**The strategies of the genes: genomic conflicts, attachment
theory and development of the social brain**

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Abstract

I describe and evaluate the hypothesis that effects from parent-offspring conflict and genomic imprinting on human neurodevelopment and behavior are central to evolved systems of mother-child attachment. The psychological constructs of Bowlby's attachment theory provide phenomenological descriptions of how attachment orchestrates affective-cognitive development, and patterns of imprinted gene expression and co-expression provide evidence of epigenetic and evolutionary underpinnings to human growth and neurodevelopment. Social-environmental perturbations to the development of normally-secure attachment, and alterations to evolved systems of parent-offspring conflict and imprinted-gene effects, are expected to lead to specific forms of maladaptation, manifest in psychiatric conditions affecting social-brain development. In particular, under-development of the social brain in autism may be mediated in part by mechanisms that lead to physically enhanced yet psychologically under-developed attachment to the mother, and affective-psychotic conditions, such as schizophrenia and depression, may be mediated in part by forms of insecure attachment and by increased relative effects of the maternal brain, both directly from mothers and via imprinted-gene effects in offspring. These hypotheses are concordant with findings from epidemiology, attachment theory, psychiatry, and genetic and epigenetic analyses of risk factors for autism and affective-psychotic conditions, they make novel predictions for explaining the causes of psychosis in Prader-Willi syndrome and idiopathic schizophrenia, and they suggest avenues for therapeutic interventions based on normalizing alterations to epigenetic networks and targeting public-health interventions towards reduction of perturbations to the development of secure attachment in early childhood and individuation during adolescence.

Introduction

Conrad Waddington coined the term ‘epigenetics’, to refer to the processes whereby interactions between genetic and environmental variation lead to the emergence of patterns in phenotypic variation via development (Haig 2004a). In 1957, Waddington explicated in detail his theory of how natural selection and other processes mediate the evolution of ontogenetic trajectories, described by the concept of progressively-increasing canalization as depicted in adaptive-developmental landscapes. His ‘strategy of the genes’ thus centres on the evolution of co-operative developmental-genetic networks that can, in part via epigenetic modifications, produce relatively-viable phenotypes in response to, and in spite of, genetic and environmental perturbations due to alterations in genes or their patterns of expression.

Epigenetic landscapes represent metaphors for how gene regulation directs pathways of development from the largest to smallest scales - from the first deviation in totipotency of embryonic stem cells, to gene expression signatures, cell fate determinants and tissue type differentiation into organs, and to phenotypes that include conditional behavior (Figure 1). Much of modern developmental genetics focuses on elucidating the causal processes that underly subsections of such landscapes, in the contexts of human ontogenies and disease, yet epigenetics itself, the impetus for Waddington’s conception of development, has only recently re-emerged as a central focus of research in understanding the orchestration of phenotypic development.

For humans, development proceeds via growth and differentiation of body, brain and behavior under the joint influences of genes and, for environment, mainly interacting humans. Throughout much of the most formative, early years, the mother holds centre stage, providing both physiological nurture from uterus, placenta and breast, and, increasingly, as the infant grows, psychological guidance through interactive processes of bonding, instruction and other behaviour. These developmental processes, perhaps more than many others, are expected to be strongly canalized, yet also sensitive to relatively-predictable perturbations, such that epigenetic modifications to gene expression should direct neurodevelopment along conditionally adaptive pathways unless perturbations are too severe. As such, and as Waddington (1957) described, epigenetic landscapes may be considered as structures shaped by long evolutionary histories of selection, representing in their form some more or less long-term integration of past social environments and genomes.

From Waddington’s mid-20th century perspective, the adaptive strategies of all genes in an individual coincide, and aspects of the environment, such as the agents of other genomes, are not expected to pursue strategies that conflict. Two levels and forms of genetic conflict are now well-documented in their effects: conflicts between

individuals who are genetically unrelated to some degree, and conflicts within the genomes of individuals, between sets of genes with different patterns of inheritance and genetic relatedness to potential interactants (Hamilton 1964, 1996; Trivers 1974; Haig 1997, 2006; Burt and Trivers 2006; Fox et al. 2009). Both forms of conflict lead to differences in the phenotypic optima towards which they are, and have been, directed by natural selection. Optimal developmental trajectories of a given individual, and thus epigenetic landscapes, may thus vary in systematic ways between mother and child, and between sets of genes, such as imprinted genes that are silenced when inherited from either the mother or the father (Haig 2002). From evolutionary theory, and now-abundant empirical data (e. g., Hrdy 1999; Maestripieri 2002), offspring are expected to solicit more investment from parents, especially mothers as the main caregivers, than parents have been naturally-selected to provide, due ultimately to parent-offspring relatedness of only one-half for autosomal genes. Similarly, paternally-expressed imprinted genes in the child are expected to exert phenotypic effects that extract more investment from the mother than do maternally-expressed imprinted genes, due to a history of paternally inherited genes exhibiting lower genetic relatedness within sibships and matrilineages (Haig 2002, 2004b).

Outcomes of conflict between individuals, and between sets of genes, are difficult to predict, but may include stable equilibria, tugs-or-war over resource allocation, one party 'winning' due to asymmetries in control over resource allocation, or continued conflict (e. g., Royle et al. 2004; Smiseth et al. 2008). Conflicts such as genomic imprinting also potentiate liability to phenotypes associated with disease (Crespi 2010), due to functional haploidy of imprinted genes, dysregulation of tug-of-war based systems that evolved in this context, and the expected general higher liability of epigenetic gene-expression control systems (based on methylation and histone modifications) compared to the liability of DNA alterations via mutation. Such disease effects from imprinting have been documented extensively for disorders related to human placentation, overall growth, and neurodevelopment (e. g., Angiolini et al. 2006; McMinn et al. 2006; Wagschal and Feil 2006; Davies et al. 2008).

The main thesis of this article is that genomic conflicts and cooperation, especially the epigenetic effects of genomic imprinting, centrally mediate core aspects of mother-child developmental interactions – most notably the processes of attachment – with important consequences for psychological well-being throughout life. I first describe the roles of imprinted genes in development, and recent discoveries of imprinted-gene networks that control growth. Next, I explicate the hypothesis that human early-childhood social development, mainly via interaction with the mother, involves a network of brain-expressed imprinted genes that modulate attachment – the process whereby children, in environments characterized

by secure and responsive maternal care, internalize psychological constructs derived from external mother-child interactions, to develop a self and psyche centred in their social context (Bowlby 1969; Bretherton 1997). The idea of imprinted genes mediating attachment was originally suggested by Isles and Holland (2005), and I extend and evaluate the hypothesis using information from patterns of imprinted gene expression and coexpression, phenotypes of imprinting-based disorders, Bowlby's attachment theory, and psychiatric conditions involving the social brain. Finally, I discuss the implications of these ideas and data for pharmacological and behavioral therapies, public-health strategies, and the integration of epigenetic perspectives derived from Waddington into research programs focussed on understanding the genetic bases of human development. Most generally, I integrate and synthesize evidence from evolutionary biology, developmental psychology, human genetics and epigenetics, and psychiatry of social-brain disorders, to develop and evaluate explicit, testable hypothesis regarding roles of genomic conflicts and epigenetics in human development and evolution.

Genomic imprinting in human growth

Haig and Moore (1991) developed the kinship theory of imprinting in the context of conflictual interactions in fetal mice between paternally-expressed *Igf2*, which drives growth, and maternally-expressed *Igf2r*, which acts as a 'decoy' receptor to reduce *Igf2*'s growth-stimulating effects. Although the predicted pattern of paternally-expressed imprinted genes tending to foster overall growth, and maternally-expressed imprinted genes constraining it, has been abundantly supported in studies of placentation and body size (e. g., Plagge et al., 2004; Weinstein et al., 2004; Kelsey 2007), the simple, direct tug-of-war system exemplified by *Igf2* and its receptor has proven to be atypical of imprinted-gene effects generally. The first clear evidence for a much more extensive system of imprinted-gene interaction - imprinted-gene networks - emerged from work by Arima et al. (2005), who demonstrated that the imprinted genes *ZAC1*, *LIT1*, and *CDKN1C* jointly mediate growth of human cells. Varrault et al. (2006) used information from experimental mouse knockouts, and microarray databases, to document more directly the existence of a co-regulatory imprinted-gene network; thus, gains and losses of *Zac1* altered the expression levels of the imprinted genes *Igf2*, *H19*, *Cdkn1c* and *Dlk1*, and a broad pattern of imprinted-gene coexpression, involving these five genes as well as *Grb10*, *Gtl2*, *Peg1* (*Mest*), *Sgce*, *Dcn*, *Gatm*, *Gnas*, *Ndn*, and *Peg3*, emerged from analyses of gene-coexpression in pooled datasets from mouse muscle and other tissues. Liu et al. (2008) subsequently identified a set of 11 imprinted genes in this network, all of which influence aspects of cell proliferation, whose expression levels across multiple tissues paralleled trajectories of overall body growth, and

Gabory et al. (2009) showed that H19 gene acts as an important trans regulator of this imprinted gene network that may also 'fine-tune' gene co-expression patterns to moderate effects from perturbations; network interactions among unrelated genes are indeed postulated as a major cause of robustness against mutations (Wagner 2000), which should be especially important for functionally-haploid, imprinted genes. Gabory et al. (2009) also demonstrated that such regulation via H19 apparently did not operate in the placenta, which implies a notable degree of tissue and stage specificity of imprinted-gene network dynamics. Most recently, loss of expression of the ATRX gene in mice has been shown to cause altered postnatal expression of a suite of imprinted genes including Igf2, H19, Dlk1, Zac1, and Peg1, as well as the Rett-syndrome gene MeCP2, suggesting a role for ATRX in trans-regulation of the imprinted-gene network (Kernohan et al. 2010) and corroborating effects of MeCP2 expression in the regulation of imprinted genes (Miyano et al. 2008).

Two independent lines of data provide further evidence for fundamental roles of imprinted gene networks in development. First, two of the best-understood human genetic syndromes, Beckwith-Wiedemann syndrome and Silver-Russell syndrome, are each mediated by alterations to different imprinted genes in the network, which convergently generate similar phenotypes involving, respectively, overgrowth or undergrowth (Eggermann et al. 2008; Eggermann 2009). Similar convergent effects, whereby different epigenetic or genetic alterations produce highly similar phenotypes, have also been described for Prader-Willi syndrome (Crespi 2008a), and Angelman syndrome (Jedele 2007; Crespi 2008a). Convergence from diverse genetic or epigenetic perturbations, to similar phenotypes across multiple traits, represent clear examples of developmental canalization. Such canalization effects can also be generalized to idiopathic conditions, such as autism and schizophrenia, each of which also exhibits diverse genetic, epigenetic and environmental causes converging to a relatively small set of cognitive, affective, and behavioral phenotypes (Happé 1994; Owen et al. 2007; Abrahams and Geschwind 2008). As imprinted-gene networks have presumably evolved in part due to selection for coordinated, robust control of mammalian growth – yielding specific, syndromic phenotypes when sufficiently perturbed – genomic and epigenetic networks orchestrating human neurodevelopment and behaviour may likewise be expected to yield predictable patterns from different forms of alteration.

A second line of evidence pertinent to gene-expression networks in general, and imprinted genes in particular, is the recent discovery of mechanisms whereby imprinted domains interact across different chromosomes, via allele-specific physical juxtaposition of long-range chromatin loops in interphase nuclei (Smits and Kelsey 2006; Zhao et al. 2006). Such interactions occur genome-wide (Ling and Hoffman 2007), but are strongly enriched to imprinted regions (Zhao et al. 2006), with an

apparent central role for the imprinted RNA gene H19 as a hub for transvection of parent-of-origin specific effects to both imprinted and non-imprinted loci on other chromosomes (Sandhu et al. 2009). Inter-chromosomal interactions that involve imprinted loci provide a genome-scale mechanism for coordinated expression of imprinted genes (in addition to mechanisms involving, for example, transcription factors such as *Zac1*, and protein-protein interactions such as those between *p57kip2* and *Nurr1*)(Joseph et al. 2003), and for control of non-imprinted genes and loci by specific imprinted genes, that may serve to increase their relative influence on development.

In the context of Haig's kinship theory of imprinting, imprinted-gene networks can be hypothesized as multidimensional generalizations of simple, two-dimensional tugs-of-war, which apparently evolved step by step with the accrual of imprinted domains along the lineages leading to the origins of metatherian and eutherian mammals (Renfree et al. 2009). This conception of imprinted-gene networks shows how co-operation, in a literal sense of the word, can evolve from conflict, when the interests of different mutually-dependent parties, here paternally-expressed and maternally-expressed imprinted genes, overlap partially yet broadly. Thus, paternal and maternal genes, as well as additional genetic 'factions' such as genes on the X chromosome (Haig 2006a), share a common interest in successful development via reducing physiological costs of conflict, and (within limits) increasing the robustness of development to perturbations, although natural selection continues to favor paternal-gene variants that solicit marginally more investment from mothers, and maternal and X-linked alleles that reduce such imposition of increased costs.

Consideration of the tissue and stage specificities of imprinted gene expression, in the context of the kinship theory of imprinting, leads to the inference that more or less different imprinted-gene networks should characterize each of the three main arenas for imprinted-gene effects: (1) placentation, (2) overall post-natal growth, and (3) behavioral interactions with the mother, as influenced by imprinted-gene expression in the brain. Indeed, the network presented in Varrault et al. (2006), represents a conglomeration of gene coexpression patterns across multiple tissues and stages, and some central genes in the network, such as *Ndn*, apparently do not exert effects on overall growth (Tsai et al. 1999). Eutherian placentation is known to be orchestrated by imprinted genes in a manner consonant with predictions of the kinship theory (e. g., Bressen et al. 2009), and alterations to imprinted-gene expression underly a considerable proportion of risk for the major disorders of human pregnancy (e. g., Charalambous et al. 2007); Fauque et al. (2010) describe evidence for imprinted-gene coregulation effects in mouse placentation, which coordinate gene-expression changes in relation to early-embryonic conditions. Post-natal growth effects are similarly mediated by imprinted genes, which appear to predominantly exert their influences through effects on cell proliferation at the tissue

level (Reik et al. 2001), and glucose and lipid metabolism at the levels of physiology and metabolism (Sigurdsson et al. 2009). The body growth enhancement effects of Beckwith-Wiedemann syndrome, and growth reduction in Silver-Russell syndrome, indeed represent paradigmatic examples of imprinted-gene disorders with primary effects on both prenatal and postnatal growth. Microarray studies that focus on placental gene expression, and gene expression across the tissues most-directly involved in prenatal and postnatal growth, are thus expected to reveal imprinted-gene networks that comprise partially-overlapping sets of genes, with imprinted genes exerting effects that are more or less tissue specific. The tissue with the most pervasive effects on growth, development and behaviour – the brain - remains, however, the least well understood.

Genomic imprinting in the brain

The study of imprinted-gene effects in brain development was pioneered by Keverne, whose studies of chimeric mice showed differential contribution of paternally-expressed imprinted genes to development of limbic brain regions (especially the hypothalamus), and maternally-expressed genes to development of the neocortex (Allen et al. 1995; Keverne et al. 1996; Keverne 2001a,b). Functional and evolutionary hypotheses for the effects of brain-expressed imprinted genes have been described in detail; these include diverse effects on affect, cognition, attention, feeding behavior, and other central brain functions (Isles et al. 2006; Wilkinson et al. 2007; Davies et al. 2008; Champagne et al. 2009), some of which apparently influence resource-related interactions between mothers and offspring. These hypotheses have proven difficult to evaluate critically due to the complexity the mechanisms involved, and the difficulty of testing alternative hypotheses of neurobehavioral adaptation compared to pleiotropic byproduct.

Adaptation is most commonly recognized, at least initially, as convergence or parallelism in causal patterns consistent with theory. For imprinted brain-expressed gene, clear convergent effects of paternally-expressed genes on neurodevelopment have been described for the roles of *Peg3*, *Peg1*, and *Ndn* in promoting development of hypothalamic neurons that secrete oxytocin, the peptide hormone that most strongly mediates social bonding (Davies et al. 2008; Ross and Young 2009; MacDonald and MacDonald 2010). Moreover, in the *Zac1* network (Varrault et al. 2006), these three genes occupy central locations as ‘hubs’, prominently connected, like *Zac1* itself, to relatively large numbers of both imprinted and non-imprinted genes. These findings, from three lines of evidence (mouse knock-outs, functional gene-expression data, and gene coexpression networks), suggest a functional and evolutionary role for imprinted genes in fostering bonding and attachment of offspring to mothers, in the context of an imprinted-gene network that

affects expression of offspring behaviors that regulate levels of resource accrual from mothers. In mice, bonding of pups to mothers involves olfactory, tactile and auditory cues, which foster safety and suckling; moreover, suckling behavior is differentially disrupted in mouse knockouts of the paternally-expressed genes *Peg3* and *Gnasxl* (Curley et al 2004; Plagge et al. 2004).

In humans, which like mice are highly altricial as neonates, attachment involves the same three categories of sensory cue as in mice, and early suckling and feeding are impaired in the two genomic conditions, Silver-Russell syndrome and Prader-Willi syndrome, that involve strong maternal-gene biases (Blisset et al. 2001; Holland et al., 2003; Dudley et al. 2006), as well as in humans with paternal deletion of *GNASxl* (Genevieve et al. 2005); by contrast, macroglossia (enlarged tongues, which are expected to facilitate suckling) has been reported in both Beckwith-Wiedemann syndrome and Angelman syndrome (Cohen 2005). But much more extensively than in mice, human cognitive-affective interactions guide early development of the child's 'social brain' – the distributed, integrated set of neural systems that control acquisition, processing and deployment of socially-interactive information (Frith 2008). Such interactions have motivated the development of a large body of theory and empirical work in psychology, attachment theory, with direct implications for other fields from genetics, epigenetics and neurodevelopment to analyses of the etiology of psychiatric conditions that involve alterations to early development and function of the social brain.

Attachment theory and human social development

Attachment theory was developed by John Bowlby and Mary Ainsworth to help explain the adaptive significance of physical and psychological interactions between young children and close caregivers (primarily the mother), and how children deprived of care, or subject to dysfunctional forms of caregiver-child interaction, develop along lifelong trajectories characterized by altered emotional and cognitive systems which are explicable in part by the nature of these early perturbations (Bowlby 1969). The majority of children develop 'secure' attachment, whereby their intimate interactions with the mother provide for physical safety, nutritional sustenance, and social-emotion-cognitive guidance that generates a 'secure base', increasingly explorative behavior with age, and an environment conducive to development of a social brain – internalized schema - with robust sense of self, well-developed theory of mind, and ability to nurture secure attachment to one's own children in later life.

Deviations from secure attachment, as assayed by the 'strange situations test' that tests a child's behavior towards its mother when subject to short separations, take a small set of forms: (1) avoidant attachment, whereby children with unmet

expectations of attachment security come to at least provisionally reject significant others, (2) anxious/ambivalent attachment, with unmet solicitation leading to 'escalation' of distress and behavior characterized by contact-seeking combined with anger and ambivalence, and (3) disorganized attachment, with lack of a coherent, organized 'strategy' for interacting with the caregiver (e. g., Shaver and Mikulincer 2002). These deviations have been interpreted in the context of developmental responses by the child to variation in caregiver sensitivity, that is, provision of consistent physical and psychological support, in contrast to neglectful, hostile or inconsistent care.

The framework for interpretation of childhood attachment patterns has developed in the combined contexts of post-freudian psychodynamics, evolutionary-ethological constructs for the study of animal behavior, and psychological theories of stages and processes in child social development, such as the social-behavioral internalization theories of Vygotsky (Bretherton 1992; Thompson 2008). In her book *Mother Nature*, Hrdy (1999) first conceptualized an evolutionary-genetic basis for understanding central aspects of attachment, unappreciated by previous work, that follow directly from W. D. Hamilton's inclusive fitness theory. Due ultimately to genetic relatedness between mothers and children of only one-half, mother-child interactions are expected to comprise complex mixtures of cooperation and conflict, with children having been selected to solicit higher levels of behavioral as well as nutritional investment than mothers have been selected to provide. The theory underlying parent-offspring conflict has been well-supported by empirical studies (Bowlby 1969, p. 203; Haig 1993; Hinde and Kilner 2007), and Hrdy (1999) interprets a broad swath of human-specific childhood phenotypes, from high levels of neonatal fat, to precocious neurological development of eye contact, facial expression, and vocalization, as subject to a long history of selection in the context of child signalling of vigor and solicitation of increased energetic and psychological investment. Childhood attachment to mother – from placenta, to breast, to psychological development – is thus expected to be centrally mediated by both cooperation and conflict, which should be expressed in patterns of child attachment behaviors that represent largely adaptive responses to the behavior of the mother, who is in physical control of investment. The major patterns of child attachment have indeed been interpreted by attachment theorists as conditionally-adaptive responses of children to sensitive, hostile, neglectful or inconsistent mothering, though not in terms of strategies grounded by the fundamentals of evolutionary genetic and epigenetics.

Parent-offspring conflict theory applies to autosomal genes with conditional, temporally-restricted effects in children, and autosomal genes expressed in mothers. The primary implication of this theory is that evolved systems of mother-child interaction (and father-child interaction, given some degree of paternal care) should

be characterized in part by conflicts – mainly centered on increased demands from the child, and responses from mother conditioned on marginal benefits to her from incremental investment in child vs. benefits from other fitness-accruing activities. Haig (1993) describes evidence of such dynamics in the context of human maternal-fetal interactions, as do Wells (2003) and Soltis (2004), for suckling and crying; these authors also demonstrate how the major disorders of food provision via placenta and breast, including intrauterine growth restriction, pre-eclampsia, gestational diabetes, excess post-natal weight gain, failure to thrive, and colic, can usefully be understood in part as forms and effects of dysregulation to systems of evolved mother-child conflict – conflicts that are revealed most clearly in cases of genetic or environmental perturbation from 'normal' development. Mother's primary form of investment in children beyond food is, of course, psychological training and guidance, and mother-child conflicts in this arena are expected to exhibit constrained-conflict dynamics squarely manifest in attachment, with disorders of mental health, for the grown child, more likely to result when dynamics are perturbed (Berry et al. 2007, 2008; Lyons-Ruth 2008).

To understand the expected role of imprinted genes in attachment, conflicts due to imprinted genes must be conceptually distinguished from, and related to, conflicts between parents and offspring. Imprinted-gene conflicts are thus expected, from the kinship theory of imprinting, to involve interactions between paternally-expressed genes in the child, and maternally-expressed genes, also in the child. As such, imprinted genes are predicted, through the integration of their effects, to influence the child's 'set level' of resource demand imposed upon the mother. An example of such an economic system, in a physiological situation, is provided by expression of the imprinted gene *Cdkn1c* in fetal mouse development: levels of its protein product, p57kip2, have been experimentally demonstrated to act as a 'rheostat' for embryonic growth, with ultimate levels of growth determined by the balance between fetal demand and maternal supply (Andrews et al. 2007). In the context of child psychology and behavior, imprinted genes are expected to similarly mediate levels of imposed demand, here for psychological time and energy; more generally, they should exert effects that result, by any mechanism, in higher or lower, longer or shorter, levels of investment from the mother. Small alterations to such systems, towards, for example, stronger effects from paternal gene expression that lead to higher investment, are expected to benefit the child, and his or her paternally-expressed imprinted genes, at a small cost to the mother and to the child's maternally-expressed imprinted genes. By contrast, large alterations, which like any large genetic or epigenetic effects surmount the homeostatic effects of canalized development, are expected to result in disorders of psychological development that are detrimental to both mother and child, and to all genomic parties concerned. The nature of such disorders, however, provides useful tests of evolutionary theory

involving genomically-based conflicts, and insights into strategies for therapy, prevention, and research (Crespi 2008b; Crespi et al. 2009).

These considerations from attachment theory, parent-offspring conflict theory, and the kinship theory of imprinting generate a simple conceptual framework for understanding normal and dysregulated social-behavioral interactions between mothers and small children (Figure 2). From birth, young children exhibit some level of social-behavioral ‘demand’, manifest in solicitations of interaction via facial and auditory cues, as well as in the contexts of crying, fussing, and suckling. Such levels are expected to vary between children, and over time in response to levels and forms of reciprocal and unsolicited maternal behavior. Child-specific, dynamic ‘demand’ is matched, less or more, by levels of maternal sensitivity and responsiveness to such cues – varying from neglect, to solicitous, attentive care, to controlling over-involvement.

Evolutionary histories of parent-offspring conflict, and imprinted-gene conflict, have generated conditional behavioral adaptations, in child and in mother, that potentiate the possibility of mismatches between demand and response, which may result in maladaptation for one or both parties. Thus, relatively-low social-behavioral demand from the child may delay or dysregulate social-brain development, but provide marginal benefits to the mother in terms of her lifetime inclusive fitness. By contrast, relatively-high demands may, if matched by supply, provide benefits to the child at some cost to mother; if not matched or if too insistent, however, such demands may provoke neglect, ambivalence, or even hostility, if they interfere sufficiently with a given mother’s perceived optimal life-history trajectory. Levels of maternal ‘supply’ higher than child demand – ‘over-involvement’ – may, by contrast, come to interfere with the child’s ability to explore and increasingly detach, physically and social-emotionally, from its secure base of the controlling maternal brain, to individuate its own psyche.

The outcomes of such conflicts are difficult to predict *a priori*, but they should depend upon the relative fitness costs and benefits to the child and mother of the alternative behaviours, and the degree to which each party controls aspects of the interaction. Thus, tactics available to young children include auditory and facial expressions of positive and negative affect, crying, suckling intensity, and physical movement varying with age; by contrast, mothers control access to breast and physical presence, and provision of information and social interaction crucial to the child’s affective and cognitive development. Indeed, as Bowlby (1951, p. 53) noted:

“In dealing here with the embryology of the human mind one is struck by a similarity with the embryological development of the human body, during the course of which undifferentiated tissues respond to the influence of chemical organizers. If growth is to proceed smoothly, the tissues must be exposed to the influence of the appropriate

organizer at certain critical periods. In the same way, if mental development is to proceed smoothly, it would appear necessary for the undifferentiated psyche to be exposed during certain critical periods to the influence of the psychic organizer – the mother”. Thus, during infancy and early childhood, “she is his ego and his super-ego.”

The primary usefulness of a keynesian, supply-demand model for attachment is that it provides a framework, compatible with both developmental psychology and evolutionary-genetic theory, that generates novel explanations and predictions for alternative patterns of social-brain development. The model can be conceptualized as a developmental landscape, canalized to secure attachment and its sequelae but with different optimal trajectories for mother and child, and for child's paternal and maternal imprinted genes. Child development along the landscape initially proceeds via basic emotional-behavioral attachment mediated in part by paternal imprinted-gene effects, which serve as an affective-attentional scaffold upon which the social, maternal brain is gradually built, via maternal-gene effects and interactions with the mother and other caregivers. Actual trajectories for any child are determined by some dynamic integration of genetic, epigenetic, and environmental inputs into social-brain development, and into mother-child interaction; most importantly for mental health, relatively-large genetic, epigenetic, or environmental alterations to this system are expected to generate predictable consequences, manifest in major disorders of the social brain, such as schizophrenia, depression, and autism. The assumptions and predictions of the model can be evaluated using information from human imprinted-gene syndromes, and studies on the etiology of schizophrenia and autism, in the contexts of attachment and evolutionary-genetic theory.

Prader-Willi syndrome

Haig and Wharton (2003) describe how the complacent nature of Prader-Willi infants (with low levels of crying and wakefulness), and their compulsive self-foraging for food after the usual age of weaning, can be interpreted in the context of reduced demands on mothers, as expected under imprinted-gene biases involving loss of paternal-gene expression. Prader-Willi syndrome is known to centrally-involve hypothalamic alterations and relatively low levels of oxytocin (Swaab et al. 1995; Holland et al. 2003; Hoybye 2004; Goldstone 2006), which is consistent with the oxytocin-reducing effects of Ndn gene knockouts in mice (Davies et al. 2008) and the expected behavioral effects of lower oxytocin levels – reduced motivation towards social bonding behavior. These considerations suggest that Prader-Willi syndrome should involve insecure attachment in children, especially among cases due to maternal uniparental disomy where the genomic deviations towards maternal imprinted-gene effects are more extensive. This suite of behavioral and other

alterations in Prader-Willi syndrome may involve, in part, disruptions to genes that underly a human-lineage trajectory towards earlier weaning and shorter interbirth intervals (Sellen 2007; Haig 2009; Humphrey 2009), a transition expected to impose strong selection in the context of maternal-offspring and imprinted-gene conflicts given generally high rates of early-childhood mortality.

The extensions of attachment theory described here provide a simple, novel hypothesis to help explain one of the other major features of Prader-Willi syndrome: the extremely high levels of affective psychosis upon reaching adolescence (Soni et al. 2008; Webb et al. 2008). By this hypothesis, Prader-Willi infants and children may essentially undergo a process of self-induced maternal deprivation, whereby their low levels of care solicitation lead to reduced interaction with the mother and dysregulated social-emotional development. The primary line of evidence supporting this hypothesis, in addition to the theory and data described above, is that maternal deprivation, due to diverse causes including reduced physical care, temporary early separation or permanent loss, is a well-documented, highly-penetrant causal factor in the etiologies of depression (e. g., Pesonen et al. 2007; Tyrka et al. 2008; Liu et al. 2009), schizophrenia (reviewed in Read and Gumley 2008) and schizotypy (Anglin et al. 2008). Convergent evidence for interactions of maternal deprivation with imprinted gene expression comes from a study of mice, where 2 (5.4%) of 37 genes significantly upregulated in the hypothalamic paraventricular nucleus of young mice in response to maternal deprivation were imprinted (*Gtl2* and *Ipw*), a higher proportion than expected given an approximate 1.2% (120 of 10,000) (<http://igc.otago.ac.nz/table.html>) of brain-expressed genes imprinted in the mouse genome ($\chi^2 = 5.43$, $P < 0.05$).

To the extent that affective psychosis in Prader-Willi syndrome is mediated by gene-environment interaction in this context, alterations to early maternal-social environments, and facilitation of early bonding via behavioural and hormonal therapies, may help to alleviate the psychiatric sequelae of this large-scale epigenetic disruption. Similar considerations should apply to genetic and epigenetic alterations that yield phenotypes overlapping with Prader-Willi syndrome (Crespi 2008a) and, perhaps, to effects from reduced size of the paraventricular nucleus in patients with bipolar disorder and major depression, compared to controls (Manaye et al. 2005). More generally, an evolutionary trajectory towards earlier weaning and shorter interbirth intervals in humans might be expected to have increased vulnerability to affective-psychotic conditions, unless attachment through alloparents and fathers (Hrdy 2009) compensates for abbreviated maternal care.

Angelman syndrome

In contrast to children with Prader-Willi syndrome, Angelman syndrome children are highly active, with reduced duration of sleep, frequent suckling attempts, and enhanced levels of socially-directed positive affect (Cohen et al., 2005; Oliver et al. 2007). These diverse phenotypes have been interpreted as reflecting increased behavioral and energetic demands on the mother, as predicted by the direction of imprinted-gene deviation, towards reduced relative effects from the maternally-expressed imprinted gene UBE3A (Oliver et al. 2007). Such an increased 'set-level' of demands imposed on mothers might be expected to lead to insecure forms of attachment, unless the demands are met, whereupon social-emotional development should proceed as normally as possible under the circumstances of severe intellectual disability that characterize this syndrome. A high prevalence of autistic traits in Angelman syndrome (Sahoo et al. 2006; Bonati et al. 2007; Jedele 2007) has also been interpreted in the context of selectively-reduced social-brain development and high demands imposed on the mother in the context of paternal imprinted-gene bias (Brown and Consedine 2004; Isles et al. 2006; Crespi and Badcock 2008).

Schizophrenia and attachment

Schizophrenia represents a set of conditions, due to diverse causes, with some combination of symptoms that may include hallucinations, delusions, thought disorder, flat affect, and anhedonia (Read et al. 2004). An attachment-theory perspective on schizophrenia was first provided by Bowlby (1973, pages 174-177, 318-319), in his description of continuities between forms of abusive and dysfunctional psychological treatment of children by parents and the later development of specific schizophrenic symptoms. Systematic analyses of attachment in relation to aspects of schizotypy and schizophrenia (Berry et al. 2007, 2008; Gumley et al. 2008; Tiliopoulos and Goodall 2009) have documented higher than normal levels of insecure attachment in these conditions, with general support for Bowlby's prediction of linkages between childhood experiences and psychotic-behavioral profiles. Thus, in non-clinical populations avoidant attachment has been associated with negative schizotypal traits, and anxious attachment with positive schizotypy (Wilson and Constanzo 1996; Berry et al. 2006); insecure attachment has also been linked with paranoia in schizophrenia (Pickering et al. 2008), and disorganized attachment may be related to dissociative cognitive states that accompany schizophrenia in some patients (Berry et al. 2008; Liotti and Gumley 2008).

One of the best-replicated patterns reported in families with an adolescent or young-adult schizophrenic offspring is high levels of 'expressed emotion' – some mix of parental hostility, criticism and over-involvement (Read et al. 2004), which commonly occurs in the context of emotional over-involvement by one or both parents but low levels of actual care. Higher expressed-emotion predicts higher rates of relapse after a first psychotic episode, and also appears to be linked with the initial development of schizophrenic symptoms themselves (Read and Gumley 2008; Read et al. 2004). The causal bases for such associations have puzzled psychiatrists for many years, but perspectives from attachment theory and genomic conflict offer novel, testable insights. Thus, parental over-involvement might be expected to involve attempted control over offspring behavior, interfering with the usual processes of physical and emotional separation of the child from attachment figures, which becomes most pronounced in adolescence (Harrop and Trower 2001). Moreover, extended controlling influences on the offspring psyche by the mother – the 'maternal brain' of genomic imprinting theory (Badcock 2009, pages 154-157) – as expressed in the mother's behavior and in maternal-gene influences on development within her child – are expected to engender notably higher risk of schizophrenia. Such a prediction is broadly compatible with maternal imprinted-gene biases, and their correlates, being differentially associated with higher schizophrenia risk (Crespi 2008a; Crespi and Badcock 2008), but additional, targetted tests are required for robust evaluation. More generally, evolutionary theory provides clear, specific predictions regarding the presence and causes of conflicts within families (Emlen 1995, 1997; Surbey 1998), which underpin and complement psychodynamic and socioeconomic perspectives on such conflicts, as well as providing a basis for understanding conflicts within the minds of normal 'individuals', and those beset with such conditions as schizophrenia or depression (Read et al. 2004; Haig 2006b; Badcock 2009). As Laing and Esterson (1970, p. 12) inquired, 'are the experiences and behaviour that psychiatrists take as symptoms and signs of schizophrenia more socially intelligible than has come to be supposed?'

Long-term prospective studies, using high-risk populations, are required to evaluate patterns of cause and effect in relating childhood experiences and attachment patterns to the risks and forms of depression, schizophrenia, and other conditions. Evolutionary theory provides a conceptual framework to guide such studies, a framework that is fully compatible with both a psychoanalytic focus on childhood social-brain development in the family context and a strong role for interactive genetic and epigenetic effects in modulation of risk. In this context, the mother represents the primary environment of the child from conception until well past weaning, an environment that intimately modifies gene expression, and neurodevelopment, in the growing child. As such, supportive public-health interventions during early child development and in adolescence, which are sensitive

to the main causes of conflicts within families, are expected to yield disproportionate returns in reducing the incidence, severity, and recurrence of schizophrenia and depression, and more-generally increase emotional well-being in society (e. g., Gumley et al. 2008).

Autism and attachment

Idiopathic autism represents a spectrum of related conditions, with many genetic, epigenetic and environmental causes, characterized by differential under-development of the social brain from earliest infancy (Kanner 1943; Happé 1994; Abrahams and Geschwind 2008). A central focus in attachment-theory research on autism has been whether or not autistic children can indeed develop secure attachment with the mother, given that Kanner's (1943) original description of autism posited lack or disturbance of affective contact as a central feature. Rutgers et al. (2004) reviewed sixteen studies of attachment in autistic children, finding that autism was associated with lower levels of secure attachment overall, but that this difference 'disappeared in samples of children with higher mental development' or less severe symptoms, suggesting that attachment security is compatible with at least relatively high-functioning autism. By contrast, van Ijzendoorn et al. (2007) and Rutter et al. (2009) question the applicability and validity of attachment theory itself to autism, given the unusual nature of social relationships in this condition and uncertainties concerning whether autistics can develop internal working models of self and others, which form the bases for linguistic discourse. Psychological perspectives based in Vygotsky's work indicate, for example, that linguistic interactions with mother mediate childhood progress from listening, to private speech, and eventually to inner speech as thoughts (Fernyhough 1996), a process which is absent or underdeveloped in autism but may by contrast, be dysregulated via 're-expansion' in the auditory hallucinations of schizophrenia (Fernyhough 2004).

A general view of autism posits that under-development of the social brain should, as described by Kanner, centrally involve weak social-emotional connections with other individuals. Such differential social deficits, however, need not preclude relatively basic forms of attachment to the mother, as described by Bowlby for mother-offspring relations across most mammals. Indeed, from the perspective of parent-offspring conflicts and genomic imprinting, some subset of autism cases might also be considered to involve pathological over-expression of increased levels of demand imposed on mothers by offspring (Badcock and Crespi 2006; Crespi and Badcock 2008). Such demand may be imposed either directly, through behaviors that solicit forms of investment as in Angelman syndrome, or indirectly, through self-oriented, non-social behavior that precludes or delays physical independence, requiring mothers or others to provide longer-term, more highly-intensive care. This

hypothesis is concordant with several lines of evidence, including: (1) accelerated brain and body growth in young children with autism and increased relative effects from paternally-expressed imprinted genes (Crespi and Badcock 2008), (2) imprinted gene effects on reaction to novelty, and dispersal, in mice (Isles et al. 2002; Plagge et al. 2005), (3) a higher incidence of autism in males, who are more costly than females to rear (Gibson and Mace 2003; Rickard et al. 2007; Tamimi et al. 2003), (4) myriad reports of close and sustained, if atypical, relationships between mothers and their autistic children (e. g., Hoffman et al. 2009), and (5) temperaments of autistic children that involve higher rates of activity, impulsivity, and non-compliance (e. g., Garon et al. 2009).

The degree to which autism spectrum traits in non-clinical populations actually engender higher levels of early maternal or biparental investment has yet to be investigated, and indeed, many childhood social abilities are expected to have evolved in the context of soliciting higher investment from mother via providing her with positive-affect emotional benefits contingent on social skill development (e. g., Hrdy 1999), in addition to imposing negative-affect costs through behaviors such as refusal, tantrums, and, perhaps, insistence on sameness. For analyzing behavioral interactions between mothers and offspring, it is crucial to bear in mind that 'disorders' such as autism are postulated to represent sequelae to dysregulation of mechanisms that evolved in contexts of both conflict and cooperation, with evolutionary and behavioral conflicts potentiating increased levels of risk (Crespi 2010).

A primary implication of attachment theory, and behavioral-evolutionary genetics, for elucidating the causes of autism, is that early-childhood social motivation, in the context of 'demands' imposed on mothers via physical, social-emotional and linguistic interactions, should drive cascading effects on social-brain development that are either normal or deviate towards autistic phenotypes. The neurological and endocrine bases for social motivation and affective bonding in infants (e. g., Bowlby 1969 p. 203-204; Moriceau and Sullivan 2005; Grossmann et al. 2008) and children (e. g., Bartz and Hollander 2008) have been much less studied than those in mothers (e. g., Strathern et al. 2009), though their relevance for understanding mother-child interactions should be no less consequential. Studies of plasma oxytocin levels in autism have yielded unusual results: two studies found lower plasma oxytocin in children with autism (Modahl et al. 1998; Green et al. 2001), but unexpectedly, oxytocin levels were positively associated with degree of social impairment (Modahl et al. 1998); in the single study of adults, autistic individuals showed significantly higher levels of plasma oxytocin than did controls (Jansen et al. 2006). Might oxytocin in autistics subserve, to some degree, positive reinforcement of non-social stimuli, or might epigenetically-based reduction of oxytocin receptor expression (Gregory et al. 2009) follow from early social-

interaction deficits? The μ -opioid system represents another important candidate mechanism, in addition to oxytocin, for neuroendocrine regulation of attachment, given links of allelic variants in the ν -opioid receptor gene OPRM1 with attachment patterns, sensitivity to social rejection, drug dependence, and risk of schizophrenia (Insel 2003; Barr et al. 2008; Way et al. 2009; Mague and Blendy 2010; Serý et al. 2010) and evidence for parent of origin effects influencing phenotypic effects from this gene (Lemire 2005).

An imprinted-gene network for attachment of the social brain

Three lines of evidence: (1) demonstrations that imprinted-gene expression and coexpression centrally mediate prenatal and postnatal growth, (2) diverse forms of data on imprinted-gene expression effects in the brain, and (3) expectations from theory that mother-offspring interactions should involve genomic conflicts, lead to the prediction that a brain-specific imprinted-gene coexpression network should exist, and should modulate aspects of human mother-child attachment. The presence of such a network in humans was evaluated by testing statistically for differentially-frequent coexpression of brain-expressed imprinted genes, compared to expression of imprinted genes with other genes independent of imprinting status. For each of the 64 verified human imprinted genes (<http://igc.otago.ac.nz/table.html>), a set of highly coexpressed genes was generated using the Gemma co-expression database (<http://www.chibi.ubc.ca/Gemma/searchCoexpression.html>). These sets of coexpressed genes were combined, to generate a list of genes that were highly coexpressed with four or more imprinted genes. The list comprised 188 genes in all, of which approximately 0.6% ($64 / \sim 10,000$ total brain-expressed genes) should be imprinted under a null model of coexpression random with regard to imprinting status. Six (3.1%) of the 188 coexpressed genes were imprinted, an approximate five-fold excess ($\chi^2 = 17.6$, $P < 0.001$). The highly coexpressed imprinted genes included PEG3 and NDN, two genes that mediate development of oxytocin-secreting neurons (Davies et al. 2008); NDN may also be involved in risk of schizophrenia (Le-Niculescu et al. 2007), and both PEG3 and NDN are members of a network of genes differentially coexpressed in the prefrontal cortex of schizophrenics (module 16 of Torkamani et al. 2010). Additional relatively-highly coexpressed genes in the network included three genes with genetic-association or copy-number variation links to both autism and schizophrenia, CNTNAP2, NRXN1, and BOLA2 (reviewed in Crespi et al. 2010; coexpressed with 6, 7 and 11 imprinted genes respectively). Additional data implicating this network, and imprinting effects, in autism and schizophrenia includes: (1) the presence of parent of origin effects for the associations of CNTNAP2 with autism (Arking et al. 2008) and for the speech-language associated gene FOXP2 (Feuk et al. 2006) that interacts directly with

CNTNAP2 (Vernes et al. 2008), and (2) co-localization of the imprinted, schizophrenia-associated gene LRRTM1 (Francks et al. 2007) with NRXN1 at glutamatergic synapses (Brose 2009).

This analysis requires replication using other data sets, and more-detailed bioinformatic dissection of coexpression patterns, but it provides preliminary evidence of interactions between brain-expressed imprinted genes that mediate aspects of mother-offspring interaction and social-brain disorders. The existence and structure of brain-specific imprinted-gene network should have important implications for pharmacological interventions; for example, of the 11 genes most-highly altered in expression from treatment of mice with the mood-stabilizer drug valproic acid (Chetcuti et al. 2006), two are imprinted (Peg3 and Sfm2), one is predicted to be imprinted (Zic1)(Luedi et al. 2007), one interacts directly with the imprinted gene Wt1 (Par-4)(Richard et al. 2001), and one (Kcna1) interacts directly with Cntnap2 (Strauss et al. 2006). Such a striking concentration of imprinted-gene related expression changes is consistent with the molecular function of valproic acid as a histone deacetylase inhibitor, an agent that exhibits differential epigenetic effects on imprinted genes (e. g., Baqir and Smith 2006); moreover, valproic acid during human or rodent pregnancy is a highly-penetrant cause of autism in offspring (Rinaldi et al. 2008; Dufour-Rainfray et al. 2010), and valproic acid partially restores levels of MeCP2 in a mouse model of Rett syndrome (Vecsler et al. 2010). Might such epigenetic treatments exert their effects through canalizing or decanalizing neurological-pathway functions of interacting imprinted genes?

Conclusions

Understanding human social development requires integration of theory and data from diverse, highly-specialized, disciplines, including genetics, development, neuroscience, psychology and psychiatry. Conrad Waddington's still-nascent science of epigenetics serves as a conceptual and experimental platform to connect social-environmental variation with the gene expression patterns that drive development, as genes and family, especially the mother, jointly sculpt developing brains. Like other traits, epigenetic landscapes of social development have evolved, subject to the conflicts and confluences of genetic interest that form the cornerstone of modern evolutionary theory. Effects from parent-offspring conflicts, and the intragenomic conflicts of imprinting, are predicted from such theory to modulate normal development and to potentiate specific directions and forms of maladaptive trajectory, due to genetic, epigenetic, and social-environmental perturbations. As such, dovetailing of predictions from evolutionary genetics and epigenetics with the conceptual constructs and experimental tools of developmental psychology, neuroscience and epigenetics should yield novel insights into the the evolutionary

underpinnings of the human social brain and its disorders, and the strategies of the genes involved.

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References

Abrahams BS, Geschwind DH (2008) Advances in autism genetics: on the threshold of a new neurobiology. *Nat Rev Genet.* 9:341-355

Allen ND, Logan K, Lally G et al. (1995) Distribution of parthenogenetic cells in the mouse brain and their influence on brain development and behavior. *Proc Natl Acad Sci U S A.* 92:10782-10786

Andrews SC, Wood MD, Tunster SJ et al. (2007) Cdkn1c (p57Kip2) is the major regulator of embryonic growth within its imprinted domain on mouse distal chromosome 7. *BMC Dev Biol.* 7:53

Angiolini E, Fowden A, Coan P et al. (2006) Regulation of placental efficiency for nutrient transport by imprinted genes. *Placenta* 27 Suppl A:S98-102

Anglin DM, Cohen PR, Chen H (2008) Duration of early maternal separation and prediction of schizotypal symptoms from early adolescence to midlife. *Schizophr Res.* 103:143-50

Arima T, Kamikihara T, Hayashida T et al. (2005) ZAC, LIT1 (KCNQ1OT1) and p57KIP2 (CDKN1C) are in an imprinted gene network that may play a role in Beckwith-Wiedemann syndrome. *Nucleic Acids Res.* 33:2650-2660

Arking DE, Cutler DJ, Brune CW et al. (2008) A common genetic variant in the neurexin superfamily member CNTNAP2 increases familial risk of autism. *Am J Hum Genet.* 82:160-164

Badcock C (2009) *The Imprinted Brain*. Jessica Kingsley, London.

Badcock C, Crespi B (2006) Imbalanced genomic imprinting in brain development: an evolutionary basis for the aetiology of autism. *J Evol Biol.* 19:1007-1032

Baqir S, Smith LC (2006) Inhibitors of histone deacetylases and DNA methyltransferases alter imprinted gene regulation in embryonic stem cells. *Cloning Stem Cells* 8:200-213

Barr CS, Schwandt ML, Lindell SG, Higley JD, Maestripietri D, Goldman D, Suomi SJ, Heilig M. (2008) Variation at the mu-opioid receptor gene (OPRM1) influences attachment behavior in infant primates. *Proc Natl Acad Sci U S A*. 105:5277-5281

Berry K, Barrowclough C, Wearden A (2007) A review of the role of adult attachment style in psychosis: unexplored issues and questions for further research. *Clin Psychol Rev*. 27:458-745

Berry K, Barrowclough C, Wearden A (2008) Attachment theory: a framework for understanding symptoms and interpersonal relationships in psychosis. *Behav Res Ther*. 46:1275-1282

Berry K, Wearden AJ, Barrowclough C, Liversidge T. (2006) Attachment styles, interpersonal relationships and psychotic phenomena in a non-clinical student sample. *Pers Individ Diff* 41:707-718

Blissett J, Harris G, Kirk J (2001) Feeding problems in Silver-Russell syndrome. *Dev Med Child Neurol*. 43:39-44

Bonati MT, Russo S, Finelli P et al. (2007) Evaluation of autism traits in Angelman syndrome: a resource to unfold autism genes. *Neurogenetics* 8:169-178

Bowlby, J. (1951). *Maternal Care and Mental Health*. Schocken Press, New York.

Bowlby J (1969). *Attachment and Loss: Attachment* (Vol. 1). Basic Books, New York.

Bretherton I (1992) The origins of attachment theory: John Bowlby and Mary Ainsworth. *Devel Psychol*. 28:759-775

Brose N (2009) Synaptogenic proteins and synaptic organizers: "many hands make light work". *Neuron* 61:650-652

Bressan FF, De Bem TH, Perecin F et al. (2009) Unearthing the roles of imprinted genes in the placenta. *Placenta* 30:823-834

Bretherton I (1997) Bowlby's legacy to developmental psychology. *Child Psychiatry Hum Dev.* 28:33-43

Brown WM, Consedine NS (2004) Just how happy is the happy puppet? An emotion signaling and kinship theory perspective on the behavioral phenotype of children with Angelman syndrome. *Med Hypotheses* 63:377-385

Burt A, Trivers RL (2006) *Genes in Conflict: The Biology of Selfish Genetic Elements*. Belknap Press, Cambridge

Champagne FA, Curley JP, Swaney WT et al. (2009) Paternal influence on female behavior: the role of *Peg3* in exploration, olfaction, and neuroendocrine regulation of maternal behavior of female mice. *Behav Neurosci.* 123:469-480

Charalambous M, da Rocha ST, Ferguson-Smith AC (2007) Genomic imprinting, growth control and the allocation of nutritional resources: consequences for postnatal life. *Curr Opin Endocrinol Diabetes Obes.* 14:3-12

Chetcuti A, Adams LJ, Mitchell PB, Schofield PR (2006) Altered gene expression in mice treated with the mood stabilizer sodium valproate. *Int J Neuropsychopharmacol.* 9:267-276

Cohen MM Jr. (2005) Beckwith-Wiedemann syndrome: historical, clinicopathological, and etiopathogenetic perspectives. *Pediatr Dev Pathol.* 8:287-304

Cohen D, Pichard N, Tordjman S et al. (2005) Specific genetic disorders and autism: clinical contribution towards their identification. *J Autism Dev Disord.* 35:103-116

Crespi B (2008a) Genomic imprinting in the development and evolution of psychotic spectrum conditions. *Biol Rev Camb Philos Soc.* 83:441-493

Crespi, B (2008b) Turner syndrome and the evolution of human sexual dimorphism. *Evolutionary Applications* 1:449-461

Crespi B (2010) The origins and evolution of genetic disease risk in modern humans. *Year in Evolutionary Biology* (in press)

Crespi B, Badcock C (2008) Psychosis and autism as diametrical disorders of the social brain. *Behav Brain Sci.* 31:241-61; discussion 261-320

Crespi B, Summers K, Dorus S (2009) Genomic sister-disorders of neurodevelopment: an evolutionary approach. *Evolutionary Applications* 2:81-100

Crespi B, Stead P, Elliot M. (2010) Comparative genomics of autism and schizophrenia *Proc Natl Acad Sci U S A*. 107:1736-1741

Curley JP, Barton S, Surani A, Keverne EB (2004) Coadaptation in mother and infant regulated by a paternally expressed imprinted gene. *Proc Biol Sci*. 271:1303-1309

Davies W, Isles AR, Humby T, Wilkinson LS (2008) What are imprinted genes doing in the brain? *Adv Exp Med Biol*. 626:62-70

Davies W, Lynn PM, Relkovic D, Wilkinson LS (2008) Imprinted genes and neuroendocrine function. *Front Neuroendocrinol*. 29:413-427

Dudley O, Muscatelli F (2007) Clinical evidence of intrauterine disturbance in Prader-Willi syndrome, a genetically imprinted neurodevelopmental disorder. *Early Hum Dev*. 83:471-478

Dufour-Rainfray D, Vourc'h P, Le Guisquet AM et al. (2010) Behavior and serotonergic disorders in rats exposed prenatally to valproate: a model for autism. *Neurosci Lett*. 470:55-59

Eggermann T (2009) Silver-Russell and Beckwith-Wiedemann syndromes: opposite (epi)mutations in 11p15 result in opposite clinical pictures. *Horm Res*. 71 Suppl 2:30-35

Eggermann T, Eggermann K, Schönherr N (2008) Growth retardation versus overgrowth: Silver-Russell syndrome is genetically opposite to Beckwith-Wiedemann syndrome. *Trends Genet*. 24:195-204

Emlen ST (1995) An evolutionary theory of the family. *Proc Natl Acad Sci U S A*. 92:8092-8099

Emlen, ST (1997) The evolutionary study of human family systems. *Social Science Information* 36: 563-589

Fauque P, Ripoché MA, Tost J et al. (2010) Modulation of imprinted gene network in placenta results in normal development of in vitro manipulated mouse embryos. *Hum Mol Genet*. (in press)

Fernyhough C (1996) The dialogic mind: A dialogic approach to the higher mental functions. *New Ideas In Psychology* 14:47-62

Fernyhough C (2004) Alien voices and inner dialogue: towards a developmental account of auditory verbal hallucinations. *New Ideas In Psychology* 22:49-68

Feuk L, Kalervo A, Lipsanen-Nyman M et al. (2006) Absence of a paternally inherited FOXP2 gene in developmental verbal dyspraxia. *Am J Hum Genet.* 79:965-972.

Fox M, Sear R, Beise J et al. (2010) Grandma plays favourites: X-chromosome relatedness and sex-specific childhood mortality. *Proc Biol Sci.* 277:567-573.

Francks C, Maegawa S, Laurén J et al. (2007) LRRTM1 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia. *Mol Psychiatry* 12:1129-39, 1057

Frith CD (2008) Social cognition. *Philos Trans R Soc Lond B Biol Sci.* 363:2033-2039

Gabory A, Ripoche MA, Le Digarcher A et al. (2009) H19 acts as a trans regulator of the imprinted gene network controlling growth in mice. *Development* 136:3413-3421

Garon N, Bryson SE, Zwaigenbaum L et al. (2009) Temperament and its relationship to autistic symptoms in a high-risk infant sib cohort. *J Abnorm Child Psychol.* 37:59-78

Geneviève D, Sanlaville D, Faivre L et al. (2005) Paternal deletion of the GNAS imprinted locus (including Gnasxl) in two girls presenting with severe pre- and post-natal growth retardation and intractable feeding difficulties. *Eur J Hum Genet.* 13:1033-1039

Gibson MA, Mace R (2003) Strong mothers bear more sons in rural Ethiopia. *Proc Biol Sci.* 270 Suppl. 1:S108-109

Goldstone AP (2006) The hypothalamus, hormones, and hunger: alterations in human obesity and illness. *Prog Brain Res.* 153:57-73.

Gregory SG, Connelly JJ, Towers AJ et al. (2009) Genomic and epigenetic evidence for oxytocin receptor deficiency in autism. *BMC Med.* 7:62

Grossmann T, Johnson MH, Lloyd-Fox S et al. (2008) Early cortical specialization for face-to-face communication in human infants. *Proc Biol Sci.* 275:2803-2811.

Gumley AI, Schwannauer M, MacBeth A, Read J (2008) Emotional recovery and staying well after psychosis: An attachment based conceptualisation. *Attachment* 2: 127-148

Haig D (1993) Genetic conflicts in human pregnancy. *Q Rev Biol.* 68:495-532

Haig, D. (1997) The social gene. In Krebs, J. R. & Davies, N. B. (eds) *Behavioural Ecology: an Evolutionary Approach*, Blackwell, London, pp. 284-304

Haig, D. (2002) *Genomic Imprinting and Kinship*. Rutgers University Press, New Brunswick, New Jersey.

Haig, D. (2004a) The (dual) origin of epigenetics. *Cold Spring Harbor Symposia on Quantitative Biology* 69: 1-4.

Haig D (2004b) Genomic imprinting and kinship: how good is the evidence? *Annu Rev Genet.* 38:553-585.

Haig D (2006a) Intragenomic politics. *Cytogenet Genome Res* 113: 68-74

Haig D (2006b) Intrapersonal conflict., In *Conflict*. M. K. Jones & A. C. Fabian (eds.) Cambridge University Press, Cambridge. Pages 8-22

Haig D (2009) Transfers and transitions: Parent-offspring conflict, genomic imprinting, and the evolution of human life history. *Proc Natl Acad Sci U S A.* (in press)

Haig D, Graham C (1991) Genomic imprinting and the strange case of the insulin-like growth factor-II receptor. *Cell* 64:1045-1046

Haig D, Wharton R (2003) Prader-Willi syndrome and the evolution of human childhood. *Am J Hum Biol.* 15:320-329

Hamilton WD (1964) The genetical evolution of social behaviour I and II. *J Theor Biol* 7: 1-16 and 17-52

Hamilton WD (1996) *Narrow Roads of Gene Land* vol. 1: *Evolution of Social Behaviour* Oxford University Press, Oxford. ISBN 0-7167-4530-5

Happé F (1994) *Autism: an Introduction to Psychological Theory*. UCL Press, London

Harrop C, Trower P (2001) Why does schizophrenia develop at late adolescence? *Clin Psychol Rev.* 21:241-265

Hinde CA, Kilner RM (2007) Negotiations within the family over the supply of parental care. *Proc Biol Sci.* 274:53-60

Hoffman CD, Sweeney DP, Hodge D (2009) Parenting stress and closeness in mothers of typically developing children and mothers of children with autism. *Focus on Autism and other Developmental Disabilities* 24:178-187

Holland A, Whittington J, Hinton E (2003) The paradox of Prader-Willi syndrome: a genetic model of starvation. *Lancet* 362:989-991

Höybye C (2004) Endocrine and metabolic aspects of adult Prader-Willi syndrome with special emphasis on the effect of growth hormone treatment. *Growth Horm IGF Res.* 14:1-15.

Hrdy S (1999) *Mother Nature: a History of Mothers, Infants, and Natural Selection*. New York, Pantheon Books

Hrdy S (2009) *Mothers and Others: The Evolutionary Origins of Mutual Understanding*. Harvard University Press.

Humphrey LT 2009. Weaning behaviour in human evolution. *Semin Cell Dev Biol.* (in press)

Isles AR, Holland AJ (2005) Imprinted genes and mother-offspring interactions. *Early Hum Dev.* 81:73-77

Isles AR, Davies W, Wilkinson LS (2006) Genomic imprinting and the social brain. *Philos Trans R Soc Lond B Biol Sci.* 361:2229-2237.

Isles AR, Baum MJ, Ma D, Szeto A, Keverne EB, Allen ND (2002) A possible role for imprinted genes in inbreeding avoidance and dispersal from the natal area in mice. *Proc Biol Sci.* 269:665-670

Jansen LMC, Gispen-de Wied CC, Wiegant VM (2006) Autonomic and neuroendocrine responses to a psychosocial stressor in adults with autistic spectrum disorder. *J Autism Devel Dis* 36:891-899

Jedele KB (2007) The overlapping spectrum of Rett and Angelman syndromes: a clinical review. *Semin Pediatr Neurol*. 14:108-117

Joseph B, Wallén-Mackenzie A, Benoit G et al. (2003) p57(Kip2) cooperates with Nurr1 in developing dopamine cells. *Proc Natl Acad Sci U S A*. 100:15619-15624

Kanner L (1943) Autistic disturbances of affective contact. *Nerv Child*. 2:217-50

Kelsey G (2007) Genomic imprinting--roles and regulation in development. *Endocr Dev*. 12:99-112

Kernohan KD, Jiang Y, Tremblay DC, Bonvissuto AC, Eubanks JH, Mann MR, Bérubé NG. (2010) ATRX partners with cohesin and MeCP2 and contributes to developmental silencing of imprinted genes in the brain. *Dev Cell*. 18:191-202

Keverne EB (2001a) Genomic imprinting and the maternal brain. *Prog Brain Res*. 133:279-285

Keverne EB (2001b) Genomic imprinting, maternal care, and brain evolution. *Horm Behav*. 40:146-155

Keverne EB, Fundele R, Narasimha M et al. (1996) Genomic imprinting and the differential roles of parental genomes in brain development. *Brain Res Dev Brain Res*. 92:91-100

Laing RD, Esterson A (1970) *Sanity, Madness and the Family*. Tavistock Publications, London.

Lemire M. (2005) A simple nonparametric multipoint procedure to test for linkage through mothers or fathers as well as imprinting effects in the presence of linkage. *BMC Genet*. 6 Suppl 1:S159

Le-Niculescu H, Balaraman Y, Patel S et al. (2007) Towards understanding the schizophrenia code: an expanded convergent functional genomics approach. *Am J Med Genet B Neuropsychiatr Genet*. 144B:129-158

Ling JQ, Hoffman AR (2007) Epigenetics of long-range chromatin interactions. *Pediatr Res*. 61:11R-16R

Liotti L, Gumley A (2008) An attachment perspective on schizophrenia: the role of disorganized attachment, dissociation and mentalization. In *Psychosis, Trauma and Dissociation*, A Moskowitz, I Schafer, MJ Dorahy (eds) John Wiley & Sons, New York, pp 117-133

Lui JC, Finkelstein GP, Barnes KM, Baron J (2008) An imprinted gene network that controls mammalian somatic growth is down-regulated during postnatal growth deceleration in multiple organs. *Am J Physiol Regul Integr Comp Physiol*. 295:R189-196

Liu Z, Li X, Ge X (2009) Left too early: the effects of age at separation from parents on Chinese rural children's symptoms of anxiety and depression. *Am J Public Health*. 99:2049-2054

Luedi PP, Dietrich FS, Weidman JR, Bosko JM, Jirtle RL, Hartemink AJ (2007) Computational and experimental identification of novel human imprinted genes. *Genome Res*. 17:1723-1730

Lyons-Ruth K. (2008) Contributions of the mother-infant relationship to dissociative, borderline, and conduct symptoms in young adulthood. *Infant Ment Health J*. 29:203-218

Macdonald K, Macdonald TM (2010) The peptide that binds: a systematic review of oxytocin and its prosocial effects in humans. *Harv Rev Psychiatry*. 18:1-21

Maestripieri, D (2002) Parent-offspring conflict in primates. *International Journal of Primatology* 23:923-951

Mague SD, Blendy JA. (2010) OPRM1 SNP (A118G): Involvement in disease development, treatment response, and animal models. *Drug Alcohol Depend*. (in press)

Manaye KF, Lei DL, Tizabi Y et al. (2005) Selective neuron loss in the paraventricular nucleus of hypothalamus in patients suffering from major depression and bipolar disorder. *J Neuropathol Exp Neurol*. 64:224-229

McMinn J, Wei M, Schupf N et al. (2006) Unbalanced placental expression of imprinted genes in human intrauterine growth restriction. *Placenta* 27:540-549

Miyano M, Horike S, Cai S, Oshimura M, Kohwi-Shigematsu T. (2008) DLX5 expression is monoallelic and Dlx5 is up-regulated in the Mecp2-null frontal cortex. *J Cell Mol Med.* 12:1188-1191

Modahl C, Green L, Fein D et al. (1998) Plasma oxytocin levels in autistic children. *Biol Psychiatry.* 43:270-277

Moriceau S, Sullivan RM (2005) Neurobiology of infant attachment. *Dev Psychobiol.* 47:230-242

Oliver C, Horsler K, Berg K et al. (2007) Genomic imprinting and the expression of affect in Angelman syndrome: what's in the smile? *J Child Psychol Psychiatry* 48:571-579

Owen MJ, Craddock N, Jablensky A (2007) The genetic deconstruction of psychosis. *Schizophr Bull.* 33:905-911

Pesonen AK, Räikkönen K, Heinonen K et al. (2007) Depressive symptoms in adults separated from their parents as children: a natural experiment during World War II. *Am J Epidemiol.* 166:1126-1133

Pickering L., Simpson J, Bentall RP (2008) Insecure attachment predicts proneness to paranoia but not hallucinations. *Pers Individ Diff.* 44:1212-1224

Plagge A, Gordon E, Dean W et al. (2004) The imprinted signaling protein XL alpha s is required for postnatal adaptation to feeding. *Nat Genet.* 36:818-826

Plagge A, Isles AR, Gordon E et al. (2005) Imprinted Nesp55 influences behavioral reactivity to novel environments. *Mol Cell Biol.* 25:3019-3026

Read J, Gumley AI (2008) Can attachment theory help explain the relationship between childhood adversity and psychosis? *Attachment: New Directions in Psychotherapy and Relational Psychoanalysis.* 2:1-35

Read J, Seymour F, Mosher LR (2004) Unhappy families. In: *Models of Madness: Psychological, Social and Biological Approaches to Schizophrenia.* Read J, Bentall R, Mosher L (eds), pp. 253-268

Reik W, Davies K, Dean W et al. (2001) Imprinted genes and the coordination of fetal and postnatal growth in mammals.

Novartis Found Symp. 237:19-31; discussion 31-42

Read J, Mosher L, Bentall, R (2004) *Models of Madness: Psychological, Social and Biological Approaches to Schizophrenia*. Routledge Press, Basingstoke, UK

Renfree MB, Hore TA, Shaw G et al. (2009) Evolution of genomic imprinting: insights from marsupials and monotremes. *Annu Rev Genomics Hum Genet.* 10:241-262

Rickard IJ, Russell AF, Lummaa V (2007) Producing sons reduces lifetime reproductive success of subsequent offspring in pre-industrial Finns. *Proc Biol Sci.* 274:2981-2988

Richard DJ, Schumacher V, Royer-Pokora B, Roberts SG (2001) Par4 is a coactivator for a splice isoform-specific transcriptional activation domain in WT1. *Genes Dev.* 15:328-339

Rinaldi T, Perrodin C, Markram H (2008) Hyper-connectivity and hyper-plasticity in the medial prefrontal cortex in the valproic acid animal model of autism. *Front Neural Circuits.* 2:4

Ross HE, Young LJ (2009) Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior. *Front Neuroendocrinol.* 30:534-547

Royle NJ, Hartley IR, Parker GA (2004) Parental investment and family dynamics: Interactions between theory and empirical tests. *Pop Ecol* 46: 231-241

Rutgers AH, Bakermans-Kranenburg MJ, van Ijzendoorn MH, van Berckelaer-Onnes IA (2004) Autism and attachment: a meta-analytic review. *J Child Psychol Psychiatry.* 45:1123-1134

Rutter M, Kreppner J, Sonuga-Barke E (2009) Emanuel Miller Lecture: Attachment insecurity, disinhibited attachment, and attachment disorders: where do research findings leave the concepts? *J Child Psychol Psychiatry.* 50:529-543.

Sahoo T, Peters SU, Madduri NS et al. (2006) Microarray based comparative genomic hybridization testing in deletion bearing patients with Angelman syndrome: genotype-phenotype correlations. *J Med Genet.* 43:512-516

Sandhu KS, Shi C, Sjölander M et al. (2009) Nonallelic transvection of multiple imprinted loci is organized by the H19 imprinting control region during germline development. *Genes Dev.* 23:2598-2603

Sellen DW (2007) Evolution of infant and young child feeding: implications for contemporary public health. *Annu Rev Nutr.* 27:123-148

Serý O, Prikryl R, Castulík L, St'astný F. (2010) A118G polymorphism of OPRM1 gene is associated with schizophrenia. *J Mol Neurosci.* 41:219-222

Shaver PR, Mikulincer M (2002) Attachment-related psychodynamics. *Attach Hum Dev.* 4:133-161

Sigurdsson MI, Jamshidi N, Jonsson JJ, Palsson BO (2009) Genome-scale network analysis of imprinted human metabolic genes. *Epigenetics* 4:43-46

Smiseth PT, Wright J, Kölliker M (2008) Parent-offspring conflict and co-adaptation: behavioural ecology meets quantitative genetics. *Proc Biol Sci.* 275:1823-1830

Smits G, Kelsey G (2006) Imprinting weaves its web. *Dev Cell.* 11:598-599

Soltis J (2004) The signal functions of early infant crying. *Behav Brain Sci.* 27:443-458; discussion 459-490

Soni S, Whittington J, Holland AJ et al. (2008) The phenomenology and diagnosis of psychiatric illness in people with Prader-Willi syndrome. *Psychol Med.* 38:1505-1514

Strauss KA, Puffenberger EG, Huentelman MJ et al. (2006) Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. *N Engl J Med.* 354:1370-1377

Surbey MK (1998) Parent and offspring strategies in the transition at adolescence. *Human Nature* 9:67-94

Swaab DF, Purba JS, Hofman MA (1995) Alterations in the hypothalamic paraventricular nucleus and its oxytocin neurons (putative satiety cells) in Prader-Willi syndrome: a study of five cases. *J Clin Endocrinol Metab.* 80:573-579

Tamimi RM, Lagioui P, Mucci LA et al. (2003) Average energy intake among pregnant women carrying a boy compared with a girl. *British Med J* 326:1245-1246

Thompson RA (2008) Attachment-related mental representations: introduction to the special issue. *Attachment Human Devel* 10: 347-358

Tiliopoulos N, Goodall K (2009) The neglected link between adult attachment & schizotypal personality traits. *Pers Individ Diff* 47:299-304

Torkamani A, Dean B, Schork NJ, Thomas EA. (2010) Coexpression network analysis of neural tissue reveals perturbations in developmental processes in schizophrenia. *Genome Res.* 20:403-412

Trivers RL (1974). Parent-offspring conflict. *Amer Zool* 14:249-264

Tsai TF, Armstrong D, Beaudet AL (1999) Necdin-deficient mice do not show lethality or the obesity and infertility of Prader-Willi syndrome. *Nat Genet.* 22:15-16

Tyrka AR, Wier L, Price LH et al. (2008) Childhood parental loss and adult psychopathology: effects of loss characteristics and contextual factors. *Int J Psychiatry Med.* 38:329-344

Varrault A, Gueydan C, Delalbre A et al. (2006) *Zac1* regulates an imprinted gene network critically involved in the control of embryonic growth. *Dev Cell.* 11:711-722

van Ijzendoorn MH, Rutgers AH, Bakermans-Kranenburg MJ et al. (2007) Parental sensitivity and attachment in children with autism spectrum disorder: comparison with children with mental retardation, with language delays, and with typical development. *Child Dev.* 78:597-608

Vecsler M, Simon AJ, Amariglio N et al. (2010) MeCP2 deficiency downregulates specific nuclear proteins that could be partially recovered by valproic acid in vitro. *Epigenetics* (in press)

Vernes SC, Newbury DF, Abrahams BS et al. (2008) A functional genetic link between distinct developmental language disorders. *N Engl J Med.* 359:2337-2345

Waddington C (1957) *The Strategy of the Genes*. Macmillan, New York

Wagner A (2000) Robustness against mutations in genetic networks of yeast. *Nat Genet.* 24:355-361

Wagschal A, Feil R (2006) Genomic imprinting in the placenta. *Cytogenet Genome Res.* 113:90-98

Way BM, Taylor SE, Eisenberger NI. (2009) Variation in the mu-opioid receptor gene (OPRM1) is associated with dispositional and neural sensitivity to social rejection. *Proc Natl Acad Sci U S A.* 106:15079-15084

Webb T, Maina EN, Soni S et al. (2008) In search of the psychosis gene in people with Prader-Willi syndrome. *Am J Med Genet A.* 146:843-853

Weinstein LS, Liu J, Sakamoto A et al. (2004) Minireview: GNAS: normal and abnormal functions. *Endocrinology* 145:5459-5464

Wilson JS, Costanzo PR (1996) A preliminary study of attachment, attention, and schizotypy in early adulthood. *J. Soc. Clin. Psychol.* 15:231–260

Wells JC (2003) Parent-offspring conflict theory, signaling of need, and weight gain in early life. *Q Rev Biol.* 78:169-202

Wilkinson LS, Davies W, Isles AR (2007) Genomic imprinting effects on brain development and function. *Nat Rev Neurosci.* 8:832-843

Zhao Z, Tavoosidana G, Sjölander M et al. (2006) Circular chromosome conformation capture (4C) uncovers extensive networks of epigenetically regulated intra- and interchromosomal interactions. *Nat Genet.* 38:1341-1347

Figure 1. Waddington's (1957) conceptualization of an epigenetic landscape, with the pegs as genes and the strings as developmental effects from gene expression.

Figure 2. A simple model for potential interactions of levels of maternal social-behavioral provision/imposition with levels of child social-behavioral solicitation/imposition.