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Hormones and human developmental plasticity

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ABSTRACT

Natural selection favors the evolution of mechanisms that optimize the allocation of resources and time among competing traits. Hormones mediate developmental plasticity, the changes in the phenotype that occur during ontogeny. Despite their highly conserved functions, the flexibilities of human hormonal systems suggest a strong history of adaptation to variable environments. Physiological research on developmental plasticity has focused on the early programming effects of stress, the hypothalamus-pituitary-adrenal axis (HPAA) and the hypothalamus-pituitary-gonadal axis (HPGA) during critical periods, when the hormones produced have the strongest influence on the developing brain. Often this research emphasizes the maladaptive effects of early stressful experiences. Here we posit that the HPAA and HPAG systems in human developmental plasticity have evolved to be responsive to complex and dynamic problems associated with human sociality. The lengthy period of human offspring dependency, and its associated brain development and risks, is linked to the uniquely human combination of stable breeding bonds, extensive paternal effort in a multi-male group, extended bilateral kin recognition, grandparenting, and controlled exchange of mates among kin groups. We evaluate an evolutionary framework that integrates proximate physiological explanations with ontogeny, phylogeny, adaptive function, and comparative life history data.

1. Introduction

Organisms adjust their development and adult phenotypes in response to challenges, a phenomenon known as phenotypic plasticity (West-Eberhard, 2003). Phenotypic plasticity is mediated in part by hormones, molecules that aid in the coordination of metabolic tasks needed for growth, maintenance, survival, and reproduction. Hormones and endocrine regulatory systems are ancient evolutionary features that are highly conserved across taxonomic groups. Several molecules with a biochemical structure similar to hormones have been found in unicellular organisms (Le Roith et al., 1980), and it is estimated that estrogen receptors were already present in chordates 525 million years ago (Baker, 2003).

While endocrine systems are highly conserved, endocrine function is highly variable, and this variation can occur at different levels. For example, variation can be observed in hormone production and secretion, in the distribution and expression of membrane and nuclear receptors, in rates of enzymatic conversion, in rates of hormone uptake into tissues, and in the concentrations of carrier proteins in circulation. The highly conserved functions of endocrine systems combined with flexibilities in regulatory features suggest a history of selection for hormone-dependent traits that are key for organismal survival in variable environments, permitting flexible responses to variations in environmental stability (Roney, 2016).

For evolutionary and behavioral endocrinologists, integrating the study of proximate mechanisms with ultimate functions of hormones is necessary to understand the design of endocrine systems and individual variation in disease susceptibility (Anacker, 2014; Muehlenbein and Bribiescas, 2005; Muehlenbein et al., 2017). The complexity of the endocrine system and its ability to create both positive and negative correlations between traits raises the question of whether hormonal responses to environmental stimuli reflect an evolved adaptation, an evolutionary constraint, or a byproduct of other hormonal functions (Adkins-Regan, 2008; Ketterson and Nolan, 1999).

In the present article, we take an evolutionary perspective and present the theoretical basis that characterizes our scientific research. Because natural selection favors the evolution of strategies that optimize the way resources and time are efficiently allocated among competing traits, we argue that an evolutionary life history approach provides an important model for understanding the evolutionary functions of hormones and variation in phenotypes (Flinn et al., 2011; Habecker and Flinn, 2019; Hau, 2007; Nepomnaschy et al., 2009; Spencer, 2017).

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We first provide a brief overview of the proximate functions of hormones and endocrine systems, followed by a summary of the evolutionary life history of the human child and family. Then, using an ontogenetic approach, we focus specifically on a life history theory perspective of the functions of the hypothalamic-pituitary-adrenal axis (HPAA) and hypothalamic-pituitary-gonadal axis (HPGA) in humans.

2. An overview of the proximate functions of hormones

Hormone-based regulatory systems mediate the coordinated physiological and behavioral responses of organisms to biotic and abiotic environmental stimuli (Prall and Muehlenbein, 2014). Peptides and steroids, the two broad hormone categories, are typically released into the circulatory system from endocrine glands in response to, or in anticipation of, specific internal or external signals. Hormonal effects depend on the type of receptor they bind with and on the type of tissue where the receptors are found (Griffin and Ojeda, 1992). Tissues differ in their intracellular signaling composition and in the type of receptors they express.

Variations in tissue response to hormones are a consequence of the genetic make-up of an individual, and they are mediated via epigenetic mechanisms in response to internal and external cues. For example, when epinephrine (Epi) binds to alpha adrenergic receptors, it causes vasoconstriction, whereas when it binds to beta receptors, it causes vasodilation. In a challenging situation, these two effects serve to divert blood glucose from the intestine to skeletal muscles, for a successful fight or flight response. The intensity and duration of the response will be modulated, in part, by the distribution and density of receptors. Furthermore, Epi can have different effects, even when it binds to the same receptor, which illustrates the role tissue-specific intracellular signaling systems play in regulating hormone-receptor responses. The differential effects of Epi when it binds to beta receptors in the liver versus those found in blood vessels provides a good example. In the liver it causes the breakdown of glycogen into glucose, whereas in blood vessels it induces vasodilation. Epi thus prepares the body for a perceived impending challenge by coordinating the activities of different tissues to produce a successful response. In this case the response requires an increase of the glycemic state and of glucose delivery to relevant organs.

Importantly, hormones do not work independently. They interact in complex ways with each other and their target tissues, producing a phenomenon known as “physiological epistasis” (Cheverud and Routman, 1995; Ketterson and Nolan, 1999) which mediates organisms’ responses to environmental (physical, social, etc.) conditions. In an emergency situation, the metabolic and systemic effects of Epi are assisted synergistically by other hormones such as glucocorticoids (Sapolsky et al., 2000).

Circulating levels of hormones are regulated by mechanisms that begin in the central nervous system. Until recently, these central regulatory mechanisms were thought to maintain organismal homeostasis, with hormone levels fluctuating within ranges that allow for the defense and maintenance of vital functions after responding to internal or external challenges. However, alternative views are emerging. Indeed, organisms may not have an ideal set point for every function as originally believed. Instead, internal status appears to be continuously changing in anticipation of, or in response to, those endogenous and exogenous perturbations. Consequently, alternative terms to homeostasis, such as rheostasis (Mrosovsky, 1990), hormesis (Mattson and Calabrese, 2010), polystasis (Weisfeld, 1982) and allostasis (McEwen and Wingfield, 2010) have been proposed. While this debate falls outside the scope of this article, we do expect that the body's adjustments to specific cues depend on past and current organismal states, its developmental stage, and even transgenerational events. Because an organism's internal state must be expected to vary, representing them as fixed set points can be misleading.

3. Developmental phenotypic plasticity and life history trade-offs

The ultimate role of hormone-based regulatory systems is to guide adaptive phenotypic changes. This process, known as phenotypic plasticity, refers to the changes in morphology, physiology, and behavior (i.e., all aspects of the phenotype) produced by organisms in response to variable internal and external environmental cues (West-Eberhard, 2003). An example of phenotypic plasticity is the sex change observed in the bluehead wrasse (*Thlassoma bifasciatum*). Many coral reef fishes develop as a small size female, later becoming male when reaching a larger size (West-Eberhard, 2003; Warner, 1975). Interestingly, in low population density conditions, when a large male can monopolize reproduction, sex reversal is favored (Warner, 1984), mediated by the effects of neuropeptides and sex steroids such as 11-ketotestosterone (Moore, 1991; Semsar and Godwin, 2004). This type of phenotypic plasticity appears to be evolutionarily adaptive as the sex change allows fish to switch reproductive strategy in response to individual size, population sex ratio, and population density.

Phenotypic plasticity requires that the organism uses current environmental information to efficiently allocate resources toward competing life history traits. The central tenet of life history theory is that the resources available to an organism (and which contribute towards the organism's fitness) are limited. Consequently, organisms must selectively distribute those resources in a way that best increases overall reproductive success. Organisms face trade-offs in terms of resource allocation as they cannot invest energy both in somatic (growth and maintenance) and reproductive effort (Stearns, 1989). For example, energy invested in growing a large body cannot be simultaneously invested in reproduction or immunological defenses. This allocation problem produces multiple types of trade-offs, including current versus future reproduction, quantity versus quality of offspring, reproduction versus survivorship, and growth versus maintenance. Such trade-offs can produce variation within and between species in major life history traits like age and size at sexual maturity, number of offspring, and length of life, as well as behavioral outcomes associated with mating and parenting efforts (Kaplan and Gangestad, 2005).

Developmental phenotypic plasticity refers to irreversible changes in the phenotype that occur during development. While early life effects on development can constrain adult phenotypes (Frankenhuis et al., 2019; Monaghan, 2007), these changes can also be adaptive when they allow organisms to survive challenges that occur early during development, or which allow them to adjust to environmental contexts they will find later in life (Barker, 2002; Gluckman et al., 2005; Ellison and Jasienka, 2007; Nepomnaschy et al., 2009; Flinn et al., 2011). The latter is referred to as the “Predictive Adaptive Response” (PAR) (Gluckman et al., 2005). PAR only works when current conditions provide an accurate forecast of future events (Lachman and Jablonka, 1996; Nettle et al., 2013). Short-term predictions tend to be more accurate than long-term ones, and the accuracy of predictions depends on environmental stability. Organisms from populations facing stable ecological cycles can extend their assessment period to produce more reliable predictions. Consequently, long-term predictions (as well as predictions that require longer periods of assessment) tend to be riskier and costlier (DeWitt et al., 1998). Hence organisms face trade-offs between early specialization and a longer period of plasticity (Flinn et al., 2011; Nettle and Bateson, 2015). The balance between predictability and specialization during development influences the ontogenetic trajectories of phenotypic plasticity. “Critical” or “sensitive” periods for environmental input involve this inherent temporal trade-off between the reliability of cues and the advantages of earlier specialization (Alexander, 1990; Mousseau et al., 2009; Shettleworth, 2010).

Within this context, much research has been conducted on developmental plasticity of two critical axes: the “stress” or hypothalamus-pituitary-adrenal axis (HPAA) and the reproductive or hypothalamus-pituitary-gonadal axis (HPGA), wherein their hormonal products strongly influence the developing brain during critical periods. The

timing and length of these critical periods is species- and trait-specific, but gestation and the early post-natal period are critical windows for the development of the HPAA and its associated phenotypic traits (Champagne et al., 2008; Lupien et al., 2009; Maccari et al., 2003; Nepomnaschy and Flinn, 2009). In particular, because of its flexibility and pervasive action, the HPAA has been proposed as one of the primary endocrine mechanisms regulating human life history trade-offs (Del Giudice et al., 2011). Likewise these are periods during which sex steroids have important effects on the development of morphology, physiology, and behavior (Arnold, 2009; Breedlove, 2010; Wallen, 2009).

The existence of more than a critical period for plasticity has been suggested for those species with an extended juvenile development characterized by different stages of growth (e.g., humans) (Schulz and Sisk, 2016). In such cases, each critical period is hypothesized to allow for the integration of past and current experiences in order to calibrate the phenotype to the next life stage (Del Giudice et al., 2011). These phenotypic recalibrations are hypothesized to be mediated by the activity of the HPAA and HPGA (and hormones in general), which are expected to integrate environmental information over time and to allocate resources in an optimal way. Humans have a particularly long period of development, which potentially allows for several extended periods during which the organism may be sensitive to plasticity. In humans these periods of enhanced plasticity correspond to the prenatal and extended postnatal developmental period. The functions of the HPAA and HPGA activity in humans is expected to have evolved in such a way to be critically tuned to the environmental cues that characterized human evolution, especially those that may have been important for social and ecological learning. In the following sections we will describe the concepts of parent-offspring conflict, parental investment, and of human life history evolution. These may help to explain variation in HPAA and HPGA functioning and the functioning of human phenotypic plasticity.

4. The evolution of human life history and developmental phenotypic plasticity: mothers, others, and the human family

An extended period of development, a large brain, and complex sociality covary in many species of mammals, but humans represent an extreme in all three of these traits. Hominin cranial capacity tripled, from an average of about 450 cc to1350 cc, in less than two million years (Lee and Wolpoff, 2003). This increased brain growth during human evolution was accompanied by changes in life history patterns (Dean et al., 2001). Gestation (pregnancy) was lengthened as infants became more altricial (Rosenberg, 2004). Human babies had to be carried, fed, and protected for longer periods than those of other primates. Yet despite the higher levels of maternal investment in time and energy required for the survival and development of each infant, humans present shorter interbirth intervals than other hominoids (Galdikas and Wood, 1990; Hrdy, 2007).

The lengthening of the human developmental stage could have been the result of energetic constraints at some point of our evolutionary history. However, the peculiarities of the human growth curve seem difficult to explain using only a simple model of food scarcity. Other hominoids (e.g., chimpanzees, gorillas, orangutans) grow at similar overall rates, but mature earlier (Leigh, 2004). Additionally, the general timing of growth spurts does not appear to be strictly linked to a pattern of caloric surpluses. While increased body fat is associated with earlier puberty for girls, genetic factors, birth weight, and psychosocial stress also appear to be relevant (Walvoord, 2010; Karaolis-Danckert et al., 2009), and body fat does not appear to be critical for boys sexual pubertal transition (Lee et al., 2010a,b). Hence, though it is clear that human female growth and reproductive maturation are sensitive to fat accumulation (Ellison, 2001: Sloboda et al., 2007), the lengthening of the juvenile period during human evolution seems likely to have involved more than simple energetic constraints on growth.

Our long developmental stage could be evaluated as an adaptation, at least in part, to allow for the appropriate development of cognitive traits, including complex social skills and emotional regulation (Alexander, 1987; Flinn, 2006; Konner, 2010). The human child is an extraordinarily social creature, motivated by and highly sensitive to interpersonal relationships (Gopnik et al., 1999). Learning, practice, and experience are imperative for social success. The information processing capacity used for human social interactions is considerable, and perhaps significantly greater than that involved in foraging, locomotion, tool-making, and other subsistence skills, highlighting the link between social success and reproductive success (Rilling et al., 2002; Roth and Dicke, 2005). There were likely a number of potential sources of selection for the development of our species-specific neurobehavioral traits, as described below.

4.1. The evolutionary life history of human prenatal and postnatal development

In species with internal fertilization, mothers represent the offspring's first environment. Maternal conditions can affect the offspring's phenotype and their chances of survival, even before the child is conceived (Barker et al., 1989; Kuzawa, 2005; Wagner, 2010). The mother and fetus both benefit from accurate information gauged from the maternal environment. However, genetic interests are not completely concordant for mothers and children, and thus mothers and children are hypothesized to engage in a tug-of-war over resources from the moment of conception onwards. Pregnancies conceived or maintained when maternal or environmental conditions are poor or when the future looks bleak, may negatively affect the mother's lifetime reproductive success (Flinn et al., 2011; Penn and Smith, 2007).

Natural selection is expected to have favored mechanisms that allow mothers to regulate resource allocation among their descendants according to their expected chances of survival and future reproductive success (Wells, 2014). In extremely poor conditions, women may suppress their reproductive function altogether (Ellison, 2001; Nepomnaschy et al., 2007). This proposition is consistent with studies showing that extreme physical activity or high levels of physiologic stress can lead to hypothalamic amenorrhea, lower ovulatory frequency, poor luteal function, and increased risk of miscarriage (Nepomnaschy et al., 2004, 2006, 2007). Offspring are hypothesized to have evolved mechanisms to reduce the risk of miscarriage (Nepomnaschy et al., 2006, 2007), and it would be in their interest to manipulate the maternal mechanisms that regulate investment (Haig, 1993).

In addition to gestation, the next phases of human development (childhood, juvenility, and adolescence) are also exceptionally lengthy (Bogin, 1999; Del Giudice, 2009; Leigh, 2004). Infancy is defined as the period between birth and weaning (Bogin, 2009). Once infants are weaned, they are at a developmental stage characterized by their inability to meet their nutritional needs by themselves, and their motor skills are still poorly developed. This developmental period is defined as childhood, and it lasts until the onset of adrenarche (Bogin, 2009; Campbell, 2006). During childhood, children are still highly dependent on adult support for feeding and protection, and alloparents play a fundamental role (Bogin, 1999; Sear, 2016). During this life history transition, maternal care is intense and prolonged, including an important energetic investment with breastfeeding, transportation, and care of highly altricial offspring.

Through breastfeeding and continuous contact with her infant, the mother is a source of protection, buffering the developing infant against ecological challenges (Wells, 2019). By providing a safe base for bonding, the mother is crucial for the development of her child's emotional system. Ultimately, this will depend on the activity of her offspring's HPAA (Lupien et al., 2009). Furthermore, depending on ecological conditions, the presence/absence of a supportive kin network, and on the mother's past and current phenotypic status (maternal

capital: Wells, 2019), a mother could allocate different resources toward her offspring, for example by changing the level and quality of parenting, by trading off the quality versus quantity of milk (Hinde, 2009), or by deciding when to wean (Quinlan et al., 2003, 2005). Through this differential investment at the postnatal stage, mothers can program their offspring's stress response. Importantly, the limbic system is a target of these early effects. Animal models of early life stress and maternal effects show that maternal care and experience can affect offspring phenotypes that are possibly adapted to future ecological conditions (Champagne et al., 2008).

Juvenility (mid-childhood) is a life stage characterized by very slow physical growth. In humans, it lasts until the onset of the growth spurt (7–10 years for girls, and until 12 years for boys) (Bogin, 2009). During this time, brain growth and reorganization requires high energetic investments. Synaptic pruning occurs first in motor and sensory cortical areas and in areas important for emotional regulation (Lenroot and Giedd, 2006). Concomitantly with these brain maturational processes, children's learning and behavioral skills improve and they become more independent from parents. They may begin to procure some of the calories they consume (Bogin, 1999; Locke and Bogin, 2006). In many traditional societies, children (especially girls) are expected to follow social norms such as foraging with same sex adults (Marlowe, 2010) or performing house chores (Konner, 2010). In Westernized societies, sex segregation is strong and social interaction with peers can have long lasting effects, as is the case for the stability of social dominance in boys from industrialized societies (Weisfeld et al., 1987).

Mid-childhood is an important human life history stage for calibrating between- and within-sex differences in reproductive strategies (Del Giudice et al., 2009; Del Giudice and Belsky, 2011). From an evolutionary perspective, it is not surprising to observe that boys and girls are invested differently in social interactions, with boys engaging more in large group networks and competitive/aggressive interactions while girls being more emotionally invested with few members of their same sex. For boys, higher competitiveness and good skills in dealing with coalitions of peers may have long lasting positive effects, as popularity in mid-childhood predicts dominance and popularity in adolescence (Weisfeld et al., 1987) and this may reflect an evolutionary history of within- and between-group male-male coalitionary competition (Geary, 2010). On the contrary, girls' higher empathic, stronger interpersonal engagement and emotional investment toward dyadic and triadic relationships reflect an evolved psychology necessary to express successful parenting (Ellis, 2013). These changing social dynamics may expose children to sources of stress that are unique to each gender (Rose and Rudolph, 2006).

With the onset of pubertal maturation, adolescence is a life history stage characterized by a shift from investment in growth to reproductive effort (Muehlenbein and Flinn, 2011). In humans, successful reproduction requires that, in addition to reaching reproductive maturity, individuals acquire the necessary social, material, and energetic resources to succeed (Isler and van Schaik, 2012). These are not trivial, and puberty and adolescence may provide the time to acquire such resources (Kaplan et al., 2003). However, in high mortality environments, taking time to acquire resources increases the chances of dying without reproducing. Risky environments are therefore hypothesized to be associated with accelerated pace of reproductive maturation in both sexes (Chisholm et al., 1993). In contrast, non-lethal challenges, such as non-extreme nutritional restriction or social instability, may exert different effects in girls and boys.

In girls, food uncertainty and socially challenging environments have been linked to earlier menarche, emergence of secondary sexual traits, sexualized behaviors, and age at first birth (Chisholm et al., 2005; Ellis and Garber, 2000). In this case, early reproductive maturation has been argued to attract valuable energetic, material, and social resources from potential partners (Gillette and Folinsbee, 2012; Hoier, 2003), and these relationships may also offer protection from coercion and aggressions from other males (Amir et al., 2016; Belsky 2011; Belsky et al., 1991; Ellis and Garber, 2000). In boys, the effects of non-lethal challenges may be more complex. Some studies report that environments with non-lethal challenges lead to earlier reproductive maturation, while others report the opposite (Lee et al., 2010a,b; He and Karlberg, 2001; Kaplowitz, 2008). Postponing reproductive maturation could be adaptive for boys as it delays the onset of risky confrontations with mature, strong, socially successful competitors and provides more time for the acquisition of energetic, material, and social resources required for the boys to develop physically, mentally, and socially in a stringent environment (Hochberg and Belsky, 2013). Thus, the level of male-male aggression among different human social groups could have a modulating role on the effects of other non-lethal challenges on the timing and rate of reproductive maturation.

4.2. The role of grandparents and fathers during child development

Extension of the pre-reproductive developmental period can carry increased risks and costs; the delay in reaching the reproductive phase involves prolonged exposure to extrinsic and intrinsic causes of mortality as well as longer generation intervals. It follows that the amount of alloparental investment in offspring development, as well as the length of time during which that investment has to be provided, must be unusually high, often well into adulthood and, in some cases, even after the death of the parents (Hill and Kaplan, 1999; Mace, 2000; Muehlenbein and Flinn, 2011). Two species-distinctive characteristics stand out as unusually important in this regard: grandparenting and fathering (i.e., extensive and specific investment by males).

Grandparents and grandoffspring share on average 25% of their genes by descent; this constitutes a significant opportunity for kin selection (Perry and Daly, 2017). Few species, however, live in groups with multiple overlapping generations of kin. Fewer still have significant social relationships among individuals two or more generations apart. Grandparenting is cross-culturally ubiquitous and pervasive (Sear, 2016; Voland et al., 2005). Our life history pattern allows for significant generational overlaps, including an apparent extended post-reproductive stage in women facilitated by menopause (Alexander, 1974; Hawkes, 2004). This extended post-reproductive period allows grandparents to invest resources toward their children and grandchildren that could otherwise be used to directly increase their own 'direct' reproduction (Coall and Hertwig, 2010; Hawkes, 2004; Perry and Daly, 2017). This investment has a positive effect on child survival and eventual reproductive success of grandchildren (Hawkes, 2004; Perry and Daly, 2017; Sear and Mace, 2008). In addition to the physical basics of food, protection, and hygienic care, psychological development of the human child is strongly influenced by the dynamics of the social environment (Konner, 2010), and both grandparents and fathers can play important roles in all of these.

Paternal care in humans appears to be facilitated by relatively stable pair bonds, and these relatively exclusive mating relationships are characteristic of most human societies (Flinn and Low, 1986). Competition for females in multiple-male groups usually results in low confidence of paternity (e.g., bonobos and chimpanzees). The estimated rate of cuckoldry in human historical populations is around 2% (Larmuseau et al., 2016), suggesting that paternity confidence was central for the evolution of human sociality. However, paternal care in humans is facultative and varies substantially between populations, cultures, and even by socioeconomic status (Fernandez-Duque et al., 2009; Geary, 2000), suggesting that other factors in addition to paternity certainty play an important role. In general, human fathers often provide protection, information, food, and social status for their children (Gray and Anderson, 2010).

The positive role that fathers play in survival of their children has been demonstrated in some populations of hunter-gatherers even though father presence does not seem to substantially influence child survival over all (Sear and Mace, 2008). However, studies from high fertility societies suggest that when maternal kin are not available,

fathers may engage in more paternal care (Meehan, 2005). Moreover, while fathers may not have a direct impact on child survival and wellbeing (Winking et al., 2011), they may have a substantial impact on their children's future social status and social capital. For example, father death in late childhood or early adolescence predicts lower educational attainment (Shenk and Scelza, 2012), and fathers may increase the social competitiveness of their children when they reach adulthood (Scelza, 2010). The effects of paternal care are arguably different from those of overall paternal investment in humans. The latter gains importance later during development, and it is related to patterns of inheritance and social capital.

To summarize our argument to this point, while the prenatal and early postnatal experiences are key in programming future phenotypic development (especially, but not exclusively, in terms of somatic development), the extended periods of childhood and adolescence may be viewed as life history stages that are necessary for acquiring information/practice to build/refine the mental algorithms critical for negotiating social relationships that are key to individual reproductive success (Geary and Flinn, 2001; Flinn et al., 2009). Mastering the social environment presents special challenges for the human child. Social competence is difficult because the targets (other children and adults) are constantly changing and similarly equipped with theory of mind and other cognitive abilities. Selection for flexible cognitive problem solving would also enhance complementary development of more sophisticated ecological skills such as hunting and complex extractive foraging (Kaplan et al., 2003), which may have further increased selection for these cognitive traits.

In this regard, the family environment is a primary source and mediator of the ontogeny of information processing abilities, including social competencies and group cooperation. Human biology has been profoundly affected by our evolutionary history as unusually social creatures, immersed in networks of family, kin, and dynamic intercommunity coalitions. The care-providing roles of fathers, grandparents and other kin are unusually important in humans (Hrdy, 2007, 2009), particularly with regard to protection and social power, but they are flexible components of the human family. In addition to the effects of direct parental care, paternity provides the basis for critical bilateral kinship links that extend across communities and generations. Thus, parents, grandparents, and other kin may be especially important for the mental development of the child's social and cultural maps, because they can be relied upon as landmarks who provide relatively honest information. From this perspective, the evolutionary significance of the human family in regard to child development is viewed more as a nest from which social skills may be acquired than just as an economic unit centered around the gendered division of labor (Flinn and Ward, 2005).

An understanding of the trade-offs associated with human parental and alloparental investment, from conception to the postnatal stages of development, seems key to understanding the roles that hormones play in regulating human developmental plasticity. Given the relative importance of each alloparental figure throughout human evolution and the ecological, cultural, and context-specific constraints on alloparental investment, the development and functions of the HPAA response to these investments are expected to be variable. Its primary role may be to fine-tune the child's developing brain and body to fit the sociocultural niche. In the following sections, we will follow the same model of human life history and review the ontogeny of the HPAA and HPGA and their effects throughout human development. Where possible, we describe the influence of the presence caretakers other than mothers may have on the development of these endocrine systems and their phenotypic targets.

5. Human life history and the HPAA and HPGA ontogeny: possible roles in human developmental plasticity

5.1. Conception and prenatal life: HPAA

Many of the effects exerted by the physical and social environments are mediated by the HPAA. This system acts as a mediator between individuals and their environments, allowing them to respond and temporarily adapt to internal and external challenges through the modulation of circulating glucocorticoids levels. The ontogeny of this vital axis appears to be sensitive to developmental exposures (Reynolds, 2013). Stressors experienced during early life have been linked to HPAA departures from specific profiles defined by traits such as glucocorticoid circadian rhythms and stress responsivity; a phenomenon often referred to as “HPAA programing”.

Emerging evidence is consistent with the proposition that HPAA ontogeny is more vulnerable to prenatal than postnatal exposures (Barha et al., 2018; Behie and O'donnell, 2015; Kapoor and Matthews, 2008). In particular, maternal glucocorticoid levels, a marker of HPAA responsivity, during mid- and late-gestation have been linked with offspring postnatal HPAA activity (Bosch et al., 2012; Elzinga et al., 2008; Entringer et al., 2009; Nepomnaschy et al., 2011, 2012). Weekly patterns of variation in maternal cortisol levels immediately following conception have also been hypothesized to modulate fetal HPAA development which begins shortly after conception (Schoenwolf 2009). Moreover, maternal depression and high levels of social anxiety during pregnancy are associated with low birth weight, elevated HPAA reactivity, and subsequent disease risk for offspring (Gluckman et al., 2007).

The links between maternal prenatal HPAA activity and offspring postnatal HPAA activity could be mediated by stress-related programming of the offspring HPAA-related genes (Nepomnaschy et al., 2007), including those associated with corticotrophin releasing hormone (CRH) and the glucocorticoid receptor (NR3C1). For example, offspring of holocaust survivors and of women exposed to partner violence during pregnancy have increased methylation of the promoter region of NR3C1 (Bowers and Yehuda, 2016; Yehuda et al., 2014). These and other prenatal effects arguably depend on the time of exposure during pregnancy (Yehuda et al., 2005).

In order to learn more about the role of early post-conception maternal environments on HPAA ontogeny, Barha et al. (2018) conducted the first study to evaluate the relationship between maternal cortisol levels (a marker of HPAA activity) during the early post-conception period (EPCP), and their children's pre-pubertal HPAA activity. To that end, they collected maternal first-morning urinary cortisol every other day from 107 sexually active women. Starting before conception, they continued with the sample collection protocol for the first 8 weeks after the detection of pregnancy. This design allowed them to capture maternal post-conception cortisol levels for 22 mothers. Twelve years later, they collected those participant's children's daily first-morning urine for three weeks, starting a week before the onset of the school year (non-experimental challenge), as well as salivary cortisol responses to the Trier Social Stress Test (TSST) for children (an experimental challenge). They also collected buccal epithelial cell tissue from each child to identify potential epigenetic markers left by EPCP exposures.

The study found maternal cortisol during the EPCP to be significantly associated with children's baseline cortisol, as well as changes in response to the start of the school year, and the experimental challenge. While maternal cortisol during the EPCP was associated with children's buccal epithelial cells' DNA methylation at 867 sites, and that children's HPAA activity was associated with five CpG sites, no CpG sites were related to EPCP cortisol or to children's HPAA activity. Further research based on larger sample sizes is necessary to confirm the link between EPCP maternal cortisol and childrens' HPAA activity and responsivity and to investigate its causes, including the potential role of shared genes and environments for the mother-child dyads,

possible roles of fathers and alloparents, and epigenetic mechanisms.

5.2. Conception and prenatal life: HPGA

The activity of the HPGA during fetal life is necessary for the development of sexual differences in brain and behavior (Wallen, 2009). In humans, sex chromosomes influence the development of the male gonads, which in turn, through the secretion of testosterone, influence the development of primary sexual characters. Within the organizational-activational model of sex differentiation, exposure to early androgens influences the organization of brain structures that are activated by the same hormones during puberty (McCarthy and Arnold, 2011). Given their potential for programming target areas of the developing brain, early fetal exposure to androgens may have important roles for the development of phenotypic plasticity.

Prenatal exposure to androgens may help explain individual differences in sexually-selected domains and traits, where higher variance in outcome variables has been reported (e.g., sociosexuality, spatial cognition, general intelligence; see Del Giudice et al., 2018 for a new model). Girls with congenital adrenal hyperplasia (exposed to high levels of androstenedione during fetal development) have a more masculine style of play, prefer toys that are marketed for boys, and show preferences for same-sex partners (Hines, 2011). For boys, the relationships seems to be more complex as male fetuses exposed to higher levels of androgens do not show hypermasculine psychosexuality, suggesting the possibility of a ceiling effect (Breedlove, 2010).

Prenatal exposure to androgens influences the second to fourth digit length (2D:4D) ratio, such that exposure to larger amounts of androgens causes a smaller ratio (with a longer fourth digit). A correlation between this biomarker and typically masculine traits has been found for dominance and competitiveness (Manning and Taylor, 2001; Manning and Fink, 2008). Moreover, a smaller ratio has been found in individuals afflicted by disorders with a male bias in incidence, such as autism and attention deficit disorders (ADHD), but not in those with a larger incidence of women, such as eating disorders (Breedlove, 2010).

Animal models show that mothers, depending on their physical status and social environment, can strategically manipulate the levels of prenatal androgens that their offspring can be exposed to. By doing so, mothers can influence their offspring life history trajectories without necessarily affecting their sexual differentiation (Carere and Balthazart, 2007). For example, in birds early exposure to testosterone in the yolk influences the levels of aggressiveness of juveniles, their growth, and mortality (Partecke and Schwabl, 2008; Rhen and Crews, 2002; Schwabl et al., 2012). In polytocous mammalian species where fetuses develop in adjacent positions, females that grow between two males are exposed to higher doses of prenatal testosterone (Vom Saal and Bronson, 1978) which may delay their pubertal onset and influence their reproductive strategies (McCoy and Shirley, 1992; Rhees et al., 1997).

Variation in prenatal exposure to androgens can be the result of maternal social experiences. For several species of birds, the experience of aggressive female-female competition results in higher levels of androgens in the yolk (Whittingham and Schwabl 2002; Mazuc et al., 2003; Guibert et al., 2010). The influence of these organizational effects of said prenatal exposures may require or reflect events occurring at different life stages postnatally. In females of several mammalian species, prenatal stress has been linked to phenotypic variation in the timing of puberty (vom Saal et al., 1991). In male rodents, exposure to prenatal stress during the last third of gestation affects the timing of testosterone secretion by the fetus' testes (Ward and Weisz, 1980). This results in the demasculinization of adult reproductive behaviors (Ward, 1972). Lower testosterone levels in response to prenatal stress are also linked to increases in HPAA reactivity in male animal models (Kapoor and Matthews, 2011). The effects of prenatal stress on sexual development and pubertal timing may also apply to humans, as there is some evidence that prenatal stress may masculinize human females (Barrett et al., 2014) and modulate reproductive development (James et al., 2012). More studies are needed to investigate the role of maternal social and physical stressors during gestation and prenatal exposures to androgens in the development of offspring's HPAA and HPGA, their reproductive development, function, and related behaviors across the lifespan.

5.3. Childhood and the HPAA

During infancy and childhood, the HPAA appears to be partially buffered from environmental stressors. It has been proposed that the human infant experiences (similarly to rodents) a stress hyporesponsive period during which the HPAA does not respond to stressors as typically observed in newborns and adults (Gunnar and Quevedo, 2007). Since one-year-old infants do not produce a reliable increase in cortisol during laboratory stressors or medical examinations, it has been hypothesized that the HPAA of a child is under strong social regulation (Gunnar and Quevedo, 2007). The presence of a supportive, sensitive caregiver reduces the infant's HPAA responsiveness, and partially protects the developing nervous system from the costs of hypercortisolism (Gunnar and Quevedo, 2007). Consistent with these observations, low postnatal maternal care increases the child's risk of depression and anxiety, while warm and nurturing families increase resistance to stress-induced illness (Zhang et al., 2013).

Children physically or emotionally neglected during their early life can develop dysregulation of the HPAA (Bruce et al., 2009; Doom et al., 2014; Flinn and England, 1995, 1997; Gunnar et al., 2001; Mills-Konce et al., 2011; van der Vegt et al., 2009). Early-stressed children show higher sympathetic tone (Gunnar et al., 2009), and low maternal sensitivity is associated with a hyper-reactive stress system in infants (Hane and Fox, 2006; Tarullo and Gunnar, 2006). Maternal depression predicts higher evening cortisol levels in their infants (Essex et al., 2002), a potential risk for developing depression. Separation from mothers *and* fathers during infancy also has effects on the stress response to laboratory psychosocial challenges in adulthood (Pesonen et al., 2010). Father negativity can even influence infant's cortisol response to emotional laboratory tasks (Mills-Konce et al., 2011).

Few studies have examined the effects of alloparents on children's HPAA functions. Evidence from our long-term field study shows the importance of grandparents in buffering their grand offspring's HPAA. Children residing in bi-parental homes, single mothers with kin, and grandparental households have moderate cortisol levels with a higher proportion of elevations occurring in the context of positive-affect situations, such as competitive play, physical work, and excitement regarding novel situations (Flinn and Leone, 2006). Children with early family trauma but with higher levels of grandparental care have lower average cortisol levels, lower morbidity, and higher growth percentiles (Flinn and Leone, 2006).

The effects of fathers on their children's HPAA activity have been studied, especially in industrialized, low fertility populations. Infants whose fathers scored more negativity during a 10-min laboratory interaction with their children had higher cortisol reactivity in a standardize emotional laboratory task at seven and 24 months of age (Mills-Koonce et al., 2011). In a cross-cultural study, Flinn and colleagues reported age- and sex-specific effects of father absence on daily variation of the HPAA activity. Male infants whose fathers were absent exhibited lower levels of cortisol compared with girls, but the pattern was reversed for older children (Flinn et al., 1996). Moreover, data from the same rural community suggest that, on average, children living in households with stepparents or single mothers have higher baseline levels of cortisol (Flinn and England, 1995, 1997). High cortisol levels in children from this rural community are temporally associated with traumatic family events (e.g., residence change of child or parent/caregiver, punishment, “shame,” serious quarreling, and/or fighting) within a 24-h period (Flinn and England, 2003). But overall, individual children usually have fairly stable “profiles” of cortisol activity (Flinn,

2009).

During mid-childhood there is an increase in HPAA activity. At the beginning of this life stage, the stress hyporesponsive period ends (Gunnar and Quevedo, 2007), HPAA reactivity to ecological signals is stronger, and basal levels of cortisol increase progressively with age. Concomitantly, with increased HPAA activity, adrenal glands secrete large amounts of the adrenal androgens dehydroepiandrosterone (DHEA) and its sulfated ester (DHEAS), which have been shown to have antiglucocorticoid effects with neuroprotective functions (Campbell, 2006, 2011). During the transition to mid-childhood, sex differences in HPAA activity become evident. As reviewed by Hollanders et al., 2017, at this age girls appear to have a steeper daily curve of cortisol secretion and higher cortisol upon waking (Martikainen et al., 2013). The rate of diurnal cortisol decrease may be moderated by children's social experiences which could be sex specific. However, these results must be interpreted with caution, because pubertal status was not measured.

Psychosocial stressors, such as parental divorce occurring at this age may have short- and long-term effects on HPAA activity. For example, parental reports of their children's experience of negative life events during the previous 12 months was predictive of a steeper decline in boys, while girls showed overall lower levels of morning cortisol (Michels et al., 2012). Likewise, negative experiences that occurred during this developmental period have been associated with stronger HPAA reactivity to psychosocial challenges in a laboratory (Bosch et al., 2012). Overall, HPAA reactivity to stressors may be blunted during this period as several studies suggest that eight and nine year olds are not as reactive to laboratory psychosocial challenges as older individuals are (Gunnar et al., 2009b; Stroud et al., 2009).

5.4. Childhood and the HPGA

Within the first few months after birth, human males experience a surge of testosterone that, in terms of concentration, is in the same range as that of pubertal boys (Lanciotti et al., 2018). This event is necessary for male reproductive development; it correlates positively with penile and testicular growth (Boas et al., 2006), and its absence results in hypogonadism (Main et al., 2000). During the same postnatal period in girls, there is a peak in estradiol that is absent in boys, which is associated with an increase in mammary gland size and uterine growth (Kuiri-Hänninen et al., 2013).

The majority of HPGA studies in children focus on normative (or pathological) reproductive and neurobehavioral growth and are not meant to provide evolutionary or functional mechanisms. However, important insights can be gleaned, which provide information on the possible roles of this early HPGA activation, especially in relation to testosterone and the development of individual differences in somatic growth and psychosexuality. For example, levels of testosterone correlate positively with peak growth velocity during the first months of life (Kiviranta et al., 2016); higher levels predict lower body mass index up to six years of age in boys (Becker et al., 2015) and are positively correlated with boys' preference for male-typical toys and the expression of male-typical behaviors (Hines et al., 2016). Although many of these studies are characterized by small sample sizes, they draw attention to a particular event that may have programming effects on several growing tissues (including the nervous system that is highly plastic during the early post-natal period), and stimulate many questions on the possible functions of testosterone in mediating future phenotypic plasticity, beginning early during development.

During the first years of postnatal life, HPGA activity is low, with low levels of circulating androgens and estrogens. This changes during adrenarche due to the maturation of the adrenal gland, which in turn promotes the adrenal production and secretion of large amounts of weak androgens (Ibanez et al., 2000). Changes in androgen levels during adrenarche have been suggested to mediate reproductive development and reproductive strategies, and we hypothesize that the timing of this transition depends on the integration of past internal and external cues such as perinatal levels of androgens, overall storage of resources, prenatal growth. It is at this life history stage that romantic interests become explicit (Herdt and McClintock, 2000). Secretion of adrenal androgens at this time may be a mechanism important to recalibrate attachment styles which may help explain among-individual differences in adult reproductive strategies (Del Giudice, 2009).

Adrenarche plays a critical role on life history trade-offs. First, the rise in androgens coincides with maturation of children's motor skill, which supports an increase in explorative behaviors and their ability to procure and obtain their own nutrition (up to half of their energetic requirements), which in turn supports their interest in gaining independence from their parents (Kramer, 2005, 2010). At this time an increase in sex segregation within peer groups can be observed in Westernized societies (Geary, 2010). In these contexts, premature adrenarche is a forerunner for several undesired outcomes, especially in girls. For example, high adrenal androgen levels in girls are associated with higher anxiety, depression and aggression (Belsky et al., 2015; Dorn et al., 2008; Van Goozen et al., 1998).

Adrenarche seems to be sensitive to very early physical and social environmental conditions (Ponzi et al., 2015). Prenatal stress and marital conflict affect HPAA activity in early childhood, and these early exposures appear to advance the onset of adrenarche (Belsky et al., 2015; Ellis and Essex, 2007). These observations are consistent with the evolutionary hypothesis proposing that early negative life experiences should lead to early reproductive maturation, the rationale being that, in high-mortality risk environments, maturing early reduces the risks of dying without leaving descendants. Yet, it is important to point out that anticipated adrenarche is not linked with anticipated gonadarche (Ibanez et al., 2000). Likewise, while there has been a lot of emphasis on the onset of adrenarche and the function of adrenal androgens during childhood, DHEA and DHEAS peak in the mid-twenties and their lifespan curve is peculiar. We do not yet know how events occurring early in life or late in childhood influence these curves.

6. The adolescent transition: HPAA, HPGA and individual differences in reproductive strategies

In humans, gender socialization acts as a potent socio-environmental variable, affecting the way individuals are treated from birth, the challenges they face, the way they experience them and the way they are trained to respond to those challenges. Thus, gender socialization, as well as all other environmental stimuli, can affect health and wellbeing postnatally through social and biological mechanisms. The dynamic interactions between the genome, epigenome, environment, and phenotype continue across the lifespan, and the HPAA plays a critical role in these interactions. As the HPAA is linked to the HPGA, its role is particularly important when individuals begin the process of reproductive maturation. Both axes are known to undergo important sex-specific changes during puberty, and social, energetic, immune, and physical challenges are expected to impact the pace of reproductive maturation and, in girls, the quality of ovarian cycles after menarche (Gunnar et al., 2009c; Netherton et al., 2004; Stroud et al., 2009).

Only a handful of studies have examined the effects that stress exposures during development may have on HPAA maturation and activity during the childhood-adolescence transition. These studies suggest that the transition is accompanied by increases in basal HPAA activity in girls, and increased HPAA reactivity to an experimental stressor in boys (Gunnar et al., 2009c; Netherton et al., 2004; Stroud et al., 2009). In industrialized, urban populations, adolescent girls are more reactive than boys, whereas both genders exhibit increased HPAA reactivity when older (Gunnar et al., 2009).

Sex differences in HPAA reactivity to social stressors during adolescence suggest that stress response is already domain specific at this stage of development. Male and female stress responses differ in adulthood, with men exhibiting a stronger cortisol response to a performance stressor (the laboratory TSST) and women exhibiting greater

sensitivity to social exclusion (Stroud et al., 2002). This difference is also present in adolescents (Stroud et al., 2017). Differences in domain specificity in HPAA response may reflect the different selective pressures that adolescent boys and girls have undergone through human evolutionary history, resulting in sex specific patterns of physical, psychological, and cognitive development (Bogin, 1999). Consistent with this speculation, adolescent boys and girls show strikingly sexually dimorphic behaviors in terms of risk taking, antisocial behaviors, status seeking, and involvement in coalitionary competitions (Geary, 2010; Geary et al., 2003).

The extent to which HPAA-HPGA interactions influence the motivational drive underlying these behavioral differences is still being investigated (Joos et al., 2018; Shirtcliff et al., 2015). Generally, beginning with adolescence and continuing through adulthood, the functioning of these two systems are considered antagonistic (Ruttle et al., 2015). However, their co-activation and positive correlation may depend on the context, as they may vary (at least in primates) by personality trait (Sapolsky, 1986) and level of social stability (Higham and Maestripieri, 2014). Both sex steroids and glucocorticoids influence the development of the adolescent's nervous system, especially those brain regions linked to reward and decision making. Social experiences during adolescence can re-organize brain structures (Schulz and Sisk, 2016; Sisk, 2017), providing the potential for complex interaction between early life experiences, HPAA and HPGA developmental programming, cortisol and sex steroid responses to socioecological challenges (Marceau et al., 2015; Ruttle et al., 2015). In general, behaviors that increase the opportunity for current or future reproduction, such as risk taking, competition, and sex, appear to be rewarding for adolescents (Sato et al., 2008; Steinberg, 2008). Brain circuits linked to reward and pleasure, such as the dopaminergic system, should be intrinsically linked to these behaviors. In turn, within-individual variation in these behaviors should correlate with levels of testosterone and ovarian steroids. These hormones are hypothesized to influence the development and functions of neural networks associated with reward seeking. The effects of sex steroid on these regions during this developmental stage may be organizational or activational possibly representing the moderating effects of early life stress on the programming of structures of the limbic system.

During adolescence, the sensitivity and functions of the dopaminergic system are modulated by sex steroids and stress hormones (Sinclair et al., 2014). Importantly, the actions of dopamine during adolescence are key for the development of the prefrontal cortex and its associated cognitive and socio-emotional functions (Sinclair et al., 2014). Specifically, the mesocorticolimbic system develops and matures during puberty and receives inputs from regions rich in androgen receptors, such as the bed nucleus of the stria terminalis (Sato et al., 2008). It is not surprising that typical risky behaviors often observed in human adolescents reflect the functions of areas of the brain such as the ventral striatum (van Duijvenvoorde et al., 2014) and the nucleus accumbens (Braams et al., 2015), regions also rich in androgen receptors (Sato et al., 2008).

In short, during adolescence humans shift from growth to mating effort as individuals prepare for intra- and inter-sexual competition. This life history period is characterized by high levels of neuroendocrinological plasticity. Indeed, the areas representing the so-called “social brain” are still developing during this transition. They reach their final structural and functional maturity by early adulthood (Keshavan et al., 2014). These areas are very sensitive to social experiences, which may help explaining the high level of among-individual variation observed in neuro-endocrine/behavioral phenotype during the adolescent transition. One of the possible functions of sex and stress steroids during adolescence may be calibrating individuals’ reproductive strategies to match future opportunities predicted using current social contexts.

7. Development, epigenetics and the integration of environmental cues

The field of Developmental Origins of Health and Disease (DOHaD) has yielded evidence highlighting the importance of early social and physical environments on developmental trajectories, with consequences for health, cognition, and wellbeing across the life span. Parental (or even ancestral) influences on offspring development can result from exposures that predate conception. Conception is followed by a fast-paced sequence of developmental processes. Most parental methylation “marks” are erased, generating an opportunity for modifications to emerge during re-methylation. *In vitro* studies have confirmed that this process of DNA re-methylation after fertilization is extremely sensitive to environmental stimuli. Early DNA methylation modifications can be transmitted through different cell lineages affecting the development of entire biological systems. Importantly, as biological systems are interconnected, the developmental trajectory of one system can affect the trajectories of others, triggering a “domino” effect that results in substantial changes in the neonate's phenotype (Barha et al., 2018). Thus, understanding prenatal exposures is paramount to understanding developmental trajectories. Maternal exposures during early gestation are bound to exert more intense and long-lasting phenotypic effects than later environments (Barha et al., 2018). In particular, gametogenesis, fertilization, and early embryogenesis are critical for the establishment of the epigenome, which in turn, can affect all downstream ontogenetic processes. For example, maternal exposure to high fat diets can be observed in the second generation (F2), suggesting a germ line effect (Bale, 2015).

While the mother obviously has the capacity to influence fetal development directly, fathers can influence prenatal development directly via epigenetic mechanisms, or indirectly through their interactions with their pregnant partners. A number of studies in human and nonhuman animals suggest that paternal stress, dietary composition, and toxins can all affect the histone composition and methylome of spermatozoa, with consequences for their offspring's development (Marshall, 2015; Schagdarsurengin and Steger, 2016; Terashima et al., 2015). Fathers' energetic and social investment toward their pregnant partner can have either exacerbating or buffering effects (Braun and Champagne, 2014). Patrilineage can have early effects on fetal development. For example, experimentally exposing male mice to chronic stress before breeding results in changes in sperm microRNA (miRNA) gene expression that can be observed in subsequent generations (Rodgers et al., 2013). Similarly, conditioning mice to odors linked to threats results in hypomethylation of the olfr151 locus (a gene important for olfactory functioning) in the sperm, which is linked to changes in fear responses in subsequent generations (Dias and Ressler, 2014). Several of the effects that prenatal challenges have on developmental trajectories appear to be modulated by sex. *In utero*, re-methylation occurs in a sex-specific manner providing an opportunity for sex to modulate the effects of the early uterine environment (Gluckman et al., 2007b; Lucifero et al., 2004).

Developmental trajectories are also influenced by the early postnatal environment, the effects of which are mediated by the maternal soma and behavior. Animal models suggest that low quality maternal care has life-long effects on the offspring's adult physiological response to acute stress by reducing the number of glucocorticoid receptors (GR) and GR transcripts levels in the hippocampus (Liu et al., 1997). Maternal behavior also affects offspring anxiety, fearfulness, learning, and memory (Curley and Champagne, 2016). Cognitive impairments may be functional under certain environmental conditions: adult male rats who experience low maternal care show better cognitive outcomes under highly stressful conditions (Curley and Champagne, 2016). Interestingly, maternal cues can also help offspring develop protective mechanisms against other environmental stressors. For example, in mice models, maternal exposures to the odor of a predator programs her offspring's limbic system in a way that they later show higher

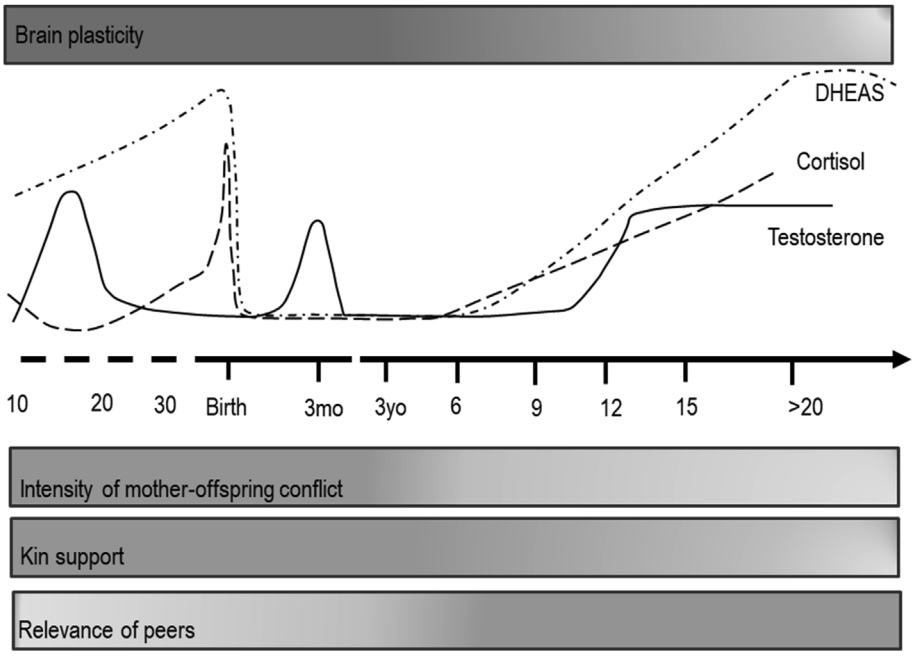

Fig. 1. This image shows the output of the HPAA and HPGA hormones during human development. On top the gray shades indicate the period of brain plasticity (darker areas indicate more plasticity). On the bottom there are three factors that we hypothesize playing an important role on the development of the HPAA and HPGA and their role on programming the brain during development (darker areas indicate stronger effect of each factor).

behavioral avoidance and higher basal glucocorticoids (for females) in response to predator cues. This neurobehavioral programming response is mediated by maternal behavior (St. Cyr and McGowan, 2015; St. Cyr et al., 2017) and it represents an advantage in environments characterized by high frequencies of predation events (Bateson et al., 2014).

Postnatal maternal effects on offspring's adult socio-emotional behavior appear to be the result of epigenetic mechanisms occurring in the limbic system. Strikingly, early maternal effects result in epigenetic markers that, from a functional point of view, are non-randomly clustered around genes and transcript factors involved in the neural pathway of the stress response (McGowan, 2015). For example, adult rats who experience poor maternal care show a decreased in GC receptors expression in the hippocampus resulting from the hypermethylation of the NR3C1 promoter region (Meaney, 2001; Turecki and Meaney, 2016). In mice, repeated bouts of mother-infant separation during early life results in demethylation of the arginine vasopressin (AVP) gene in the paraventricular nucleus of the hypothalamus which, in turn, influences long-term HPAA reactivity to stress (Murgatroyd et al., 2009; Murgatroyd and Spengler, 2011). Likewise, the brain derived neurotrophic factor (BDNF) mRNA is reduced in the hippocampus, amygdala, and frontal cortex as a consequence of hypermethylation in mice that have experienced early maternal separation (Roth and Sweatt, 2011).

Similar findings have been reported in humans. Individuals who experience early life trauma show epigenetic profiles in the NR3C1 gene, similar to those found in rats that experience low maternal care (Suderman et al., 2012). Suicide victims exposed to early trauma show decreased mRNA of the NR3C1 gene in the hippocampus, a consequence of hypermethylation of the promoter region (McGowan et al., 2009a,b). Other genes such as the SLC6a4 for the serotonin transporter may also be a target of epigenetic changes (Bowers and Yehuda, 2016). Low socioeconomic status has been associated with specific epigenetic profiles in nine-year-olds, with stronger effects than those of low maternal care (Bush et al., 2018).

Epigenetic modification may extend into adolescence. Maternal self-reported stress during their children's first year of life is associated with adolescents' increased methylation of NEUROG1 promoter, a gene important for neural development (Essex et al., 2013). These studies highlight the important role of the postnatal social environment in programming the HPAA and its impact on the development of the nervous system.

8. Conclusion

According to life history theory, natural selection favors the evolution of strategies that optimize the way resources and time are allocated among competing traits and tasks. Each individual has to modulate the allocation of time and resources to growth, maintenance, and reproduction at each life stage according to the external and internal environmental cues it perceives. This is achieved by integrating past and current information to achieve the best possible phenotype at each stage. The optimization of that process is constrained by environmental challenges faced during development and expected during adulthood. Developmental plasticity has costs and, as all other organisms, humans face trade-offs between those costs as well as the costs of early specialization. The balance between flexibility and specialization during development influences the ontogenetic trajectories of phenotypic plasticity. “Critical” or “sensitive” periods of development represent these inherent temporal trade-offs.

Hormones are considered important mediators of these life history trade-offs. Their highly conserved functions, combined with their flexibilities, suggest a strong history of selection for hormone-dependent traits that are key for organismal survival in variable environments, permitting flexible responses to variations in environmental stability. The HPAA plays an important role in detecting and integrating ecological risks (predictability and controllability) and influences many aspects of somatic and reproductive investment. This role is exemplified by its critical influence in modulating the timing and pace of reproductive maturation in response to physical and social challenges.

Humans are characterized by a *unique* combination of stable breeding bonds, extensive paternal effort in a multi-male group, lengthy childhood, extended bilateral kin recognition, grandparenting, and controlled exchange of mates among kin groups. The extended lengthy childhood-juvenile life stage carries risks, and yet it lasts for almost two decades. During this period the brain is sensitive to ecological and social experiences which are mediated by hormones (see Fig. 1); in fact the frontal cortex is the last to mature, during the mid-twenties. Human childhood is a life history stage that appears necessary and useful for acquiring the information and practice to build and refine the mental algorithms critical for confronting the social challenges that are key for

reproductive success of our species (Flinn 1997; Flinn et al., 2005; Legare, 2019). Adolescence may provide the time to achieve the social, material, and energetic resources that are necessary for successful reproduction.

The bulk of the human research on developmental programming has focused on industrialized, Westernized societies. These studies have mainly examined the roles played by the mother and/or the father on their child's socioemotional and psychophysical development in low fertility populations, wherein maternal and paternal caring are considered normative. Yet, arguably the nuclear family that characterizes much of the theoretical work on maternal and paternal attachment does not reflect what characterized the majority of the evolutionary history of our species (Sear, 2016). Within the nuclear family model, departures from the normative mother-offspring and father-offspring relationships have been proposed to result in maladaptive, pathological developmental trajectories for the offspring, often as a consequence of chronic stress.

The family environment, especially care from mothers, but also from fathers, siblings, aunts, and grandparents, appears to be a primary source and mediator of the ontogeny of social competencies and embodied capital. The HPAA of the developing child is expected to have evolved to respond flexibly to variation in these sources of investment. Yet, it is important to highlight the fact that the field is lacking investigations on how grandparents influence the phenotypic outcome of their grandchildren, their HPAA and HPGA reactivity, and socioemotional and growth patterns. Likewise it seems paramount to evaluate in which contexts flexibility in father- caring behaviors may influence their children's HPAA and psychophysical development. We must also further study paternal investment on child growth and the development of the HPAA and HPGA.

In light of these considerations, the current emphasis of the biomedical field on the maladaptive, pathological consequences of early stress warrants more consideration and deeper understanding of human evolution. It is important to investigate why natural selection should have allowed for such an extended period of altriciality and brain plasticity in humans. It is critical to acknowledge that HPAA responsiveness to physical and social stressors provides the child with time and opportunities for sampling past and current ecological conditions in order to calibrate (and recalibrate) the developing phenotype to better respond to current and predict future sociocultural conditions.

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