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Understanding well-being in the evolutionary context of brain development

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Much of the work on well-being and positive emotions has tended to focus on the adult, partly because this is when problems are manifest and well-being often becomes an issue by its absence. However, it is pertinent to ask if early life events might engender certain predispositions that have consequences for adult well-being. The human brain undergoes much of its growth and development postnatally until the age of seven and continues to extend its synaptic connections well into the second decade. Indeed, the prefrontal association cortex, areas of the brain concerned with forward planning and regulatory control of emotional behaviour, continue to develop until the age of 20. In this article, I consider the significance of this extended postnatal developmental period for brain maturation and how brain evolution has encompassed certain biological changes and predispositions that, with our modern lifestyle, represent risk factors for well-being. An awareness of these sensitive phases in brain development is important in understanding how we might facilitate secure relationships and high self-esteem in our children. This will provide the firm foundations on which to develop meaningful lifestyles and relationships that are crucial to well-being.

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1. BRAIN EVOLUTION

Allometric scaling and a large comparative database of mammalian brains have enabled assessments of brain evolution based on the widely accepted assumption that modern-day phylogenies represent evolutionary progression (Harvey & Pagel 1991). Most hypotheses of brain evolution have suggested that larger brain size correlates with greater cognitive ability, and selection pressures for such abilities have come from ecological variables where the knowledge of available food sources in time and space requires complex cognitive maps. Equally important has been the complex nature of social life, especially in primate mammals, and the cognitive skills required to process and store this social information. Although the size of the brain as a whole has been linked to different mammalian lifestyles or ecological features, this approach fails to take into account the different functions served by its component parts. For example, the hippocampus is concerned with processing spatial information and is remarkably enlarged in species which store and hide food, whereas the neocortex is enlarged in social living primates, with those living in larger groups having the larger neocortex (Dunbar 1992). Certain areas of the mammalian limbic brain (hypothalamus, amygdala, medial pre-optic area) are important for primary motivated behaviour such as maternal care, feeding, sexual and aggressive behaviour (Keverne 1985). These areas of the brain are under strong hormonal and visceral influences and in small-brained mammals are primarily activated by olfactory cues. Most mammals show maternal care only after exposure to the hormones of pregnancy and parturition, while sexual behaviour responds to the demands of the gonadal hormones that determine sexual motivation. However, large-brained human and non-human primates are spontaneously maternal, while most sexual activity is non-reproductive and emancipated from gonadal determinants in humans. How then have these differing behavioural control mechanisms been influenced by evolutionary changes in the brain and how do they impinge on subjective well-being?

While certain regions of the primate 'executive' brain have expanded relative to the rest of the brain, regions of the brain that regulate primary motivated behaviour (hunger, sex, aggression, maternal care) have become reduced in size (Keverne *et al.* 1996). Areas of the cortex that are concerned with forward planning have increased exponentially whereas those regions that respond to gonadal and visceral hormones have decreased in size. This does not mean that motivated behaviour has also declined in large-brained primates, but the controlling mechanisms for the behaviour have shifted away from tight linkage with physiological determinants in favour of deployment of cognitive behavioural strategies (Keverne *et al.* 1996).

The evolutionary remodelling of the mammalian brain has provided increased executive control of behaviour, while concomitant decreases in certain limbic areas have produced a degree of emancipation in human behaviour from hormonal determinants. Human sexual activity is not contingent on oestrus, maternal care readily occurs without the hormonal priming of pregnancy, and feeding behaviour in affluent societies is driven by habit more than by hunger. This evolution from biological to cognitive regulation of behaviour has required considerable increases in executive brainpower, which, because of the limiting capacity of the uterine placenta and birth canal, has been achieved by the

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postponing of substantial brain growth to the postnatal period. This, in turn, has required extended maternal care that goes well beyond the weaning period. Such executive brain control over behaviour not only permits a mother to extend her caregiving beyond lactation but also enables fathers, older siblings and grandparents to participate in this behaviour. However, only the mother has components of both the biology and cognition, thereby facilitating her caregiving and bonding for the infant.

2. CHILD DEVELOPMENT

As young children develop, their knowledge base expands, especially in regard to the changing ways in which their mother responds to them and, what is more important, how each is likely to respond to the other (e.g. Stevenson-Hinde & Verschueren 2002). Not surprisingly, the infant's executive brain and its connections are undergoing active growth during this same period. Indeed, the evolution of a large neocortex, which develops extensively in the postnatal period, has required an extended interdependence of mother and child and would not have been possible if parental care had ceased at weaning. The child's knowledge base steadily becomes organized in the form of internal working models of self and mother, encompassing an understanding of both her moods and intentions. Building on this early knowledge provides the infant with an ability to simulate happenings in an expanding world of relationships. Forward planning may occur with all the advantages gained, and because these working models are in constant daily use, their influence on thought, emotions and behaviour becomes routine and all-pervasive (Fonagy *et al.* 2002).

In the realm of socio-emotional development, the measurement of security of infant–parent attachment has proved a powerful predictive source of future competence in later life (Denham *et al.* 2002). From the perspective of developmental psychopathology, there are several ways in which to view the relationship between attachment and subsequent clinical disturbance. Anxious attachments may be conceived as a risk factor for subsequent socio-emotional problems. Attachment theory predicts that by middle childhood the internal working models relate to coping strategies evoked to deal with situations where distress and insecurities are aroused. Children classified as secure are more likely to seek help from others than are children classed as insecure. Anxious attachments predict more difficult, aggressive peer relationships and few good, close friends. Although inadequate peer relationships in middle childhood have been identified as a sturdy predictor of adult maladjustment (Sroufe *et al.* 1999), the expansion of the child's social world has undoubtedly been made easier by having a secure base from which to explore this world (Bretherton & Munholland 1999).

It is also important to note that in these early years of child development, when the neocortex is forming and making connections and associations with other parts of the brain, the limbic emotional brain is already well developed. The overt expression of a large emotional repertoire in young infants bears testimony to this. Understanding emotions, curbing these emotions, and channelling these emotions for beneficial purposes must represent an important phase in brain maturation. Equally important has been the interplay of emotions with cognitive development, which has undoubtedly prospered from the exaggerated expression of emotions between mother and child. The child's need for an attachment figure and the mother's predisposition to bond provides an optimal social environment in which the human executive brain can develop.

The nature of adaptive social functioning changes throughout development and these changes are accompanied by parallel reorganizations of ways to deal with emotional issues (Denham *et al.* 2002). Young children must learn to control the disorganization that stems from a tantrum and to think effectively about a distressing situation, while development of a wider social network introduces the need to meet social expectations of persons other than their parents. Managing how and when to show emotion becomes paramount, as does knowing with whom emotional experiences can be shared. Conversation assumes particular importance, and replaces the more overt behavioural emotionality. Older and wiser parents provide the foresight whereby immature brains can learn and develop strategies for regulating emotions. Children develop their emotions from parental interactions and are exquisitely attentive to parental reactions. This may, of course, contribute to weaknesses as well as strengths in emotional development.

3. MECHANISMS UNDERPINNING BEHAVIOURAL DEVELOPMENT

What do we know about the brain at a mechanistic level that might help us to understand how certain early life events or stressors may shape its developmental organization? There is considerable support for the concept of the long-term effects of developmental stress from experimental animal studies. Even in the small-brained rat, single 24 h periods of maternal deprivation in neonates, or recurrent periods of 3 h of maternal deprivation during the first 10 days of life, can result in a long-lasting alteration in stress hormones (corticosteroids) and increased anxiety-like behaviour in a range of test situations (Ladd *et al.* 1996; Caldji *et al.* 1998). In addition to the neuroendocrine and behavioural alterations, neonatal rats experiencing the 3 h repeated maternal deprivation are more likely to adopt cocaine and alcohol self-administration later in life (Ploj *et al.* 2003). Adult rats reared in this way can be treated with serotonin-selective antidepressants. However, discontinuation of the antidepressants results in the re-emergence of addictive behaviour and endocrine alterations, illustrating the long-lasting and persistent nature of these early separations.

Naturally occurring variations in maternal behaviour by rats such as licking, grooming and nursing are associated with individual differences in both behavioural and hypothalamic–pituitary responses to stress in their infants (Francis *et al.* 1999). Mothers that score high on these maternal behaviours have offspring that are less fearful, and are less susceptible to stress, compared with infants whose mothers perform these maternal behaviours at low levels. Cross-fostering studies show that it is the maternal phenotype that influences the stress responsiveness in offspring, suggesting that the style of maternal behaviour can serve as a mechanism for differences in stress reactivity across generations (Meaney 2001).

The early development (first 10 weeks) of monkey social behaviour occurs predominantly in the context of interactions with the mother. These early social interactions are almost totally under the mother's control in terms of both the amount and kinds of interaction permitted. By 40 weeks of age, infants are considerably more independent from their mother, and much of their behaviour is oriented toward peers. Nevertheless, mothers continue to monitor their infants and quickly intervene in response to risks arising during play (Simpson *et al.* 1989). The mother serves as a secure base from which the infant can obtain contact and grooming while developing and strengthening its social bonds with peers and other kin.

Administration of opioids has been shown to reduce the distress shown by infants of various species when separated from their mothers. For example, the opiate agonist morphine reduces distress vocalization rates in chicks, puppies and rhesus monkeys (Panksepp *et al.* 1997). Processes involving endogenous opioid reward may therefore underlie infant attachment and this has been investigated in young rhesus monkeys given acute treatment with the opioid receptor blocker, naloxone, and observed in their natal group (Martel *et al.* 1995). Naloxone increases the duration of affiliative infant–mother contact and the amount of time the infant spends on the nipple. This occurs even at 1 year of age when the mothers are no longer lactating. Indeed, feeding is unaffected by naloxone treatment of infants, but play activity decreases and their distress vocalizations increase. Whereas the opiate agonist morphine reduced distress in the absence of the mother, the opiate antagonist naloxone promotes distress, but in the presence of the mother the infant seeks solace by tactile social contact with her. These results may be interpreted in terms of opiate receptor blockade reducing the 'positive affect' that accrues from having developed an attachment relationship with the mother, as a result of which the young infant returns to its mother as an established secure base. Moreover, the opioid system of both infant and mother coordinates intimate contact during reunion (Kalin *et al.* 1995).

4. MATERNAL BONDING

Bowlby himself was interested in evolutionary biology and was struck by the imprinting work on birds by Conrad Lorenz, which influenced his own thinking about 'sensitive periods' for human infant development. If, as Bowlby suggested, an infant's attachment behaviour evolved jointly with maternal care-giving behaviour (George & Solomon 1999), then there is a possibility for these sensitive periods during infant attachment and maternal bonding to have common underlying mechanisms.

In most mammals, the female is committed to the major share of parental care. By virtue of internal fertilization and viviparity, the female mammal commits considerable time and resources to the developing offspring. The placenta, a lifeline for the developing foetus, produces hormones that increase maternal food intake, shut down sexual motivation, prime the brain for maternal care, and prime the mammary gland for milk production contingent on the timing of birth. These aspects of maternalism are an integral part of physiology, which not only provide for the developmental energetic requirements of the offspring but also have the capacity to physiologically plan ahead for the post-partum needs of lactation. The onset, sustainability and termination of maternal care are, therefore, tightly locked into maternal physiology and synchronized with the mother's ability to provide nutrient until the offspring is able to fend for itself.

This well-established biology has undoubtedly formed the foundations for mammalian reproductive success, but raises the question as to what has happened in the brain when the maternal behaviour of human and certain non-human primates is unlocked from this biology. The hormones of pregnancy and parturition are, at best, produced only until the termination of lactation, whereas human parental as well as alloparental care may extend well beyond this period. Moreover, female human and non-human primates are very motherly toward infants without even being pregnant. What makes this behaviour so rewarding and fulfilling when it is not determined by the hormones of pregnancy, and are the subserving neural changes that are so important for well-being also available for subversion with the changing lifestyle which we now live?

5. OPIOIDS AND MATERNAL BONDING

It has been suggested that the activation of the endogenous opioid system at parturition and during suckling promotes the positive affect arising from maternal behaviour. In the early post-partum period, a mother's social interactions are almost exclusively with her infant and opiate receptor blockade in mother has marked effects on this relationship.

Studies on naloxone treatment of post-partum rhesus monkey mothers living in social groups have addressed the importance of opioids in maternal bonding. Naloxone treatment reduces the mother's care-giving and protective behaviour shown toward their infants. In the first weeks of life when infant retrieval is normally very high, naloxone-treated mothers neglect their infants and show little retrieval even when the infant moves a distance away. As the infants approach eight weeks of age, when a strong grooming relationship normally develops between mother and infant, mothers treated with naloxone fail to develop a close grooming relationship. Moreover, they permit other females to groom their infants, while saline-treated control females are very possessive and protective of their infants (Martel *et al.* 1993).

The infant is not rejected from suckling, but a mother's usual possessive preoccupation with the infant declines with opioid receptor blockade. Mother is not the normal attentive care-giver, and mother–infant interactions are invariably infant initiated. Primates and other mammals both have in common opioid involvement in maternal care, but the consequences of opioid blockade in small-brained mammals are much greater for the biological aspects of maternal behaviour. In rodents and sheep, for example, interference with the endogenous opioid system severely impairs maternal behaviour, including suckling, whereas monkeys neglect their focused preoccupation with infant care but still permit suckling. These differences may reflect the degree of emancipation from endocrine determinants that maternal behaviour has undergone in primates, and the increased importance of 'emotional reward' for the bonding mechanism. If the endogenous opioid system in the monkey is positively linked to mother–infant bonding

then heroin addiction, which acts at the same opioid receptor, would be predicted to have severe consequences for human maternal bonding. Women who are heroin addicted have many aspects of their social and economic life disrupted, making the data difficult to disentangle. Nevertheless, the facts are that by 1 year of age almost 50% of such children are living away from their biological mothers, and by school age only 12% remain with their biological mothers (Mayes 1995). These infants have been abandoned for adoption or are taken into the care of their grandparents and other female kin. Moreover, in a follow-up of 57 methadone-maintained mothers compared with controls matched for ethnicity, socio-economic status, infant birth weight and gestational age, opiate-addicted mothers were far less likely to have remained the child's primary parent and the children were significantly more likely to have been referred to child protective care or special service agencies for neglect, abandonment or abuse.

Integral to the bonding process in large-brained primates is the endogenous opioid system, which has been shown to act on receptors in the ventral striatum (Koob & Le Moal 1997). This area of the brain is involved in 'reward' and involves the mesolimbic dopamine projection, which detects rewarding stimuli and also detects ways in which they occur differently from prediction to enable 'updating' of the stimulus (Schultz & Dickinson 2000). The mother–infant bonding process entails obsessive grooming, especially to hands, face and genitalia by mothers, and these are the phenotypic traits of infant monkeys that show the greatest changes during development. Because primates show extended post-partum care, offspring recognition requires the continual updating of any changes in these morphological features and in behavioural development. This updating of infant recognition probably involves prefrontal–ventral striatal pathways, which are also intimately linked to the emotional brain via the amygdala. The positive emotional responses that infants generate in females enable parental care to occur without the continual priming by pregnancy and parturition.

Human mothers also experience preoccupations and rituals in the context of maternal care, and even before the birth of their baby they are obsessive with cleaning and creating a safe environment. After birth, safety is a major concern and mothers frequently check on their baby even at times when they know the baby is fine (Leckman *et al.* 1999). The evolution of these obsessive psychological and behavioural states can be seen as a developmental extension of the preoccupations that all primates show for their infants. Interestingly, areas of the human brain that have been shown, using MRI, to be responsive to babies crying, include the brain's reward structures (mesolimbic dopamine from the ventral tegmental area, ventral striatum and amygdala; Lorberbaum *et al.* 2002).

The evolutionary progression away from hormonal centric determinants of maternal behaviour to emotional, reward-fulfilling activation involves dopaminergic and opioidergic activity in the ventral striatum. The enhanced role of this circuitry for regulating behaviour in humans may also provide vulnerability to various forms of psychopathology such as OCD and substance abuse. Mild forms of addictive behaviour (gambling, video games, Internet use, and consumption of caffeine and chocolate) are such indicators of this neurological predisposition for obsessive behaviour seen in humans (Greenberg *et al.* 1999), which are not conducive to well-being. OCD itself is characterized by intrusive thoughts and preoccupations, rituals and compulsions. *In vivo* neuroimaging studies identify the orbital frontal cortex, head of the caudate and closely associated ventral striatum and anterior cingulate as being involved in OCD (Rauch 2000), while acquired OCD occurs later in life in patients with striatal lesions (Chacko *et al.* 2000). There is also evidence that cerebrospinal fluid levels of the neuropeptide oxytocin are elevated in OCD, and this peptide also plays a fundamental role in many obsessive aspects of maternalism (Leckman *et al.* 1994). Not surprisingly, therefore, OCD is more common in women, and female OCD probands have a higher rate of relatives with OC spectrum disorders. The influence of gonadal hormones on periodicity of OCD (Weiss *et al.* 1995) and the post-partum exacerbation of OCD symptoms in women suggest that the course of this disorder may be influenced by the hormones of pregnancy (Williams & Koran 1997). Moreover, psychological challenges directed at the PFC are predictive of severity of OC symptoms in female patients and this predictive value discriminates between males and females (Zohar *et al.* 1999). OCD is less common in males although the obsessional behaviour of males, especially in the post-pubertal period when first experiencing romantic love, shows remarkable similarities with mother–infant love (Leckman & Mayes 1999). Hence, there are components of behaviour that occur in the post-pubertal and post-partum period that are influenced by hormones, but interestingly they relate to areas of the brain concerned with reward and not motivation.

6. PUBERTY AND BEHAVIOURAL DEVELOPMENT

Puberty is a vulnerable period for the development of numerous behavioural problems including eating disorders, OCDs, addictive disorders, onset of depression and, in some cases, suicide. What is happening in the brain at puberty that makes this a special developmental period for consideration, and why do these problems appear to be occurring both more frequently and at a progressively younger age (Fombonne 1998*a*) than in previous generations?

In early and middle adolescence there is a marked increase in the symptoms of depression, and this is more prevalent in girls than boys (Grant & Compass 1995). Increased instability and higher demands, both in society and within families, have been proposed to play important etiological roles explaining increased prevalence rates of depressive conditions among young people in recent decades (Goodyer 1995). Chronic daily stress and daily aggravation have been strongly associated with depressive symptoms among adolescents, with girls reporting more interpersonal stressful events than boys. In an extensive study of psychosocial correlates of depressive symptoms in 12–14-year-old adolescents, daily hassles (e.g. someone criticized me), stressful life events especially at school, gender and lack of friends correlated very strongly with depressive symptoms (Sund *et al.* 2003). In adolescents, identity formation and self-esteem are central issues in psychological development, and having more than four close friends seems to be protective against the development of depressive symptoms.

Several studies in recent years have revealed an earlier age of onset for psychosocial disorders, with most of these disorders starting in early adolescent years (Joyce *et al.* 1990). Findings over the past three decades have also revealed a progressive increase in disorders and a progressively earlier age of onset. It is paradoxical that at a time when economic conditions and physical health are improving, psychosocial disorders of youth are also increasing in most developed countries (Fombonne 1998*a*). Of even more concern is the finding that many of the psychiatric disorders that have an onset in adolescence have a strong continuity with adult disorders (Fombonne 1998*b*).

Considerable clinical literature has evaluated the possible impact of early and ongoing psychosocial stress in the onset and recurrence of unipolar and bipolar affective disorders. In a population of 258 patients who were followed prospectively with clinical assessments, those with a positive history of early adversity (physical or sexual abuse) not only experienced an earlier onset of bipolar illness and more suicide attempts, but these patients were relatively more treatment resistant in the prospective follow-up (Leverich *et al.* 2002). Puberty has always been a life event that produces a challenge for well-being, but why is it becoming more of a problem? Can we attribute these problems to failures in early development, or does the protracted developmental period produce problems in its own right that are exacerbated by modern lifestyles?

7. PREDISPOSING FACTORS FOR EARLY PUBERTY ONSET

One major difference in human reproduction and in that of other mammals is the extended developmental period between birth and puberty. In the mouse this is *ca*. 40 days, in the monkey it is 2–3 years and in humans at the start of the twentieth century it was *ca*. 16–17 years. This long interval between birth and reproductive age enables the brain to mature in its ability to establish and manage peer relationships, to regulate emotions, and through knowledge of self, gained by experience, to develop high self-esteem. On the basis of secure attachment, the extended period from infancy to puberty, longer for humans than for any other primate, has enabled the expansion of social relationships, which provide a buffer for regulating the emotional turmoil of puberty.

In the past 100 years there has been a significant trend towards early puberty in boys and early menarche in girls. The age at which girls first menstruate has decreased from 16–17 years, according to records for Norway, Germany, Finland and Sweden (Tanner 1966), to between 12 and 13 years in modern-day populations. Healthcare and socio-economic living standards have improved during this time, and of particular importance has been nutrition. Body weight, and notably body fat signalled to the brain via the hormone leptin, is a critical factor in the onset of puberty in many mammalian species (Apter 2003). Evidence in support of this viewpoint in humans is abundant (Biro *et al.* 2003; Klentrou & Pyley 2003). Malnutrition is associated with delayed menarche while moderately obese girls experience earlier menarche than lean girls. Amenorrhoea is common in ballerinas, who tend to be at the low end of fatness, and also in female athletes who may have greater than normal lean body mass but almost undetectable levels of fat. Hence, it would appear that for humans, like other mammals, body size and fat reserves that are sufficient to deal with the energetic demands of pregnancy are a signal for the brain to commence the neuroendocrine cascade that initiates puberty. The trend towards obese phenotypes in recent decades is likely to have contributed to this shortening of childhood and early puberty onset (Shalitin & Phillips 2003). It is certainly the case that body fat at age five predicts earlier pubertal development among girls at age nine (Davison *et al.* 2003).

8. BRAIN DEVELOPMENT AT PUBERTY

Longitudinal studies of brain development from childhood through to adolescence have shown that the volume of white matter (myelinated nerve fibres) increases linearly between 4 and 22 years of life (Sowell *et al.* 1999, 2001*b*). Changes in the volume of cortical grey matter (neural cell bodies) are nonlinear and regionally specific. In the frontal lobes, grey matter increases to maximum at puberty (age 12.1 years in males, 11 years in females) and is followed by a decline during post-adolescence. Temporal lobe grey matter development is also nonlinear and peaks at 16.5 years. In contrast to non-human primates, development of the human neocortex is non-synchronous, with changes occurring in the visual and auditory cortex long before those in the frontal and temporal cortex. The pre-adolescent increase and post-adolescent decrease in prefrontal cortical grey matter are also shown in positron emission tomography studies of glucose metabolism and in electroencephalographic studies. Electrocortical recordings of the brain indicate a wave of synaptic proliferation in the frontal lobes around the age of puberty. If this increased frontal cortex activity is related to a wave of synaptic overproduction, it may herald a stage of pubertal development when psychosocial and emotional activities guide selective synapse elimination during adolescence. *In vivo* structural imaging studies (high-resolution MRI) from childhood to adolescence (age 12–16 years) have shown an inverse relationship between the reduction of grey matter and increased brain growth, particularly in areas of the frontal cortex that control executive cognitive functioning (Giedd *et al.* 1999). These events are thought to represent the loss of neurons that fail to make appropriate connections (synaptic pruning) and progressive myelination of neural connections that do make appropriate connections. This frontal cortex remodelling is also associated with improved memory functioning (Sowell *et al.* 2001*a*).

Frontal cortex grey matter peaks 1 year earlier in females than in males, corresponding to the earlier age of puberty onset. Studies have revealed significant sex-by-age interactions in cerebral grey and white matter volumes and suggest that there are age-related sex differences in brain maturational processes (De Bellis *et al.* 2001). In tests of emotional cognition, where subjects were required to make a decision about emotion expressed in a face or a word or both, reaction times slowed significantly at the onset of puberty and stabilized by 15 years of age. Girls started to react more slowly a year before boys, and had longer reaction times between the ages of 15 and 17 years, but this sex difference was transient and not present in 18–22-year-olds (Bremmer *et al.* 2001). It is also noteworthy that while adults relative to adolescents are better able to engage the

orbitofrontal cortex (executive brain) when required to attend to different facial expressions, adolescents relative to adults exhibit greater modulation of emotional circuitry (amygdala, ventral striatum, anterior cingulate and frontal cortex) based on these same tasks (Monk *et al.* 2003). This emotional circuitry is rich in opioid receptors.

Studies show the effects of opioid receptor blockade on attachment in infant monkeys (already described) to be the same in males and females, such that both increase their contact time with their mother. At puberty, however, feral males tend to leave their natal social group whereas females stay with the group. This type of social organization in Old World monkeys, where females remain with the group, is referred to as being 'female bonded'. Why do we find this sex difference in social bonding, and if the mechanisms serving infant attachment extend to social bonding why should it differ between males and females? In males entering puberty, opioid receptor blockade results in significant increases in the time these males spend with mother and decreases the time they spend with others. At the same age, females tend to spend more time alone than males, but when subjected to opioid receptor blockade they spend more time with other females, not with their mother (Keverne *et al.* 1997). This suggests that female monkeys have a predisposition to develop other socially meaningful relations and have expanded their secure base beyond their mother, although these social relationships are invariably with matrilineal kin. Post-pubertal males running to their mother would not be favourably tolerated by dominant males, would invite aggression and hence the peripheralization and subsequent mobility of young males from the natal social group. In this context it is interesting that synthetic androgenic steroids increase opioid activity in the ventral striatum, hypothalamus and peri-aqueductal grey brain regions which regulate dependence, defensive reactions and aggression. The attachment that rhesus monkey infants develop with the matriline is especially enduring in females, lasting a lifetime, whereas in males it rarely lasts beyond puberty.

Puberty is undeniably a period of great emotional turmoil when changes in physical phenotype synchronize with reorganization of the PFC, an area of the brain intimately concerned with emotional regulation and forward planning. The fact that girls are likely to experience psychological problems earlier than boys may be related to the consistent findings that they enter puberty earlier, and also undergo the developmental changes in the brain earlier. A major change in the past few decades has been an even earlier onset of puberty in boys and girls as a result of better nutrition. Whether this earlier onset of puberty is responsible for the progressively earlier symptoms of psychological disturbance needs more rigorous study. It is certainly the case that more body fat in girls at 5 years of age is predictive of early puberty at 9 years (Davison *et al.* 2003), and it is also the case that we are seeing unprecedented increases in childhood obesity. The human body and brain have evolved in synchrony for millions of years. Is the maturation of the body phenotype becoming out of phase with brain development or prematurely precipitating brain maturation? If so, does this underpin vulnerability to adolescent disorders of the psyche?

9. FUNCTIONAL BRAIN DEVELOPMENT IN AN EVOLUTIONARY FRAMEWORK

Our mammalian ancestors gained mobility and the possibility of exploring land environments away from water by virtue of ovoviviparity, which entailed internal fertilization, placentation, and the ability to protect offspring from predators by transporting them internally. There was an inherent need to plan ahead, in the sense that increased food intake early in pregnancy enabled reserves to be laid down to meet the extra demands of the exponential growth of their offspring later in pregnancy, and for the production of milk needed for post-partum lactation. This investment of time and energetic resources throughout pregnancy ensured the female is biologically committed to maternal care and to provision her offspring with food and water (milk) and warmth until they became independently able to regulate thermogenesis and forage for themselves. Most female mammals spend many weeks or months engaged in maternal care but a very few hours of their lives engaged in sexual behaviour.

Both pregnancy and post-partum care are regulated by neuropeptides and hormones, but an important difference between these hormones and those that regulate other aspects of behaviour has been established for the hormones of pregnancy that prime the brain for maternal behaviour. These are produced or regulated by the foetal placenta, while the infant's post-partum suckling sustains this behaviour by activating neural pathways to those brain areas primed by hormones during pregnancy. The sequence of events that represent maternalism are an exquisite piece of biology determined by hormones acting in the mother that are under the control of the foetal genome.

A major progression across mammalian evolution has been the massive increase in brain size relative to body size. This has required some important adjustments in the biology, not least of which are those involved with the mother–infant relationship. Brain is limited in its growth within the mother because of size constraints of the uterus and birth canal. Hence, in those primate mammals that have the largest brains, much of the brain and body growth is postponed to the postnatal period. This extensive postnatal growth and development of the brain, especially in humans, requires extended maternal, paternal and alloparental care. Breaking the link in the chain that binds maternal care to hormonal mechanisms has required extensive modification in the mother's brain, while the infant's brain, by virtue of postponing much of its development to the post-partum period, has constructed a niche for itself that transforms the evolutionary dynamic. Much of the brain's connectivities that are made during the postnatal period are under epigenetic control. The multiplicity of axonal projections and synaptic connections made in the brain are determined not by any specific genetic programme but by activity in other neurons, and many of the misconnections that are hence inevitably made are eliminated by programmed cell death. In this way, human brain development comes under the prolonged influence of the postnatal social environment in which the infant is reared.

Mother and infant behaviour have evolved as a unit. While the mother's brain has been maternalized by the hormones of pregnancy generated by the foetus, the infant's developing brain requires social stimulation from a mother committed to providing the emotional rewards of warmth

and suckling. Not only do infants have to learn to sit, stand and eventually walk and talk, but they also have to learn social rules and emotional control. It is clear that the process of infant socialization benefits from this close relationship, but whether this occurs during a critical period in brain development is open to question. We know, for example, that the ability to learn language arises from a synergy between early brain development and language experience and is seriously compromised when language is not experienced early in life (Mayberry *et al.* 2002). It is, therefore, probably safer to think of this whole early developmental period as critical, but modifiable while the brain remains in a plastic state. The synergy between early brain development and the learning of social rules is also likely to be compromised when the developing infant–mother relationship is compromised early in life. Certainly, mother–infant separations in monkeys are known to have long-term consequences (Hinde *et al.* 1978) and extreme consequences for infant abuse when infants are separated from their mother and reared with peers (Harlow & Harlow 1965; Kraemer & Ebhert 1991). However, provided we are able to recognize developmental problems and provided they are not too traumatic, the plasticity of the developing brain may provide for remedial action. Humans tend to worry about the uterine environment and toxic agents or drugs, which may damage the fingers and toes of babies, but perhaps we should pay more attention to the postpartum period when the social environment exercises its effects on the developing brain and lays down the foundations for future well-being.

10. PREFRONTAL CORTEX

A second major evolutionary event unique to the hominid brain has been the extended development of the PFC and its connections with the striatum (dorsal and ventral) and the cingulate cortex. The pattern of brain maturation in the post-adolescent period is distinct from earlier development and is localized to large areas of the dorsal, medial and orbital frontal cortex together with striatum (Sowell *et al.* 1999). This patterning of development elucidated from using MRI is supported by post-mortem studies of the brain and the development of cognitive functions attributed to these structures. Neuropsychological studies show that these regions of frontal cortex are essential for such functions as forward planning and organization, emotional regulation and the ability to block a habitual behaviour and execute a less familiar behaviour. The latter function depends on the lateral PFC and the anterior cingulate cortex. The anterior cingulate is thought to detect conflicts between plans of action, and in response to these conflicts the anterior cingulate recruits greater cognitive control in the lateral PFC (Bolvinick *et al.* 1999). An important question about the nature of cognitive control is how the processes involved in implementing control become engaged. Recent studies, using MRI, have demonstrated that conflict-related activity engages both greater PFC, preceded by activity in the anterior cingulate, which consequently provides for adjustments in behaviour. These findings support a role for the anterior cingulate in conflict monitoring and the engagement of prefrontal cognitive control (Kerns *et al.* 2004). Forward planning inevitably depends on learning experiences, especially those experiences that have proved rewarding in the past, while decision-making sometimes depends on 'gut feelings' that are linked with visceral brain connections to the amygdala. The amygdala may be viewed as providing an emotional bias to fronto-striatal projections that represent the neural substrates that serve for brain reward (Damasio 1998). Patients with bilateral amygdala damage fail to show the normal emotional response to reward (Bechara *et al.* 1999), while the ventral striatal region responds to actual and anticipation of reward, and the frontal cortex codes for the value of reward (Temblay & Schultz 2000).

Neurophysiological studies in patients with orbital frontal cortex lesions suggest that the deficits in decision-making shown by these patients are attributable to impaired ability to evaluate the consequences of their actions (Bechara *et al.* 2000). Responses to reward in humans have been assessed in recent functional imaging studies and it is clear that brain areas involved in secondary rewards (e.g. financial reward) overlap with regions responding to primary rewards such as food. The amygdala, dorsal and ventral striatum and the dopaminergic ventral tegmental area respond to the presence of reward regardless of its value. However, the orbitofrontal cortex responds nonlinearly, being particularly responsive to the lowest and highest reward values (Elliott *et al.* 2003). This is consistent with a role for orbitofrontal cortex in coding the complex relative values of reward.

It is clear, therefore, that different regions of the PFC that are engaged in decision-making, forward planning and emotional control, undergo a surge of development modifications at puberty that continue throughout adolescence that are complete around the age of 20–22 years and are important for adult well-being. The PFC projects heavily to the striatum, both dorsal and ventral areas, which are important for calling into action motor patterns of behaviour aided by dopaminergic inputs from the midbrain (substantia nigra→dorsal striatum; ventral tegmental area→ventral striatum). The amygdala and anterior cingulate also interrelate with different components of the PFC (amygdala→medial PFC; anterior cingulate→lateral PFC). I have already described how parts of these neural interconnections get 'locked' into creating fixed or obsessive action patterns in the context of OCD. Moreover, this same circuitry is integral to disorders such as psychosis and depression, and is vulnerable to addictive drugs. Hence the human brain has evolved a circuitry that develops in the context of social well-being and is itself crucial to social well-being. Not surprisingly, this circuitry takes years to mature in the human brain, extending its vulnerability into the adolescent period.

11. SUBVERSION OF THE NEUROCHEMISTRY OF ATTACHMENT AND BONDING

I have already mentioned the role of endogenous opioids for bonding in monkeys and the negative consequences of opiate addiction on maternal care in humans. This raises the possibility that the same neurochemical systems that form the glue of social relationships become vulnerable to drugs of abuse.

Drug addiction can be understood in terms of normal learning and memory systems of the brain that, through the action of chronically administered drugs, are pathologically

subverted. Drug use becomes compulsive and is characterized by a pattern of drug seeking and consumption that become habitual and progressively less modified (Robbins & Everitt 1999; Everitt *et al.* 2001). Many drugs of abuse (heroin, cocaine, amphetamine, nicotine and alcohol) have the common action of increasing dopamine transmission in the ventral striatum. These common findings of drug action have led to a widely held view that the mesolimbic dopamine system has a general reinforcing effect of drugs that act in mediating aspects of natural reward. For example, rats will self-administer opiates to the ventral tegmental area from which dopamine neurons project, and opiates also seem to have reinforcing effects mediated by dopamine-independent mechanisms in the ventral striatum (Koob & Le Moal 1997). Dopaminergic neurons from the ventral tegmental area project to the ventral striatum, which responds to unpredicted rewards that, with training, transfer to stimuli predictive of reward. Thus, by signalling reward prediction errors dopamine may serve as an instruction for striatal learning in the context of hedonic reward (Schultz & Dickinson 2000).

In the real world, drugs are not freely available and the drug abuser has to attend to cues that predict their availability. Drug-seeking behaviour can become powerfully associated with environmental cues. This process of associative learning, by which particular places become connected with the euphoric drug-induced state, involves brain structures that have strong anatomical links to the ventral striatum. When addicts are allowed to see the paraphernalia associated with self-administration, several interconnected areas of the ventral striatum are activated, including the amygdala and frontal cortex (Everitt *et al.* 2001). Drug abusers often undertake ritualized preparation with the paraphernalia for drug administration that themselves become rewarding. This may lead to the people developing a drug-seeking habit, even when the euphoric effects that initially encouraged it are reduced.

Hence the neural circuitry, neurochemistry and obsessive behaviour associated with numerous forms of addiction (alcohol, drugs) appear to subvert those parts of the human brain that have evolved to subserve hedonic and social reward. Experimental rats can also be addicted to drugs such as heroin but I guarantee that we will never find an addicted rat in the wild. Clearly, they have the same neurochemical/neuroanatomical reward system, but missing from the rat brain is the prefrontal association cortex that is important for decision-making and forward planning and provides the means with which to make drugs available. Since these same parts of the brain enable planning ahead and rational decision-making then why do individuals, especially teenagers, make such destructive decisions over drug abuse? Is addiction more of a problem in Western adolescents because they are reaching the age of puberty well in advance of reaching the age of reasoning?

In the past decade, the significance of self-esteem has been identified in maintaining wellness among adolescents, and adolescents treated in clinical settings for drug use problems are often observed to have low self-esteem (Vega *et al*. 1996; Modrein-Talbott *et al*. 1998). Susceptibility to peer pressure and lack of family caring have also been associated with teenage drug abuse, while lack of social support and low self-esteem measures strongly correlate with remission of adolescent addiction (Richter *et al.* 1991). In other words, how teenagers rate themselves with respect to others (self-esteem) and how they want to be seen by others are strong predisposing factors for addiction at a time when their brain is immature and insecure in these social domains.

12. CONCLUSIONS

For thousands of years, our ancestors had to contend with finding food, which required cooperation, and rearing children, which also required cooperation. This cooperation was invariably within part of an extended family grouping and any small community encompassed relatively few relationships that needed to be handled and understood. Our brains matured at a leisurely pace and the collective knowledge of the community for achieving life's comforts and well-being was no greater than any one person might understand in their lifetime. Indeed, life was short and the outcome of decision-making was relatively short-term. Decisions as to how we obtain the next meal, how to optimize child survival and how we secure warmth and comfort required a degree of forward planning for which the rewards or failures were relatively short-term. Living was made easier by the reward values of correct decisions because these kinds of decision sustained life. In modern societies, individuals are required to make decisions about careers, marriages and financial security for old age and pensions. These are the most important decisions that we have to make; they are exceptionally long-term, and there is no guaranteed way of getting them right. The outcome depends on the decisions of others and events that are far removed from the control of the decision-maker. No one person, no one community or even one nation can understand the collective accumulated knowledge of mankind, let alone predict life's well-being when expectations have expanded way beyond the basic necessities of life. Living with such long-term decisions can produce anxiety and frustration, which is not conducive to well-being.

Even though we know eating makes us fat, technology has enhanced the reward value to the brain of food enhanced with hedonic flavourings, and the hormonal signals to inhibit overeating (leptin) are no longer effective in humans. Maternal care is dissociated from the hormones of pregnancy and parturition, and the emotional rewards of the developing parent–infant relationship have many competing new relationships that tap into this very same neural circuitry. Relationships are frequently changing due to moving home, moving school and family break-up, not to mention the thousands of fantasy relationships with which we become involved through television soap dramas. This saturation with real and fantasy relationships must be potentially confusing to the adolescent brain that is desperately trying to come to terms with a whole new dimension to relationships, namely sexuality. Long gone have been ancestral rituals associated with puberty and the collective sharing and participation of the community in these rituals. It is not surprising, therefore, that infatuated romantic love of today's teenagers takes on such obsessional qualities, often to the cost of previously meaningful relationships.

Evolving from a hormonal-centric to a cognitive-centric brain emancipated human behaviour from its own internal endocrine environment. Removing these biological restrictions to behaviour has enabled the cognitive brain not only to emancipate our lifestyle from the external environment

but also to create an artificial environment that caters for and satisfies its own hedonistic needs. The brain has become a victim of its own evolutionary success. Our future well-being depends upon understanding these vulnerabilities and changing lifestyles so that the caring of our children and the nurturing of relationships takes into account the predispositions that are imposed by our protracted brain development.

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REFERENCES

Apter, D. 2003 The role of leptin in female adolescence. *Ann. N. Y. Acad. Sci.* **997**, 64–76.

Bechara, A., Damasio, H., Damasio, A. R. & Lee, G. P. 1999 Different contribution of the human amygdala and ventromedial prefrontal cortex to decision making. *J. Neurosci.* **19**, 5473–5481.

Bechara, A., Tranel, D. & Damasio, H. 2000 Characterization of the decision-making deficit of patients with ventromedial prefrontal cortex lesions. *Brain* **123**, 2189–2202.

Biro, F. M., Lucky, A. W., Simbartl, L. A., Barton, B. A., Daniels, S. R., Striegel-Moore, R., Kronsberg, S. S. & Morrison, J. A. 2003 Pubertal maturation in girls and the relationship to anthropometric changes: pathways through puberty. *J. Pediatr.* **142**, 643–646.

Bolvinick, M., Nystrom, L. E., Fissel, K., Carter, C. S. & Cohen, J. D. 1999 Conflict monitoring versus selection-for-action in anterior cingula cortex. *Nature* **402**, 179–181.

Bremmer, J. D., Soufer, R., McCarthy, G., Delaney, R., Staib, L. H., Duncan, J. S. & Charney, D. S. 2001 Gender differences in cognitive and neural correlates of remembrance of emotional words. *Psychopharmacol. Bull.* **35**, 55078.

Bretherton, I. & Munholland, D. A. 1999 Internal working models in attachment relationships: a construct revisited. In *Handbook of attachment: theory, research, and clinical application. The caregiving behavioural system* (ed. J. Cassidy & P. R. Shaver), pp. 89–111. New York: Guilford Press.

Caldji, C., Tannenbaum, B., Sharma, S., Francis, D., Plotsky, P. M. & Meaney, M. J. 1998 Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. *Proc. Natl Acad. Sci. USA* **95**, 5335–5340.

Chacko, R. C., Corbin, M. A. & Harper, R. B. 2000 Acquired obsessive–compulsive disorder associated with basal ganglia lesions. *J. Neuropsychiat. Clin. Neurosci.* **12**, 269–272.

Damasio, A. R. 1998 Emotion in the prespective of an integrated nervous system. *Brain Res. Rev.* **26**, 83–86.

Davison, K. K., Susman, E. J. & Birch, L. L. 2003 Percent body fat at age 5 predicts earlier pubertal development among girls at age 9. *Pediatrics* **111**, 815–821.

De Bellis, M. D., Keshaven, M. S., Beers, S. R., Hall, J., Frustaci, K., Masalehdan, A., Noll, J. & Boring, A. M. 2001 Sex differences in brain maturation during childhood and adolescence. *Cerebr. Cortex* **11**, 552–557.

Denham, S., von Salisch, M., Olthof, T., Kochanoff, A. & Caverly, S. 2002 Emotional and social development in childhood. In *Handbook of child social development* (ed. P. K. Smith & C. H. Hart), pp. 307–328. Oxford: Blackwell.

Dunbar, R. I. M. 1992 Neocortex size as a constraint on group size in primates. *J. Hum. Evol.* **20**, 469–493.

Elliott, R., Newman, J. L., Longe, O. A. & Deakin, J. F. W. 2003 Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. *J. Neurosci.* **23**, 303–307.

Everitt, B. J., Dickinson, A. & Robbins, T. W. 2001 The neuropsychological basis of addictive behaviour. *Brain Res. Rev.* **36**, 129–138.

Fombonne, E. 1998*a* Increased rates of psychosocial disorders in youth. *Eur. Arch. Psychiat. Clin. Neurosci.* **248**, 14–21.

Fombonne, E. 1998*b* The management of depression in children and adolescents. In *The management of depression* (ed. S. Checkley), pp. 12–26. London: Blackwell.

Fonagy, P., Target, M., Gergely, G. & Jurist, E. L. 2002 *Affect regulation, mentalization, and the development of the self*. New York: Other Press.

Francis, D. J., Diorio, J., Liu, D. & Meaney, M. J. 1999 Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science* **286**, 1155–1158.

George, C. & Solomon, J. 1999 Attachment and caregiving. In *Handbook of attachment: theory, research, and clinical applications. The caregiving behavioural system* (ed. J. Cassidy & P. R. Shaver), pp. 649–670. New York: Guilford Press.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., Paus, T., Evans, A. C. & Rapoport, J. L. 1999 Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neurosci.* **2**, 861–863.

Goodyer, I. M. (ed.) 1995 Life events and difficulties: their nature and effects. *The depressed child and adolescent*, pp. 171–193. Cambridge University Press.

Grant, K. E. & Compass, B. E. 1995 Stress and anxious-depressed symptoms among adolescents: searching for mechanisms of risk. *J. Consult. Clin. Psychol.* **63**, 1015–1021.

Greenberg, J. L., Lewis, S. E. & Dodd, D. K. 1999 Overlapping addictions and self-esteem among college men and women. *Addict. Behav.* **24**, 565–571.

Harlow, H. F. & Harlow, M. K. 1965 Effects of various mother–infant relationships on rhesus monkey behaviors. In *Determinants of infant behavior IV* (ed. B. M. Foss), pp. 15–35. London: Methuen.

Harvey, P. H. & Pagel, M. D. 1991 *The comparative method in evolutionary biology*. Oxford University Press.

Hinde, R. A., Leighton-Shapiro, M. E. & McGinnis, L. 1978 Effects of various types of separation experience on rhesus monkeys 5 months later. *J. Child Psychol. Psychiat.* **19**, 199–211.

Joyce, P. R., Oakley-Brown, M. A., Wells, J. E., Bushnell, J. A. & Hornblow, A. R. 1990 Birth cohort trends in major depression: increasing rats and earlier onset in New Zealand. *J. Affect. Disord.* **18**, 83–89.

Kalin, N. H., Sheldon, S. E. & Lynn, D. E. 1995 Opiate systems in mother and infant primates coordinate intimate contact during reunion. *Psychoneuroendocrinology* **7**, 735–742.

Kerns, J. G., Cohen, J. D., MacDonald III, A. W., Cho, R. Y., Stenger, A. & Carter, C. S. 2004 Anterior cingulate conflict monitoring and adjustments in control. *Science* **303**, 1023–1026.

Keverne, E. B. 1985 Reproductive behaviour. In *Reproduction in mammals: 4. reproductive fitness*, 2nd edn (ed. C. R. Austin & R. V. Short), pp. 133–175. Cambridge University Press.

Keverne, E. B., Martel, F. L. & Nevison, C. M. 1996 Primate brain evolution: genetic and functional considerations. *Proc. R. Soc. Lond.* B **262**, 689–696.

Keverne, E. B., Nevison, C. M. & Martel, F. L. 1997 Early learning and the social bond. In *The integrative neurobiology of affiliation* (ed. C. S. Carter, I. I. Lederhendler & B. Kirkpatrick), pp. 329–339. New York: New York Academy of Sciences.

Klentrou, P. & Pyley, M. 2003 Onset of puberty, menstrual frequency, and body fat in elite rhythmic gymnasts compared with normal controls. *Br. J. Med.* **37**, 490–494.

Koob, G. F. & Le Moal, M. 1997 Drug abuse: hedonic homeostatic dysregulation. *Science* **278**, 52–58.

Kraemer, G. W. & Ebhert, M. H. 1991 Strangers in a strange land: a psychological study of mother infant separation in rhesus monkeys. *Child Dev.* **62**, 548–566.

Ladd, C. O., Owens, M. J. & Nemeroff, C. B. 1996 Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. *Endocrinology* **137**, 1212–1218.

Leckman, J. F. & Mayes, L. C. 1999 Preoccupations and behaviors associated with romantic and parental love: perspectives on the origin of obsessive–compulsive disorder. *Child Adolesc. Psychiat. Clin. North Am.* **8**, 635–665.

Leckman, J. F. (and 10 others) 1994 The role of central oxytocin in obsessive–compulsive disorder and related normal behavior. *Psychneuroendocrinology* **19**, 723–749.

Leckman, J. F., Mayes, L. C., Feldman, R., Evans, D. W., King, R. A. & Cohen, D. J. 1999 Early parental preoccupations and behaviors and the possible relationship to the symptoms of obsessive–compulsive disorder. *Acta Psychiat. Scand.* **100**, (Suppl. 396) 1–26.

Leverich, G. S., Perez, S., Luckenbaugh, D. A. & Post, R. B. 2002 Early psychosocial stressors: relationship to suicidality and course of bipolar illness. *Clin. Neurosci. Res.* **2**, 161–170.

Lorberbaum, J. P., Newman, J. D., Horwitz, A. R., Dubno, J. R., Lydiard, R. B., Hamner, M. B., Bohning, D. E. & George, M. S. 2002 A potential role for thalamocingulate circuitry in human maternal behavior. *Biol. Psychiat.* **15**, 431–445.

Martel, F. L., Nevison, C. M., Rayment, F. D., Simpson, M. D. A. & Keverne, E. B. 1993 Opioid receptor blockade reduces maternal affect and social grooming in rhesus monkeys. *Psychoneuroendocrinology* **18**, 307–321.

Martel, F. L., Nevison, C. M., Simpson, M. D. A. & Keverne, E. B. 1995 Effects of opioid receptor blockade on the social behavior of rhesus monkeys living in large family groups. *Psychobiology* **28**, 71–84.

Mayberry, T. I., Lock, E. & Kazami, H. 2002 Linguistic ability and early language exposure. *Nature* **417**, 38.

Mayes, L. C. 1995 Substance abuse and parenting. In *Handbook of parenting: applied and practical parenting*, vol. 4 (ed. M. H. Bornstein), pp. 101–126. Hillsdale, NJ: Lawrence Erlbaum Associates.

Meaney, M. J. 2001 Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *A. Rev. Neurosci.* **21**, 1161–1192.

Modrein-Talbott, M. A., Pullen, L., Zandstra, K., Ehrenberger, H. & Muenchen, B. 1998 A study of self-esteem among well adolescents: seeking a new direction. *Issues Comp. Pediatr. Nurs.* **21**, 229–241.

Monk, C. S., McClure, E. B., Nelson, E. E., Zarahn, E., Bilder, R. M., Leibenluft, E., Charney, D. S., Ernst, M. & Pine, D. S. 2003 Adolescent immaturity in attention-related brain engagement to emotional facial expression. *Neuroimage* **20**, 420–428.

Panksepp, J., Nelson, E. & Bekkedal, M. 1997 Brain systems for the mediation of social separation-distress and social reward. *Ann. N. Y. Acad. Sci.* **807**, 78–100.

Ploj, K., Roman, E. & Nylander, I. 2003 Long-term effects of maternal separation on ethanol intake and brain opioid and dopamine receptors in male Wistar rats. *Neuroscience* **121**, 787–799.

Rauch, S. L. 2000 Neuroimaging research and the neurobiology of obsessive–compulsive disorder: where do we go from here? *Biol. Psychiat.* **47**, 168–170.

Richter, S. S., Brown, S. A. & Mott, M. A. 1991 The impact of social support and self-esteem on adolescent substance abuse treatment outcome. *Subst. Abuse* **3**, 371–385.

Robbins, T. W. & Everitt, B. J. 1999 Drug addiction: bad habits add up. *Nature* **398**, 567–570.

Schultz, W. & Dickinson, A. 2000 Neuronal coding of prediction errors. *A. Rev. Neurosci.* **23**, 473–500.

Shalitin, S. & Phillips, M. 2003 Role of obesity and leptin in the pubertal process and pubertal growth—a review. *Int. J. Obes. Relat. Metab. Disord.* **27**, 869–874.

Simpson, M. J. A., Gore, M. A., Janus, M. & Rayment, F. D. 1989 Prior experience of risk and individual differences in enterprise shown by rhesus monkey infants in the second half of their first year. *Primates* **30**, 493–509.

Sowell, E. R., Thompson, P. M., Holmes, C. J., Jernigan, T. L. & Toga, A. W. 1999 *In vivo* evidence for post-adolescent brain maturation in frontal and striatal regions. *Nature Neurosci.* **2**, 859–861.

Sowell, E. R., Delis, D., Stiles, J. & Jerrigan, T. L. 2001*a* Improved memory functioning and frontal lobe maturation between childhood and adolescence: a structural MRI study. *J. Int. Neuropsychol. Soc.* **7**, 312–322.

Sowell, E. R., Thompson, P. M., Tessner, K. D. & Toga, A. W. 2001*b* Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: inverse relationships during post-adolescent brain maturation. *J. Neurosci.* **21**, 8819–8829.

Sroufe, L. A., Carlson, E. A., Levy, A. K. & Egeland, B. 1999 Implications of attachment theory for developmental psychopathology. *Devl Psychopathol.* **11**, 1–13.

Stevenson-Hinde, J. & Verscheuren, K. 2002 Attachment in childhood. In *Handbook of child social development* (ed. P. K. Smith & C. H. Hart), pp. 182–204. Oxford: Blackwell.

Sund, A.-M., Larsson, B. & Wichstrom, L. 2003 Psychosocial correlates of depressive symptoms among 12–14 year-old Norwegian adolescents. *J. Child Psychol. Psychiat.* **44**, 588–597.

Tanner, J. M. 1966 *Growth at adolescence*. Oxford: Blackwell Science.

Temblay, L. & Schultz, W. 2000 Modifications of reward expectation-related neuronal activity during learning in primate orbitofrontal cortex. *J. Neurophysiol.* **83**, 1877–1885.

Vega, W. A., Apospori, E., Gil, A. G., Zimmerman, R. S. & Warheit, G. J. 1996 A replication and elaboration of the esteem-enhancement model. *Psychiatry* **59**, 128–144.

Weiss, M., Baerg, E., Wiseboard, S. & Temple, J. 1995 The influence of gonadal hormones on periodicity of obsessive–compulsive disorder. *Can. J. Psychiat.* **40**, 205–207.

Williams, K. E. & Koran, L. M. 1997 Obsessive–compulsive disorder in pregnancy, the puerperium, and the premenstruum. *J. Clin. Psychiat.* **58**, 330–334. Quiz pp. 335–336.

Zohar, J., Hermesh, H., Weizman, A., Voet, H. & Gross-Isseroff, R. 1999 Orbitofrontal cortex dysfunction in obsessive–compulsive disorder? I. Alternation learning in obsessive–compulsive disorder: male-female comparison. *Eur. Neuropsychopharmacol.* **9**, 407–413.

GLOSSARY

MRI: magnetic resonance imaging
OC: obsessive–compulsive
OCD: obsessive–compulsive disorder
PFC: prefrontal cortex