonance imaging (fMRI) studies to understand the exact brain regions affected, would be informative.

Conclusion

The evolutionary perspective can add a new viewpoint in trying to understand the long-term effects of prenatal stress. Fetal programming may help explain why some forms of developmental psychopathology have persisted in the population. It could be of evolutionary benefit to have a minority of individuals who are more vigilant (anxious), impulsive or with readily distracted attention (ADHD), or willing to break the rules or be aggressive (conduct disorder). In times of stress it may be adaptive to have a higher proportion of the population with these traits. With

ADHD, conduct disorder or aggression, it would be more appropriate to have these traits in the males, who have more freedom to wander and explore. With the females and their larger investment in pregnancy and child rearing, extra vigilance or anxiety might well be the most adaptive trait. The effects of prenatal stress appear to increase across the range of stress, not just at a toxic, or clinical, range. This suggests that these predictive adaptive responses may be fine-tuned to the degree of external threat or stress present.

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Key points

- Prenatal stress is associated with increased risk for a range of neurodevelopmental, behavioural and cognitive changes in the child. Not all children are affected in the same way and most are not affected at all.
- This may have been of adaptive value for our ancestors but lead to psychopathology in our modern society.
- Increased anxiety and distractible attention may have helped to increase vigilance and alertness to danger in a stressful environment, aggression to fighting predators, and impulsivity and breaking rules to seeking out new safer environments.
- This evolutionary perspective on the long-term effects of prenatal stress may stimulate new thinking for research and intervention.

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