

All our Sons: The Developmental Neurobiology and Neuroendocrinology of Boys at Risk

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Introduction

Schore's paper describes his concern for what he sees happening in the United States of America (U.S.A.) today. Higher numbers of boys than girls are exhibiting autism, early onset schizophrenia, attention deficit hyperactivity disorder and conduct disorders. He relates this to the slower rate of maturity of the emotional centre in the right side of the brain in boys than in girls, as well as the higher surges of testosterone in the right side of their brains. The patterns of the connections of nerve cells in several parts of the brain are different between the sexes, both in the limbic system (which is responsible for our emotions, including rage, fear and the distress of separation, along with affection and social behaviour, such as nurturing, playfulness and bonding) and in the cerebral cortex, responsible for reasoning and empathy.

There is rapid growth of the neurones in the brain during the last trimester of pregnancy. The brain continues to grow at a rapid pace for the next two years. The social "attachment" of the foetus to the mother via the placenta, and between the infant and the mother after birth (the dyad), is important in shaping the growth of the right hemisphere of the brain, particularly the right prefrontal areas controlling the HPA-axis (Hypothalamic-pituitary-adrenal-axis) which regulate the body's response to external stress (1). For the rest of the life of the individual, the right hemisphere regulates the HPA-axis and enables that person to cope with stresses and challenges.

1. Production of testosterone

The endocrine system called the HPG axis (Hypothalamic-pituitary-gonadal) (2) controls and regulates the levels of the gonadal hormone testosterone produced and circulating in the body. More than 95% of the testosterone is produced in the testes in males or in the ovaries in females but small amounts are also made in the outer layers of the adrenal glands in both sexes. During development, there are three notable periods of higher levels of testosterone in both young males and females. The first is during pregnancy, peaking at weeks 15-18 of pregnancy. The second is during months 1 – 3 after birth and the third is during puberty. For each of these three stages, the levels of testosterone in males are much higher than in females. The testosterone is transported to tissues in the blood stream and passes through the brain on its course round the body. The surge of testosterone in the brain is more predominant in the right hemisphere of the brain, a part of the brain responsible for coping with stresses and challenges, than the left. The frontal cortex of the brain of foetuses was analysed by Sholl and Kim (1990). There are higher levels of testosterone in male brains in the right frontal cortex than left and in male rather than female foetuses. The

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slower brain growth of boys seems to be related to this higher level of testosterone in boys (de Lacoste, 1991).

2. Permanent changes caused by abnormally high cortisol

a) Modifying the expression of genes

Males develop slower than females because the testosterone in the brain during these surges is much higher than in females. During these periods, the individuals are particularly susceptible to cortisol released from the HPA axis during stress (1). If the levels of cortisol are high, this can affect brain growth and change the function of DNA by epigenetic modification (3). A sharp increase in cortisol can be detected in a newborn male exposed to acute separation stress. Repeated separation from the mother results in hyperactive behaviour and changes to the prefronto-limbic pathways. These regions have been shown to be dysfunctional in a variety of mental disorders. If the levels of stress are great enough to cause epigenetic modification, this will alter the individual's emotional responsiveness and stress-coping strategies later in life. Once DNA has been modified in this way, the children and grandchildren of this individual may also carry the modified DNA and so carry the likelihood of being susceptible to ADHD, autism, aggression etc.

b) Changing the structure of brain cell junctions and the growth rate of the brain, especially the amygdala

The right hemisphere of the brain in girls and boys has a growth spurt from the last three months of pregnancy up to the end of their second year after birth. The non-verbal right hemisphere has a particular growth spurt in the first year and the verbal left hemisphere has its growth spurt during the second year. Schore suggests that the right hemisphere develops more slowly in male infants than in females. Boys are therefore at risk for a longer time (Taylor, 1969). The more slowly developing right brain in boys is therefore more vulnerable to periods of stress, meaning boys are less adapted to regulate stress or efficiently process it.

In the third trimester (months 6-9 of pregnancy), the brain growth spurt commences and plasticity and pruning of the developing brain is at its highest, with almost 50% of neurons in the foetal brain dying. This dying-off of cells is regulated by gonadal steroids.

In optimal foetal development, the amygdala complex (4) in the brain is structurally mature by the 8th month, the neonate is ready for birth and once out of the womb, can respond to the novel stimulation of face, eyes, smell and touch of the mother. The amygdala is known to contain many androgen receptors and is larger in males than in females (androgens are hormones responsible for the male features and reproduction). It is vulnerable to stress or endocrine disruptors that might amplify cell death in this critical period. If the intra-uterine context is chronically stressful and therefore growth-inhibiting, the amygdala will develop more slowly and will not be mature at birth. The infant will be poor at eye gaze, an essential point of contact with another human being. The amygdala further matures after birth, especially in months 2-3, when the infant can have more complex interactions with the mother. Interactive regulation is essential to infants who have a slower maturing amygdala. Mothers at

risk of postpartum depression need help and support with their babies during this vulnerable period.

c) Changing the health outcome in adulthood

Sensitivity to infections and allergens can be affected by stressors in the pre- and perinatal periods. Males are more sensitive to environmental stressors as well as infections and immune challenges, whereas females having higher levels of oestrogen, have better immunity. The health of the adult will depend on the maturation of the body's immune system in the important pre- and perinatal periods. Thus, the factors which lead to good emotional pre- and perinatal health of a child will also lead to a healthier life, with less reliance on our health service.

3. Cultural effects on boys at risk: early childcare

a) Attachment

Whilst the foetus is attached to the placenta in the mother's womb, and when the post-natal infant has a mother-infant (dyad) attachment, relationships can lead to correct and normal development of stress-regulation in the HPA-axis. This in turn allows normal development of stress-regulation as the child grows into puberty and adulthood.

Research has clearly shown that the maternal care within the attachment relationship shapes the infant's stress-regulating HPA axis (Gunnar, 2000). It is specifically the right and not the left prefrontal areas of the brain which regulate the HPA axis (Sullivan and Gratton, 2002). Also, for the rest of the lifespan, the right hemisphere regulates the HPA and thereby controls vital functions supporting survival and enabling humans to cope with stress and challenges (Schoore, 1994, Wittling, 1997).

b) Childcare

In 1994, Shore was alarmed when he reviewed published data of the increase in aggression in children in early day care settings related to an increase in the number of children who were determined as having insecure attachment especially avoidant attachments (5). By 2007 (Dmitrieva *et al*) it was reported that day care initiated early in life, especially in day-care centres, is associated with the difficult externalising behaviours of aggression and disobedience. Vandell *et al*, (2010) reported that the effects of early childcare extend into late childhood and adolescence.

Sajaniemi *et al* (2011) have published cortisol patterns of children in day care. They conclude day care may also be challenging for some children, causing abnormal cortisol patterns, harmful to the HPA axis development, indicators of stressors. In recent years young children have a higher chance of being subject to physical or psychological stressors, child care being just another, in addition to family turmoil, adverse social circumstances or various other experienced disruptions. The child's developmental disruption may be (at least partly) the consequence of chronically induced stress which is known to have detrimental effects on brain activity, emotional well-being and development.

In the U.S.A., 50% of 12 month olds and 60% of 24 month olds regularly attend some form of child care. Schoore suggests that leaving such young children in sometimes

sub-standard early day care, with some even at 6 weeks old or less, is leading to the large increase in child psychopathology in 2016 in the U.S.A. 20% of children have a diagnosable psychiatric disorder and 10% have a mental illness severe enough to impair everyday living. Putting such young children into child care is highly stressful for the parents also, who are filled with conflicting emotions. This is just at the very time that infants and mothers are developing their secure attachment.

Shore's review of attachment in the children of the U.S.A. is based on their laws which allow working mothers to return to work when their child is only 6 weeks old. He is calling for an increase to 6 months maternity leave and 2 months paternity leave. Unlike the rest of the industrialized world, the U.S.A. has a national policy which lacks support for parental leave. U.S.A. culture is now generating a significant increase in the amount of mental problems in its child, adolescent and adult citizens. With advances in the science, early intervention should be able to mitigate some of the negative effects on mental health in these citizens.

Howes and Olenick (1986) reported that boys are more adversely affected by lower quality care than girls. Research in 1998 found that boys, who experienced more than 30 hours per week of non-parental care, are more insecurely attached at 15 months old than girls in the same situation.

Schore ends this section by saying that current research is more focussed on developing the left-brain language skills and motor skills, whereas not enough research is being done for the earlier stages of the developing brain systems responsible for socioemotional and stress-regulating functions, which are the essentials to our wellbeing. Vernoit (2014) concluded that the most important childhood predictor of adult-life satisfaction is the child's emotional health followed by the child's conduct, and the least powerful predictor is the child's intellectual development. In other words, the factors which lead to good emotional health in a child are more likely to determine their future life-satisfaction.

4. External toxins affect the brain by inhibiting androgen-receptors.

Endocrine disruptors could be the cause of significant alterations to the normal surge of testosterone in the pre- and post-natal periods and are thought to be associated with hyperactivity, ADHD and schizophrenia. They have been found in higher concentrations in just these periods and can be transferred via the placenta from the mother as well as via the breast milk in post-natal periods. There is some evidence that the two sensitive periods may have a cumulative effect. The effect of these chemicals to the child is happening later in their life. The symptoms include impaired social behaviours such as autism, ADHD and oppositional defiant disorder (Miodovnik *et al.*, 2011). Industrial chemicals that injure the developing brain are among the known causes for this rise in prevalence (Grandjean and Landrigan, 2014).

Endocrine disruptors work by binding to and inhibiting androgen-receptors which are particularly abundant in the amygdala. They may cause plasticity in the synapses in certain important circuits, and give rise to abnormal amygdala structure. They are thought to be man-made compounds, used in some plasticisers and in agricultural

pesticides (insecticides, fungicides and herbicides). They are now widespread in air, water and in the ground, meaning they have become ubiquitous.

Conclusions

Boys are more at risk from:- stress-induced cortisol whilst in the womb, lack of maternal attachment if their mother has mental health problems, lack of attachment in poor day care, chronic levels of cortisol in long hours of day care and toxins in the mother's food and drink during pregnancy or during breast-feeding (including residues of environmental toxins in food). These are all particularly problematic during the periods of testosterone surges. Boys are therefore consequently more at risk of damage to the amygdala, slower growth of the right brain, pruning of essential right brain circuits, mis-regulation of the HPA axis, reduction of eye to eye contact and empathy. They are more prone to externalising behaviours of aggression, and diagnosable male-dominant neurodevelopmental disorders such as autism and schizophrenia. They are also more prone to psychiatric disorders such as ADHD and oppositional defiant disorders. By the age of 7 to 12, girls may be as much as 2 years ahead of boys in the development of social sensitivity. The delay continues into adolescence, but boys are able to catch up during adulthood.

Male and female brains differ in emotional processing; men's sensations are rooted in the outside world whilst women's sensations are from within the body. Ingallhalikaar *et al* (2014) demonstrated that male brains are structured to facilitate connectivity between perception and co-ordinated actions, as opposed to female brains that are designed to facilitate communication between analytical and intuitive processing modes; they also noted that male brains are optimised for communicating within hemispheres and female brains for communication across hemispheres. Schore concludes that adult male and female brains have adapted to be complementary.

It has been established that postnatal changes in epigenetic programming of the infant's brain are directly linked to maternal behaviour towards the child. Stress from the social environment, embedded within the maternal-infant relationship, activates epigenetic modifications.

Further Notes on scientific terms:

(1) The HPA axis is the hypothalamus and the pituitary (next to each other in the brain) which secrete corticotropin-releasing hormone and adrenocorticotrop hormone respectively, which then act on the adrenal gland (on the kidneys) to produce glucocorticoid hormones such as corticosterone and cortisol. Through a negative feedback, glucocorticoids act on receptors in the hypothalamus and pituitary to suppress adrenocorticotrop hormone and cortico-releasing hormone secretion.

(2) The HPG control centre is the hypothalamus, pituitary and gonadal endocrine system. This system controls the body's balance of testosterone (also called androgen) and oestradiol (oestrogen). Gonadotropin-releasing hormone, released by the hypothalamus causes the

pituitary gland to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH) which are gonadotropins. LH is released into the bloodstream where it travels to the male testes or female ovaries and triggers the production of testosterone from the starting chemical cholesterol. If the level of testosterone becomes too high, there is a feedback mechanism, the pituitary slows down the release of LH so the production of testosterone slows down. Similarly, FSH is involved in the up- and down-regulating the production of sperm. This system can influence human gender development and influences social, emotional and stress-regulating differences between the genders.

(3) Epigenetic modification is heritable changes in gene expression that occur without a change in DNA sequence. At the molecular level, epigenetic events belong to three major classes: DNA methylation, covalent histone modification and non-coding RNA. Epigenetic DNA Methylation determines gene expression and gene silencing during both the prenatal and postnatal periods.

(4) The Amygdala complex. The amygdala are two almond shapes structures, one in each hemisphere of the brain. The right amygdala appears larger in males and this is thought to be due to the larger number of testosterone receptors present. There is evidence for the recognition of faces to be controlled by the amygdala, and the size of the amygdala may be related to gender development as well.

(5) Avoidant attachments. This is when the child will keep quiet rather than make a fuss when they need help because they are afraid of their main care giver. They get comfort by being near the carer but not giving eye contact to them. The avoidant attachment style is formed when parents or caregivers are unavailable, preoccupied, or disinterested. Children with unresponsive or disinterested parents feel as if they aren't important and learn that their needs won't be met. So they bury their needs, rely solely on themselves, or act as if they don't have any needs.

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