

Importance of Genomic Imprinting in the Evolution and Development of the Maternal Brain

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Abstract It was the French reproductive biologist, Alfred Jost (1970), who proposed that mammalian sexual differentiation is biased in a female direction and masculine characteristics are imposed on an essentially female life plan. The reproductive success of mammals places a considerable burden of time and energy on the matriline, with some 95 % of female adult life committed to pregnancy, lactation and maternal care. Viviparity has thus provided a major selection pressure on the matriline in the evolution of these events and with particular emphasis on the placenta and hypothalamus. Increased maternal feeding, maternal care, suspension of fertility and sexual behaviour, parturition and milk provision are all integral to hypothalamic function and have evolved under the influence of the placental hormones to meet the demands of the developing infant (Keverne 2006). Viviparity has also introduced a new dimension to evolutionary genetics in providing the co-existence and continuity for three generations of matrilineal genomes (i.e., mother, developing offspring and developing oocytes) in one individual (Keverne 2011). Also unique to the mammalian matriline has been the evolution of epigenetic marks (imprint control regions) which are heritable and undergo reprogramming to regulate gene expression according to parent of origin. This imprinting of autosomal genes (genomic imprinting) plays a significant role in mammalian development, particularly development of the placenta and hypothalamus (Keverne 2009). Indeed, a number of imprinted genes are co-expressed in the placenta and hypothalamus and are important for the co-adapted functioning of these structures. Such transgenerational co-adaptation ensures the foetal hypothalamus is genetically and epigenetically programmed for ensuring optimal maternal care and nurturing (Broad and Keverne 2011). In this way the foetus not only controls its own destiny via the placenta but also that of the next generation via the developing hypothalamus.

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Introduction

The history of genomic imprinting started when reproductive biologists tried to produce parthenogenetic mammalian embryos (Surani et al. 1984). There was some success but development was poor, with major defects in the extra-embryonic membranes that form the placenta and with lethality of the embryo at the 25-somite stage of development. Similar studies were undertaken for androgenetic embryos developed from two copies of the paternal genome. Diploid XY androgenetic embryos likewise failed to complete normal development and again the primary defects were in trophoctoderm and the developing placenta. It was concluded that some form of imprinting of the genome occurred and both a male and female genome was essential for full-term development. Some 7 years were to pass before any imprinted gene was identified, but in the meantime, the creation of androgenetic and parthenogenetic chimeras was accomplished that survived both pregnancy and birth (Allen et al. 1995). This advance enabled a detailed investigation of how these disomic cells containing two copies of either the maternal or paternal genome contributed to development of the brain. A clear and distinct patterning for the distribution of these cells in the brain emerged (Keverne et al. 1996a). At birth, cells that are disomic for the paternal genome (i.e., both allelic copies are from the father) contributed substantially to those parts of the brain that are important for primary motivated behaviour (hypothalamus, pre-optic area, bed nucleus of the stria terminalis and septum). By contrast, parthenogenetic cells (i.e., both allelic copies are maternal) were excluded from these mediobasal fore-brain areas but selectively accumulated in those regions where androgenetic cells are excluded, namely the neocortex and striatum. Furthermore, growth of the forebrain of parthenogenetic chimeras is enhanced by this increased gene dosage from maternally expressed genes whereas the brains of the androgenetic chimeras were smaller, both in absolute measurements and especially relative to body weight. Neurological studies of brain function in human Prader-Willi syndrome (Horsthemke et al. 2003) and Angelman's syndrome, where a restricted region of the chromosome is uniparentally disomic for paternal or maternal imprinted genes, are congruent with these experimental findings (Saitoh et al. 2005).

Allometric scaling across different mammalian species of those distinct parts of the brain to which maternally or paternally disomic cells differentially contribute reveals that a remodelling of the brain has occurred during mammalian evolution (Keverne et al. 1996b). A certain amount of caution has to be exercised when interpreting these findings. Although we now know that many maternally expressed genes are important for neocortical development (Ferron et al. 2011) and paternally expressed genes are important for hypothalamic development (Keverne 2009), the reduced size of the neocortex with paternal disomies may be due to a failure of these cells to thrive and survive when they reach the developing cortex.

The discovery of the first imprinted genes, the maternally expressed *Igf2*-receptor and subsequently its interacting ligand, paternally expressed *Igf2*, led to the theory of mother-infant genomic conflict (Haig 1992). Haig theorised that the optimal strategy for the mammalian embryo was to extract maximal resources from the mother, with

paternal loci of imprinted genes being selected to secure this strategy. This was a plausible theory of genomic imprinting based on paternally expressed *Igf2*, which promotes foetal growth, and its maternally expressed receptor *Igf2r*, which, being a null receptor, restricts these growth-promoting effects. However, at that time point, there was still a great deal to be learned concerning the complex mechanisms that regulate and reprogramme genomic imprinting. Monoallelic silencing in the context of genomic imprinting is not a property of the gene per se but results from its positioning in the genome with respect to imprint control regions (ICRs) which, in turn, result in differentially methylated regions of DNA (Ferguson-Smith 2011). Moreover, there is a distinct non-equivalent bias towards matrilineal control over these genomic regions that epigenetically regulate these imprinted genes (Schultz et al. 2010). Successful viviparity has required extensive cooperative functioning of both the genotypes and phenotypes in the two generations and, since this functioning is dominated by the matrilineal genome in both generations and since sons benefit as much as daughters, conflict is difficult to reconcile with genomic imprinting.

Matrilineal Control Over Genomic Imprinting

The active control over genomic imprinting is firmly embedded in maternal DNA. There is a biased distribution of methylation-dependent ICRs towards the maternal germline, with the majority of imprinted gene clusters being dependent on maternal germline methylation (Bourc'his and Proudhon 2008). Only three imprinted loci have been reported to be controlled by paternal germline methylation (*H19/Igf2*, *A19/Rasgrf*, *Gt12*, *Dlk1*). Even here, the methylation of *Igf2* and *Rasgrf* does not causally determine the imprint, since parent of origin expression does not occur without the binding of maternal CTCF to the maternal ICR on the maternal chromosome (Kurukuti et al. 2006). The *H19* ICR is methylated in sperm, but it also attracts methylation even when inserted into non-imprinted loci, and in *Drosophila* it is capable of silencing a whole chromosome (Gebert et al. 2010). This finding supports the idea that *H19* is sufficient to act autonomously for methylation and does not require spermatogenic resetting, but it does require maternal CTCF binding to prevent biallelic silencing (Matsuzaki et al. 2010). Moreover, the maternal germline not only determines paternally expressed genes by maternal epigenetic marks that attract methylation and silencing but also regulates maternally expressed genes by the production in cis of non-coding RNA itself silenced on the maternal allele by DNA methylation inherited from the oocyte (Ferguson-Smith 2011).

Genomic Imprinting and Placental Hypothalamic Co-adaptation

Mammalian viviparity requires the action and interaction of two genomes in one individual, thereby providing a template for intergenomic co-adaptive function. The placenta, as part of the foetal genome, exerts considerable influence on the

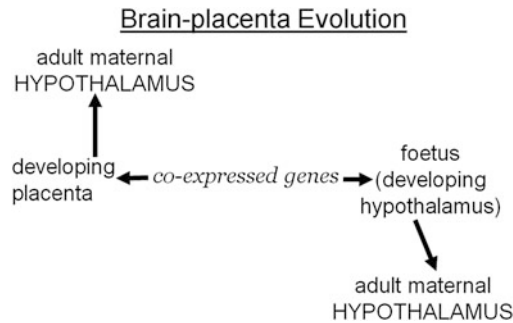


Fig. 1 Schema for co-adaptive evolution of brain and placenta. The success of the foetal genome is dependent on its placental interactions with the mother's hypothalamus. The developing placenta and foetal hypothalamus, through co-expressed genes, serve as a template for selection pressures to operate. Thus the success of this placenta-maternal interaction in determining good mothering will shape the success of the developing hypothalamus for good mothering in the next generation

maternal hypothalamus at the same time as the foetus itself develops a hypothalamus (Fig. 1). Hormones produced by the placenta, or their luteotrophic action in the ovary, influence the maternal brain, determining endocrine function and behaviour. Progesterone, in particular, suppresses maternal sexual behaviour and fertility, increases maternal food intake in anticipation of subsequent foetal demands, and promotes the synthesis of maternal hypothalamic oxytocin in anticipation of its requirements for parturition, maternal behaviour and milk ejection (Keverne 2006). In short, the foetal genome determines its own destiny via the placenta, hormonally regulating the maternal hypothalamus to serve the interests of the foetus which, at the same time, is developing its own hypothalamus. Conversely, maternal stress, glucocorticoids and insulin-like growth factors may induce changes in placental function which determine foetal programming in the context of hypertension and metabolic disease (Harris and Seckl 2011; Sferruzzi-Perri et al. 2011).

Those parts of the maternal brain which respond to placental hormones, namely the hypothalamus, undergo major development in the mouse during E11-16 (Forger 2005). This is also the period when placental vasculature becomes established and proliferation of the hormone-producing placental giant cells occurs. Many of the genes which change their expression over this developmental period (E11-12-13) are co-expressed in the placenta and hypothalamus (Fig. 2) and will demonstrate transcriptional synchrony across these co-adapted tissues. We have shown that genes which significantly change their co-expression in both hypothalamus and placenta increase from 9 % (days E11-12) of all gene expression changes to 47 % (days E12-13; Fig. 2a, b). Those genes whose expression significantly changes exclusively in the hypothalamus during this same period remain relatively stable from 37 % (days E11-12) to 36 % (days E12-13), whereas significant gene expression changes exclusively in the placenta decrease from 57 % (E11-12) to 16 % (E12-13; Fig. 2a, b; Broad and Keverne 2011). Thus a phase shift in changing

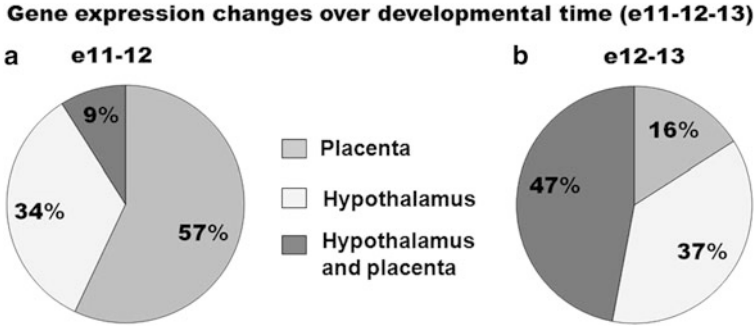


Fig. 2 Gene expression changes over developmental time. Notable increases for co-expression occur in those genes which change the expression over the period E11-12-13, (as meant?) thus making these the majority of genes that are active over E12-13

patterns of gene transcription over developmental time results in many genes that are common to, and synchronised for, expression in both the hypothalamus and placenta. Such co-expression would support this developmental period as potentially important for co-adaptive selection pressures to operate on the hypothalamus and placenta.

The maternal imprinting of specific genes, a unique epigenetic transcriptional regulatory mechanism that is restricted to viviparous mammals, has been thought to play an important role in the evolutionary development of placentation (Mess and Carter 2007; Renfree 2010). To date, 12 maternally imprinted genes have been shown to be developmentally expressed in both brain and placenta, although a recent study suggests this could be a considerable underestimate (Gregg et al. 2010). We have further considered how the transcriptional inactivation of the maternally imprinted gene (*Peg3*) influences the transcription of genes and co-expressed genes in hypothalamus and placenta over this same developmental time period. *Peg3* was selected because it is co-actively expressed in the hypothalamus and placenta during this time period and its inactivation is known to impair both placental development (reduced placenta size and impaired development of endocrine giant cells and spongiotrophoblast; Hiby et al. 2001) and hypothalamic development (reduced cell numbers in the PVN, MPOA; Broad et al. 2009). This results in impaired maternal care, milk letdown, infant suckling, metabolism and adult reproduction (Curley et al. 2005). More importantly, when *Peg3* transcription is inactivated in the hypothalamus of the pregnant mother carrying wild-type offspring, the functional phenotypic outcomes have remarkable similarities to those which occur when the same gene is selectively inactivated in the developing placenta and foetal hypothalamus in a wild-type mother (Fig. 3). These functional co-adaptations across two generations, mother and offspring, have clearly required genetic co-adaptation to occur between the developing hypothalamus and placenta across successive generations. Moreover, during development, *Peg3* is restricted to expression in the basal part of the forebrain (future hypothalamus) as well as the spongiotrophoblast and giant cells of the placenta. Thus viviparity adds a new

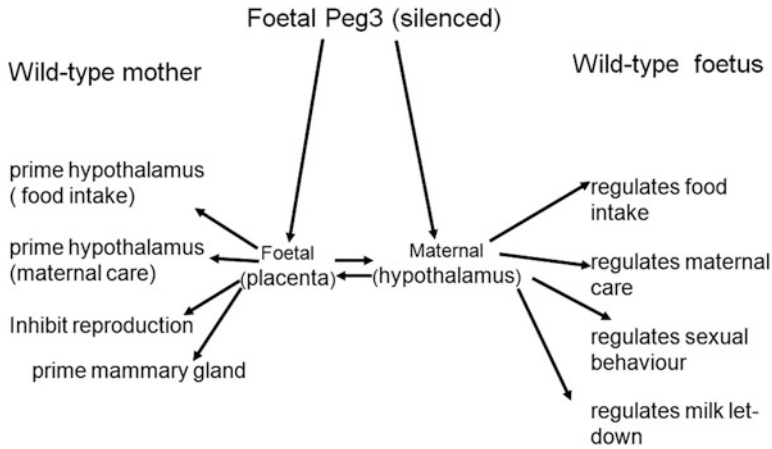


Fig. 3 Deletion of the Peg3 gene in the developing hypothalamus has remarkably similar functional consequences as deletion of this same gene in the foetal placenta. The latter results in the failure of the foetal placenta to communicate with adult maternal hypothalamus, while the former results from a failure of the foetal hypothalamus to develop an adequately responding adult maternal hypothalamus

environmental dimension of two genomes co-existing in one individual providing a template for co-adaptive selection pressures to operate, which is especially effective when this engages imprinted genes.

Between E11 and E12, Peg3 inactivation is particularly effective at targeting co-expressed genes (Fig. 4). Peg3 inactivation suppresses all of the co-expressed genes and induces co-expression of genes which are not usually co-expressed at this stage. The induced changes to co-expression by the Peg3 mutation are, however, not in synchrony; 90 % are up-regulated in the placenta, but in the hypothalamus they are all down-regulated. The next developmental period, E12-13, reveals a marked increase in hypothalamus and placental gene co-expression (up fourfold from E11-12; Fig. 4). Moreover, 59 % of these gene changes are synchronised for the direction of changed expression. At this same developmental time period, the inactivation of Peg3 suppresses 45 % of these co-expressed transcriptional changes and induces changes to a further 38 % of hypothalamus and placenta co-expressed genes (Fig. 4). Days E12-13 thus represent a period for major changes in transcriptional synchrony for genes co-expressed in the hypothalamus and placenta, and it is also the period when the Peg3 inactivation has maximal effects, not only suppressing many of these transcriptional changes but also inducing co-expression of new genes. Peg3 inactivation is thus particularly effective at desynchronising the expression of genes that are simultaneously co-expressed in hypothalamus and placenta, as well as disrupting the co-ordinated functional interactions between mother and foetus of this and the subsequent generation of wild-type offspring.

The brain and placenta are genetically co-regulated during developmentally important periods (E11-12-13) by sets of genes whose expression changes are

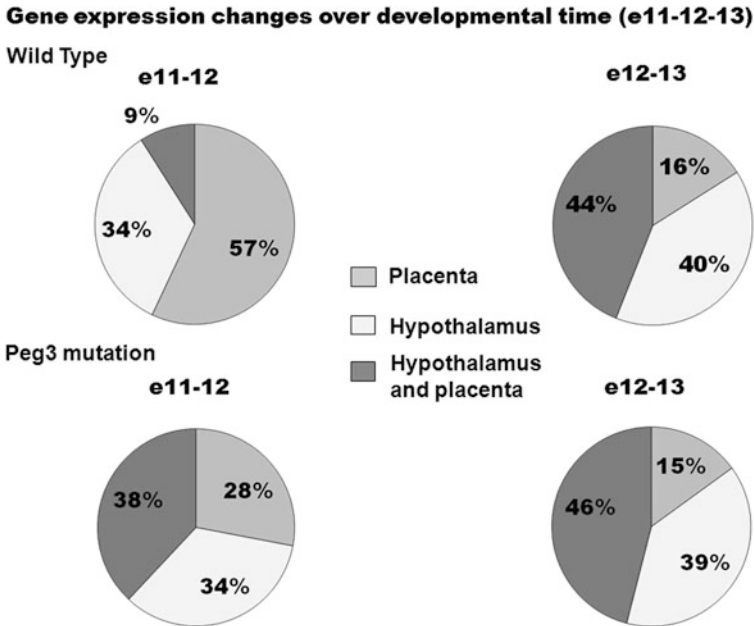


Fig. 4 Peg3 mutation is particularly effective at targeting co-expressed genes both for suppressing changes to co-expressed genes and inducing co-expression of new genes

synchronised in the placenta and hypothalamus. This co-expression is substantially disrupted by mutation to a maternally imprinted gene (Peg3), which also has significant developmental consequences for a range of phenotypes integral to successful growth and maternalism. An increase in atmospheric oxygen appears to have played a significant role in early mammalian placental evolution (Falkowski et al. 2005), and hypoxic conditions are a notable signal for Peg3 transcription in neurons (Yamaguchi et al. 2002) and in the developing placenta and for induction of vascularisation (Vaiman et al. 2005). Interestingly, although the mammalian Peg3 gene is structurally different from that of non-mammalian vertebrates, across mammalian lineages this gene and its promoter are highly conserved. The evolutionary significance of its imprinting must, therefore, be underpinned by its ability to regulate those large gene families (Prls, Psgs and Ceacams) which have themselves undergone multiple duplications and differential expansion across different mammalian species (Wildman 2011).

Evolution of functional co-adaptation between a mother's hypothalamus and the foetal placenta occurs developmentally at the level of the foetal genome but has the potential for further post-partum epigenetic modification through the mother's behavioural and endocrine responses to the offspring. In this way, offspring which receive "optimal in-utero" nourishment and improved maternal care will themselves develop a hypothalamus both genetically and epigenetically predisposed to optimal mothering (Keverne 2011).

A Reconsideration of SRY Evolution and Masculinisation of the Brain

The huge bias in the female's commitment of her time and resources to mammalian reproductive success has undoubtedly impacted on mammalian brain evolution in a major way. In terms of behaviour and neuroendocrine function during pregnancy and following parturition, mammalian brain development is dominated by the matrilineal genome, which has evolved under selection pressures that ensured successful pregnancy and maternal care. Integral to this has been the heritable matrilineal epigenetic marks which determine genomic imprinting, the co-adaptive development of hypothalamus and placenta and tight control over gene dosage. However, the question arises as to how the male brain becomes different, how maternalism is suppressed and how masculinisation is brought about? Males do not, of course, undergo pregnancy and parturition, but they nevertheless benefit from viviparity in the same way as females and have been subject to the same selection pressure of a viviparous in-utero environment. Indeed the male brain is capable of maternal behaviour in monogamous mammals (Carter and Keverne 2002), and castration at birth enables paternal care in males in many species (Lonstein et al. 2002)—hence the importance for production of testosterone in male hypothalamic masculinisation. But is this the complete story?

An important evolutionary development in masculinisation of placental mammals has been the male SRY sex-determining gene, which activates Sox9 for testes development (Sekido and Lovell-Badge 2008; Wallis et al. 2008). SRY is not present in the earliest of mammals, the egg-laying monotremes, and is thought to have evolved in parallel with the placentation. Interestingly, SRY is a hybrid gene of DGCR8 (Di-George syndrome critical region 8) and the Sox3 HMG box, regulated by the transcription factor CP2 (TFCP2; Sato et al. 2010). SRY is an intronless gene which serves as a master switch for testes formation (Kashimada and Koopman 2010). It provides the trigger for sex determination by activating Sox9, which not only brings about testes formation but blocks the genetic pathways that lead to the differentiation of ovarian cells (Veitia 2010).

Sox3, an X-linked gene from which SRY evolved, is also required for, and integral to, the formation of the hypothalamus and pituitary (Rizzoti et al. 2004). DGCR8, which became inserted upstream of the ancestral Sox3 in SRY evolution, is important for regulating the expression of micro-RNAs processed by the DGCR8-Drosha (microprocessor) complex from the non-protein coding transcript, PolIII, which is expressed exclusively in the placenta (Bortolin-Cavaille et al. 2009). Another member of the Sox gene family (Sox15), which has 75 % sequence in common with the HMG box of Sox 3, is also expressed in the placenta and plays an important role in the development of the placental giant cells that produce the hormones that regulate the adult maternal hypothalamus (Yamada et al. 2008). Are these relationships between the hybrid genes which constitute SRY, and also influence the developing hypothalamus and placenta, a coincidence? More likely they are telling us something about the evolution of mammalian hypothalamic

maternalism necessitating a critical timing for testes development to counteract such feminising events in males? Male sex determination is not new to mammals but the timing of this development is crucial, with SRY expression starting at E10.5 (mouse) in the developing testes. At E11.5, SRY induces the formation of foetal Leydig cells which produce high levels of testosterone (E15.5) without the need for luteinizing hormone (LH) stimulation (Barsoum and Yao 2010). The hypothalamus also undergoes its critical development (mouse) under the regulation of Sox3 between E11.5 and E16.5. Foetal Leydig cells are lost at birth and testosterone declines from pn1-30 until adult Leydig cells mature under the influence of LH at puberty (Chen et al. 2009).

Brain masculinisation in the mouse has long been established to be a consequence of testosterone aromatisation to oestrogen which epigenetically regulates sex-differences in neuronal composition of certain hypothalamic nuclei (BNST) and the pre-optic area (POA), both being larger in males, whereas the anteroventral periventricular nucleus (AVPN) is larger in females (McCarthy et al. 2009; Baum 2009a). However, the anatomical consequences of masculinisation are not evident until the post-natal period in the BNST, which relays pheromonal information to regions of the brain concerned with male sexual and female maternal behaviour. No sex differences were measureable on post-natal (pn) days 3, 5 and 7, but this nucleus does appear to contain significantly more neurons in the male between pn 9 and 11. Deletion of the pro-apoptotic gene, Bax, eliminated these BNST sexual dimorphisms by blocking activation of the p53 cell death pathway (Forger et al. 2004). However, this produced a significant increase in cell number in both sexes. Examining cell death, as opposed to preventing it by mutation, did provide a result which showed more cell death in the female BNST at pn 6 (Gotsiridze et al. 2007). AVPV neurons contain the peptide kisspeptin, an important regulator of GnRH in the onset of puberty, and also show post-natal sex differences which appear at post-natal day 12 (Semaan et al. 2010). The sexually dimorphic populations of dopamine neurons in this nucleus are reduced in the male post-natally by aromatisation of testosterone to oestrogen, which activates caspase-induced cell death of these dopamine neurons.

Thus there appear to be two phases in the masculinisation of the mouse hypothalamus: a pre-natal proliferative phase and a post-natal reorganizational apoptotic cell-death phase in certain hypothalamic nuclei. In the mouse, this cell death phase is particularly directed at the neural pathways concerned with processing pheromonal stimuli (Baum 2009b). Moreover, this pathway is integral to engaging appropriate sexually dimorphic behaviour, including mating and aggression in males (Stowers et al. 2002) and nursing and maternal aggression in females (Hasen and Gammie 2009). The vomeronasal sensory input is also integral to female reproduction, primarily by the AVPV release of kisspeptin and its activation of puberty in the female and by the induction of oestrous in the female in the presence of male pheromones. The imprinted Peg3 gene is expressed in all the neural relays of the olfactory system and increases fourfold in the AOB of the mother when exposed to pups (Canavan et al. 2001). In the 4- and 6-day post-partum mouse brain, inactivating Peg3 increased caspase3 induced apoptosis in

these neural relays, ameliorating any neural sex difference (Broad et al. 2009). However, the action of Peg3 is complex, interacting with the pro-apoptotic P53 and the counterbalanced anti-apoptotic p73 which has an intense signal in the VNO neurons, the AOB and its neural relays to the MPOA (Pozniak et al. 2000). Thus Peg3 may ensure a balanced regulation of apoptosis in the post-natally developing pheromonal pathways that play an integral sensory part in female maternal and male sexual behaviour.

Concluding Comments

This account has focussed on the complexity in development of the maternal brain, with special emphasis on its evolutionary origins in mammals. These events have been dependent on evolutionary changes associated with viviparity and the biased contribution of the matriline at the genetic, developmental and functional levels. Mammalian brain evolution has progressed considerably since the early appearance of viviparity some 40 Ma ago, reaching a pinnacle of complexity in the hominoids. Nevertheless, fundamental to this evolution in all mammals has been the contribution of matrilineal genomic imprinting and maternalism. To suggest, as many texts do, that 'female' is the default state fails to take into account how the matriline has actually provided the driving force for mammalian brain evolution. Indeed, both male and female mammalian brains have essential feminine components when viewed in the context of co-adaptive development of the placenta and hypothalamus. It has to be remembered that the male, too, has a placenta that communicates with its mother's hypothalamus while at the same time co-adaptively developing its own hypothalamus in utero. The male evolutionary response has been to construct the SRY gene as a master conscriptional switch for Sox9 expression and male gonadal development. SRY is a hybrid gene constructed from Sox3, which is itself important for hypothalamic development, and DGCR8, which is important for placental development. Thus the timing of male gonadal development has been a critical intervention by SRY for activating masculinisation of the maternal potential that is present in all mammalian brains. The development of secondary sexual characteristics can tolerate more variance in its onset and tends to follow development of the neocortex at puberty.

Thus, far from being a default state, maternalism of the mammalian brain has played an integral part in its evolution in both males and females. By far the most expansive growth of the mammalian brain has occurred in neocortical evolution, which mainly develops post-natally. This post-natal developmental period coincides with the close relationship that all mammals experience with their mothers, and subsequently with the social group in the case of large brain primates. Indeed, living in a social group has been hypothesised to be the important selection pressure in primate brain evolution (Curley and Keverne 2005). Mechanistically, the oxytocinergic and endorphin neurotransmitter systems that underpin and determine maternal care also provide the neural mechanisms called into action and

underpinning social reward (Broad et al. 2006). Again there is a matrilineal bias for the evolution of neural mechanisms that underpin social reward, but in the case of the neocortex the evolutionary emphasis is less dependent on genetic hardwiring. Here the brain's interconnections are epigenetically sculptured according to the social environment in which they develop and survive (Keverne 2011).

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