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Birth practices: Maternal-neonate separation as a source of toxic stress

Nils J Bergman

Department of Neonatology, Karolinska Institute, Stockholm, Sweden

Correspondence
Nils Bergman, Geijersgatan 16B, 75226 Uppsala, Sweden.
Email: nils@kangaroomothercare.com

Abstract

Maternal-neonate separation for human newborns has been the standard of care since the last century; low birth weight and preterm infants are still routinely separated from their mothers. With advanced technology, survival is good, but long-term developmental outcomes are very poor for these especially vulnerable newborns. The poor outcomes are similar to those described for adversity in childhood, ascribed to toxic stress. Toxic stress is defined as the absence of the buffering protection of adult support. Parental absence has been strictly enforced in neonatal care units for many reasons and could lead to toxic stress. The understanding of toxic stress comes from discoveries about our genome and epigenetics, the microbiome, developmental neuroscience and the brain connectome, and life history theory. The common factor is the early environment that gives (a) signals to epigenes, (b) sensory inputs to neural circuits, and (c) experiences for reproductive fitness. For human newborns that environment is direct skin-to-skin contact from birth. Highly conserved neuroendocrine behaviors determined by environment are described in this review. The scientific rationale underlying skin-to-skin contact is presented: autonomic development and regulation of the physiology leads to emotional connection and achieving resilience. Maternal-neonate separation prevents these critical neural processes from taking place, but also channel development into an alternative developmental strategy. This enables better coping in a stressful environment in the short term, but with permanently elevated stress systems that negatively impact mental and physical health in the long term. This may explain the increasing incidence of developmental problems in childhood, and also Developmental Origins of Health and Disease. Arguments are presented that maternal-neonate separation is indeed a source of toxic stress, and some suggestions are offered toward a "zero separation" paradigm.

KEYWORDS

birth, breastfeeding, emotional connection, life history, regulation, resilience, sensitization, separation, skin-to-skin contact, toxic stress

1 | INTRODUCTION

Toxic stress is a term that has successfully conveyed to the public the essence distilled from a large body of neuroscience (Garner & Shonkoff, 2012; Shonkoff & Phillips, 2000; Shonkoff, Richter, van der Gaag, & Bhutta, 2012). An eco-biodevelopmental model presents this in the context of childhood development (Shonkoff & Garner, 2012). Child is a general term and more specific terms that delineate stages are defined. A neonate is a child up to 28 days old, an infant up to 1 year old, and a toddler up until the fourth birthday. However, the critical developmental processes occur early, hence the emphasis on the "first 1000 days," being the first 2 years of life (365 days × 2) and the 270 days preceding birth (Panter-Brick & Leckman, 2013). Human development in early childhood has been shown to be highly sensitive to both nature and nurture: nature influences through epigenetic mechanisms responding to the early environment or ecology that determine subsequent biological developmental processes; nurture influences when there are unexpected disruptions and adverse events that negatively and permanently impacts learning and behavior, and physical and mental wellbeing (Shonkoff & Garner, 2012). The policy discourse has, however, been mainly aimed at toddlers, and perhaps a little to infants, but the neonatal period has been almost totally neglected, and only recently have a few articles identified the neonate as a candidate for toxic stress (D'Agata, Coughlin, & Sanders, 2018; Hallowell, Froh, Spatz,, & Expert Panel on Breastfeeding of the American Academy of Nursing, 2017; Sanders & Hall, 2017; Weber & Harrison, 2018). The definition of toxic stress is lucid enough: "the absence of the buffering protection of adult support." Parental presence in the neonatal intensive care unit (NICU) was previously (and still in some cases and places) strongly discouraged. If it is accepted that the toddler and the infant need buffering protection, the neonate has even more need of buffering, and the preterm neonate more still. Though it has taken long to realize, infants born preterm have poor long-term developmental outcomes, specifically in emotional and behavioral disorders (EBDs; Arpino et al., 2010; Baron, Erickson, Ahronovich, Baker, & Litman, 2011; Roberts, Anderson, De, & Doyle, 2010). The poor outcomes are similar to those described for adversity in childhood (Dube, Felitti, Dong, Giles, & Anda, 2003; Felitti et al., 1998), ascribed to toxic stress (Vijayendran, Beach, Plume, Brody, & Philibert, 2012). The understanding of toxic stress comes from recent knowledge after the "decade of the brain," the discovery of epigenetics (Meaney & Szyf, 2005), the microbiome (Douglas-Escobar, Elliott, & Neu, 2013), and Life Sciences theory (Narvaez, Panksepp, Schore, & Gleason, 2012). The theme of this issue is "minimizing developmental problems" through perinatal practices: this article will describe how the above discoveries provide an underlying biological and scientific rationale attributing many developmental problems to the toxic stress of early maternal-neonate separation.

2 | HISTORICAL PERSPECTIVE

It may be helpful to consider the historical perspective, and the origins of maternal-neonate separation in hospital practice. Stephane Tarnier was working as an obstetrician in Paris in the early 1890's, providing high quality community and hospital care to mothers and babies (Klaus & Kennell, 1976). His neighbor invented an "egg hatchery," providing constant warmth and humidity. Tarnier thought this might help his low birth weight babies, whom he called "weaklings." Working with his colleague Pierre Budin, they added glass windows to the hatchery, so that the mother could see her baby, and provide breastmilk and general care. There was no maternal-neonate separation in this scenario.

The method worked well, and in 1896 Tarnier sent some incubators to the Berlin Exposition. There Martin Couney apparently worked with them, and he realized that he would have greater success if he could put "living babies" inside them. A local doctor provided him with six low birth weight neonates. These came without their mothers, and Couney therefore arranged for wet-nurses to feed them, which was an accepted and standard practice at that time. The neonates all survived, and the exhibit was a commercial success. In the process, neonates became show-pieces and were separated from their mothers. Couney continued with such exhibitions, and moved to the USA, where he set up a permanent facility. This employed nurses and wet-nurses, the latter had to follow healthy diets and gave milk to the babies every 2 hr. Mothers were excluded from the care but they received free passes to visit during show times. Couney never charged the mothers for his care, relying only on revenues to pay his staff. The revenues, however, contributed to the medical profession distancing itself from him. However, there was absolutely no other kind of care available for these low birth weight neonates, and Couney was even criticized for trying to save babies that were "not intended by God to survive." In time, his results spoke for themselves, and hospitals began to adopt his methods. When they did so, they also adopted his policy of excluding the mother from care.

Parallel processes contributed to the policy of strict separation of mother from baby immediately after birth. Ignaz Semmelweis introduced handwashing around 1830 and dramatically lowered maternal mortality. He could not explain the mechanism behind the benefit of handwashing, which led to colleagues rejecting his evidence, and him. To this day, the *Semmelweis reflex* is a metaphor for the reflex-like tendency to reject new evidence or new knowledge because it contradicts established norms, beliefs or paradigms. Couney experienced the Semmelweis reflex as well. Semmelweis' knowledge and evidence were correct, but rejected.

The very year Semmelweis died, a plausible scientific rationale was being discovered to explain how handwashing worked. Researching independently, both Koch and Pasteur presented what we call the "germ theory." In 1865 Pasteur patented "pasteurization." In 1880 Koch started research that led to culture of bacteria and in 1890 published a set of famous postulates. Now there was a scientific explanation for why handwashing reduced maternal mortality. With this also came an additional justification for strict separation and isolation of small babies. Isolette is a (proud) brand of incubator. Even so, maternal neonate separation was rare until around 1950, when big commercial companies started mass producing incubators. At the same time similar companies started making artificial infant formula. Free samples were given to all maternity hospitals, with aggressive marketing and extravagant claims. In society it was also promoted as emancipating for mothers, and bottle-feeding presented as "modern and advanced." Note that with increasing mother-neonate separation, there was a reduction in breastfeeding, and so the need or necessity for breastmilk replacement also increased. By the 1960s, maternal-neonate separation was considered normal for all babies, and absolutely necessary for small babies.

Around 1960 a successful alliance between statisticians and academic physicians trying to control prescribing behaviors of colleagues, and extravagant claims from drug companies, led to a policy process that required "proof of efficacy," which required objective and unbiased trials with a control group. The first Randomized Controlled Trials had been published in 1944 and 1948 (Chalmers & Clarke, 2004). Cochrane (1989) was among the first to point out that very many medical practices and procedures lacked evidence, with obstetric practices the worst. However, maternal-neonate separation did not appear to require any evidence, by this time it was firmly established as a paradigm.

Since paradigms are deeply embedded in our cultures and psyches, challenging them cannot be undertaken lightly. In this article, I shall therefore provide as broad an overview as possible. Necessarily I must contrast the current separation paradigm with an alternative "zero separation" one. Since separation is recent, I shall describe the original nonseparation first, with respect to underlying physiological processes and observed behaviors. I shall focus on how these operate in the neonate but include some maternal aspects. In the nonseparation paradigm, I will also describe physiology and behavior in dyadic interaction, with some clinical evidence. I shall conclude with some thoughts on the future of neonatal care.

3 | LIFE HISTORY PERSPECTIVE—CARE PATTERNS

Life history theory examines the strategies used by all organisms during their life cycles, particularly their reproductive behavior. The physical and ecological environment is a crucial factor. Ecology deals with the relations of organisms to one another and to their physical surroundings. Broadly, there are four life history care patterns for mammalian newborns, with the relative maturity at birth being a key factor (Lozoff & Brittenham, 1979). The *Follow* pattern applies to precocial neonates, born mature in all respects, they can follow mother within minutes. They can suckle frequently, as a result their milk has relatively low fat and protein. The *Cache* neonate is also mature, and able to keep itself warm, however, it is "cached" or hidden in a safe place for protection. They are fed twice or three times a day only, and therefore have milk with very high protein and very high fat content. *Nest* species are less mature or altricial, and they need help in the nest to be kept warm. The mother may be a hunter or forager, giving feeds 3 or 6 hourly, therefore the milk also needs to have high fat and protein content. *Carry* care neonates are immature, and proportionately to their immaturity are dependent on immediate and continuous maternal warmth provided by direct body contact. Their milk is low in fat and very low in protein, the daily intake requirement is achieved by frequent feeds, accomplished by being carried on the mother continuously (Lozoff & Brittenham, 1979).

Homo sapiens belongs to the "carry care" group. Compared to all other mammals (except marsupials), human infants are born extremely immature (Rosenberg & Trevathan, 1995). Human milk has such extremely low fat and protein content, that humans should qualify as continuous feeders. The brain size at birth is a measure of birth immaturity: it is 25% of adult size in humans, compared to 50% in many primates, and 70% in most mammals (Rosenberg & Trevathan, 1995). As shall be described below, the human brain requires 1 hr sleep cycles in order to develop optimally. The life history strategy for the human neonate prioritizes brain time for sleep, and stretching feed time by increasing levels of lactose that last 1 hr. "Carry care" is therefore absolute nonseparation, with alternating one hourly feeds and sleeps.

The primate "carry care" pattern is estimated to be 40 million years in the making, the human hunter-gathering life strategy is estimated to be 8 million years old. Around 10,000 years ago, agriculture started: food was grown instead of gathered, animals domesticated instead of hunted. The basic pattern of infant care did change slightly, but neonates were continuously carried. However, in the last 100 years, the pattern of "carry care" has been changed to one where neonate and infant are separated and left lying still ("cache care"), fed every 4 hr ("nest care"), with formula (from a "follow care" species). Lozoff, Brittenham, Trause, Kennell, and Klaus (1977) states that these changes "alter the initiation of the mother-infant relationship, which may be strained beyond the limits of adaptability."

Adaptability or adaptation is a key concept in life history theory. The benign environment can be regarded as the "expected" environment, allowing for optimal development of the individual. There is an abundance of resources and low stress, allowing for time to develop "top-down" regulation in the social milieu, neo-cortical appraisal and reflection determines choices, allowing for a view of the bigger picture, and capacity to make long-term choices for future gain (Morgan, 2013). This is called the "slow life history strategy" (Ellis & Del Giudice, 2019). Conversely, in a harsh and impoverished environment, there is high stress. Such an environment requires a rapid response system, achieved by "bottom up" regulation, expressed as "act first, think later." There is no time to develop a bigger understanding of the world, and survival in the present time is priority. This is called the "fast life history strategy" (Ellis & Del Giudice, 2019). It is neither better nor worse than the "slow" as far as the species is concerned, it is the adaptation necessary for reproductive fitness. However, it comes with some important trade-offs. First, the permanently adjusted stress management system has adverse consequences on later adult health (McEwen, 1998). Second, the capacity for trust in others is diminished in favor of self-reliance (Teicher et al., 2003; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002), weakening the strength of social relationships over the lifespan (Belsky, Steinberg, & Draper, 1991). And third, this comes with an altered reproductive strategy, leading to earlier puberty (Ellis & Del Giudice, 2019; Kelly, Zilanawala, Sacker, Hiatt, & Viner, 2017), with more offspring born earlier in life (Teicher et al., 2002). These trade-offs are "necessary" in a harsh environment.

4 | LIFE HISTORY PERSPECTIVE—UNDERLYING SCIENCE

The ecobiodevelopmental model does not rely only on the above kind of reasoning, life history theory (or life science theory (Shonkoff, Garner, et al., 2012)) is rather used to make sense of more modern sounding concepts: the genome and epigenetics, the brain and connectome, and neurobehavior.

DNA is a single common denominator to life. Genes make up only a small fraction of the nuclear DNA. The gene pool of a species includes all the variety of genes that exist in the population and is collectively termed the *genome.* Genes make proteins, and proteins make the brain and body tissues (Nelson & Panksepp, 1998). Some genes also make hormones and neurotransmitters, and their receptors, and these determine behavior (Nestler, 2011). The genes are surprisingly few, but each gene is responsive to many epigenes. The epigenes are sensitive to the environment, adaptation and resultant neurobehavior in that environment is governed by epigenes. Some epigenes prevent or switch off gene expression, and merely the proportion that is expressed can make different behavior (Nestler, 2011). Other epigenes modify the expression of the gene in the way the protein functions. Sensory experience and appraisal after behaviors give feedback to the brain, favoring neural connections that are optimally suited to the environment; unused connections are pruned away (Heck et al., 2008; Teicher et al., 2002). The sum of all brain wiring is called the *connectome* (Crossley et al., 2014). The species measures its success, not on survival of any individual, but on its *reproductive fitness* (Ellis & Del Giudice, 2019). At a very basic level, this is the universal dogma of life: genes, brains, behavior (Panksepp, 1998); collectively the *genome*, the *connectome* and *neurobehavior.*

Critical behaviors that are most fundamental to reproductive fitness and survival, cannot always be learnt, they have to be done right the first time. Such are termed *highly conserved neuroendocrine behaviors* (Despopoulos & Silbernagl, 1986). The *highly conserved* comes from the DNA and is hardwired in the genome, the *neuroendocrine* comes from the neurotransmitters and circulating hormones from the connectome, only the behavior is what we observe. Most peripartum behaviors fit this label. The defining feature of mammals is *mamma* (Latin for breast), and breastfeeding is not learnt, it is innate. In animal husbandry such behaviors have been long known and understood and interfering with them strongly discouraged. The offspring needs to show the mother some kind of signal to which the mother responds supportively; the offspring is the active agent in going through a series of motor movements, triggered by a range of maternal sensory inputs, which eventually culminate in suckling at the breast. In the process, successful transition to extra-uterine life is accomplished, with physiological regulation of the whole organism.

It was only in 1987 that Widström described mammal-typical *highly conserved neuroendocrine behaviors* in human newborns (Widstrom et al., 1987). Until then our culture had not allowed newborn babies to remain with mothers because it was reasoned that they needed warming, glucose, and other forms of nonmaternal support to recover from the stress of being born. Widstrom et al. (2010) needed special permission from the ethics committee not to separate newly born babies, and to do nothing to them. They observed that human newborns when undrugged and left undisturbed in skin-to-skin contact (SSC) on their mothers' chests, needed ~1 hr to accomplish suckling, and in the process achieved better physiological transition than the best clinical and technological practices could accomplish. These behaviors are now well known as the "nine steps." Importantly, as we learn from life history theory, these behaviors are dependent on the *expected environment*, which is maternal-neonate SSC. Several critical sensory inputs from the human mother are necessary, the first likely being the warmth from her chest. The mother's chest is able to actively regulate infant temperature, warming and cooling her infant as needed (Ludington-Hoe et al., 2006). Direct firm touch from the

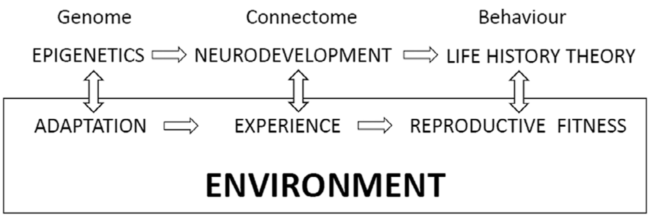

FIGURE 1 The environment is the common denominator to development. The epigene determines adaptations of gene expression adapted to the environment, the brain experiences sensory inputs firing circuits suited to the environment, and early behaviors make reproductive strategies optimized for that environment

skin may stimulate infant sensory fibers in the same tract that senses temperature (lateral and medial spinothalamic). At least as important are olfactory cues, areolar glands around the maternal nipple provide an attracting smell, more on this below (Porter & Winberg, 1999; Schaal & Durand, 2015). Visual cues (Widstrom et al., 2010), maternal voice and maternal movements also play a part. Interfering with any one of these sensations delays suckling at the breast (Doucet, Soussignan, Sagot, & Schaal, 2012), interfering with more than one sensory input can disrupt suckling, and separation makes suckling impossible. Some babies have better reserves, and some have better support and skilled help and manage to suckle and eventually breastfeed, but very many more fail. There is some resilience (tolerance of stress), and some redundancy (back-up plans), but separation from the mother is now known to be *unexpected* for the neonate. Unexpected environments and events require adaptation, and adaptations come at a long-term cost. Figure 1 depicts the above processes in relation to the environment.

5 | LIFE HISTORY PERSPECTIVE—PHYLOGENY OF THE AUTONOMIC NERVOUS SYSTEM

Because physiology is expressed by the autonomic nervous system (ANS) a deeper understanding of this part of the nervous system is necessary. Porges and Furman (2011) describes the phylogeny (evolutionary origins) of the ANS, and the ontogeny (embryological development) is considered to mirror the phylogeny. The earliest version of the ANS was primarily a visceral system, the "reptilian" brain had a parasympathetic nervous system (PSNS) and a sluggish hormonal system to augment defence responses. The response to threat was dissociation: shutting down and hiding, hoping not to be found. The early mammalian brain's advance on this was the sympathetic nervous system (SNS), with rapid choices for freeze, fight, or flight. What is often forgotten, however, is that the SNS is also for homeostasis even in benign circumstances, and that it still works in very close concert with the PSNS. And further, the PSNS is not only for visceral autonomic function, but also directly involved managing brain state and body functions during all threat responses and during stress.

Finally, the human (along with primates) has evolved a new myelinated vagal system, allowing very rapid and fine control. In contrast the old reptilian vagal system is unmyelinated, and very slow in comparison (Porges, 2007). Above the diaphragm the new vagus takes over the control of the cardiovascular and respiratory systems. It also connects intimately to the facial nerves, and to the emotional brain, hence Porges terms this the "social vagus" (Porges & Furman, 2011). In humans, threat is now managed at very much more subtle and sophisticated levels in the large social milieu, allowing for graded responses of submission and dominance and the plethora of social demands on all emotional systems. The strength of this control can be measured by the "vagal brake." The safer one feels and the more resilient and physically fit one is the stronger the "vagal brake" and the lower the heart rate (Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996). During social (or any other) stress, just easing the brake ever so slightly can increase heart rate in threat preparedness, without needing to activate the SNS. An adult can, however, become overwhelmed and revert to sympathetic choices of vigilance and freeze and even dissociation. More readily so if the development of the SNS and social vagus has been sub-optimal.

This has particular relevance to the human neonate. The old unmyelinated vagus is mature and functional at 28 weeks postmenstrual age. Neonates born before this often have severely impaired autonomic function (Haraldsdottir et al., 2018). If born after 28 weeks, the PSNS is relatively robust. At this stage, there is a functional sympathetic system, but it is immature, only maturing after 46–48 weeks. At 28 weeks the response to threat and stress for a prematurely born neonate is primarily a "reptilian" dissociation behavior. There is some capacity to freeze commensurate to the immature sympathetic system, but it is quickly followed by a robust dissociation defense. A term neonate may spend longer in freeze (a state maintained by combined maximal PSNS and SNS output), but will readily revert to dissociation (a pure PSNS state). At 2 months of age the infant has choices; what is observed is that some appear submissive and have adapted and dissociate readily, while others are more assertive and will "fight" for parental presence through crying. A key issue here is that the freeze state and the dissociation state are almost universally interpreted as sleep states, and by assumption as healthy states. Separated infants do "genuinely" sleep as well as spend time in freeze and dissociation, but their sleep architecture is abnormal. Both the freeze and dissociation states are stress determined, with adverse consequences; in addition, poor sleep architecture may contribute to adverse brain development, see more below.

While the PSNS is "primitive" in the sense that it is primordial, it is profoundly powerful. It has been called the "ultimate survival machine": partly because it has survived 400 million years, but partly because it powerfully ensures survival of the individual. The ANS is core to physiology, to every single aspect of living and being, and most of all in the period around birth.

6 | NORMAL PHYSIOLOGY AND BEHAVIOR AT BIRTH

Lagercrantz (1996) described the "stress of being born," showing that noradrenaline is considerably higher after vaginal birth than at any other time of life. Stress is not always bad, positive stress is a necessary part of development, but it is mild and of short duration, and immediately buffered by adult support (Shonkoff, Garner, et al., 2012). Ensuring that the "good" stress of being born does not become "bad" requires immediate buffering, achieved by SSC. The "excessive" stress at birth is necessary for several known reasons. The labor-induced adrenaline surge activates an epithelial sodium channel pump to achieve lung liquid clearance (Pfister, 2010). This explains why 5% of full-term caesarean births have respiratory distress (Pfister, 2010). Further, once breathing, the baby locates the breast by visual contact (Widstrom et al., 2010). But studies also show that high noradrenaline levels are needed to activate the olfactory bulb, from which a unique neural network ensures rapid and robust maternal odor learning (Raineki et al., 2010), necessary for nipple attachment and subsequent lactation. This can be termed a downstream effect, the upstream effect is as important. The olfactory bulb connects directly to the amygdala, usually identified as the emotional brain (Panksepp, 1998). It is also a primary site for threat appraisal and risk assessment (Graeff, 1994), or neuroception (Porges, 2004) Maternal smell (Porter, 1998) and maternal contact combine to reassure the newly born that the environment is safe. Appraisal of threat—is it safe or unsafe—is the highest order choice, depending on this entirely contrasting neural circuits are activated (Despopoulos & Silbernagl, 1986), with distinct autonomic programs and physiologic regulation. At birth, and more intensely in the presence of activation from high catecholamines, the amygdala that feels safe fires connections to the medial prefrontal cortex (Amodio, Master, Yee, & Taylor, 2008; Bartocci et al., 2000), determining an "approach orientation". Conversely, the unsafe environment turns on an "avoid orientation." Another connection is fired to the orbitofrontal cortex, the social brain. In this period immediately after birth, the emotional brain and the social brain are being connected (Nelson & Panksepp, 1998). I conjecture that this is the neural substrate of emotional connection. The term *emotional connection* is preferred (Frosch et al., 2019; Hane et al., 2018), bonding was originally used by Bowlby and Hofer for sensory and physiological precursor events, and attachment is a construct applicable to a toddler. Widstrom et al. (2010) has documented times for eye-to-nipple contact (around 10 min), and for subsequent eye-to-eye contact between mother and baby (after 30 min). These may be the neurobehavioral evidence of the processes just described. I suggest another reason for the extreme high catecholamines at birth is that for the relatively immature human brain, a whole hour of awakeness is needed to process these (and likely other) needed neural processes. In summary, the stress of being born supports physiological regulation and transition, it activates prelactation neural circuitry, and it initiates mother infant emotional connection. Warmth, food, and shelter: these are our basic human needs being provided.

That emotional and social intelligence begins at birth may sound surprising to some; neonates do not appear emotional or social. Jaak Panksepp has studied the emotional brain in intricate detail. In *Affective Neuroscience* he identifies the first and essential accomplishment required immediately after birth as the "integration of emotional systems for social affect" (Panksepp, 1998). Three sets of mechanisms are involved in the integration of the amygdala and prefrontal lobe: place attachment, thermoregulation, and pain. Once integration is achieved, making sense of sensory inputs, threat appraisal and emotional regulation are possible. Many years ago Heidelise Als could show with diffusion tensor imaging (MRI) that preterm neonates with parental presence in the NICU had strong amygdala to frontal lobe connections, which were almost absent in controls (Als et al., 2004). Martha Welch, in a Family Nurture Intervention with maternal odor cloths as a primary sensory input, could show profoundly enhanced EEG activity in the orbitofrontal lobe compared to controls (Welch et al., 2014). Amygdala-prefrontal connectivity in adults has been directly measured during regulation of negative emotion (Banks, Eddy, Angstadt, Nathan, & Phan, 2007). In extensive writings, Schore (2001) identifies this is the key and essential pathway for "right brain development, affect regulation, and infant mental health."

Transition to extra-uterine life does not have a defined time limit. Cardiorespiratory physiological adjustments take around 6 hr (Bergman, Linley, & Fawcus, 2004), but the underlying anatomy (foramen ovale and patent ductus changes in the heart) takes longer to finalize (Lind, Stern, & Wegelius, 1964). The gastrointestinal system is usually not considered when the term "transition" is used, nevertheless the expected processes that support transition from amniotic fluid to mother's own milk deserve attention and support. Here the essential role of colostrum is generally acknowledged (Pletsch, Ulrich, Angelini, Fernandes, & Lee, 2013). Unlike almost all other mammals, human milk volume only begins to appear after 2 days (3 days if there is separation) after birth; the reason for this is not known (Ellison, 2001). It is, however, clear that colostrum is present in relatively large amounts in the first hour after vaginal birth (Ellison, 2001; Pletsch et al., 2013), and that frequent regular suckling speeds up the arrival of milk (Salariya, Easton, & Cater, 1978). In full term neonates this volume of colostrum is swallowed, though we have not been aware of it until recently (Parker, Sullivan, Krueger, Kelechi, & Mueller, 2012; Parker, Sullivan, Krueger, & Mueller, 2015). When the neonate for reason of prematurity or illness cannot suckle and swallow, the colostrum should be expressed from the breasts, and given immediately to the neonate. Frequent emptying is the essential factor for ensuring increased milk production, the breast tissue shifts from endocrine control to autocrine control (Daly, Owens, & Hartmann, 1993), with the autocrine setting for required daily production being fixed after 2 or 3 weeks.

Alberts (1994) describes new-born highly conserved neuroendocrine behaviors in mammal studies, with some pertinent observations. The fetus in the uterus is in the right place or habitat, which sounds too obvious to state, however, it is absolutely competent and capable and "mature" for that stage of life and for the commensurate habitat (Alberts, 1994). The neonate in the right (developmentally appropriate) habitat is absolutely competent in terms of its basic biological needs and behaviors; in the human this habitat is maternal-neonate SSC on the chest, after some days anywhere on the mother's body. The philosophy to adopt is that the neonate it is not immature, it behaves in an appropriately mature manner in its correct habitat. The problem is not its maturity, but its habitat or environment. Though the term neonate is born with 25% of its final brain size, that 25% is perfectly wired and competent for its start to extra-uterine life (Schore, 2001; Winberg, 2005). The premature neonate has an even smaller brain size, it is immature to be on mother's chest, but totally unsuited to be anywhere else.

Thus, the neonatal period can be regarded as a launch period for all physiological and emotional systems, where processes begin in the first minutes and hours (at birth), and are consolidated by the end of 6 weeks (Schore, 2001). Graven (2004) refers to these as "needed neural processes" and warns that "the risk of suppression or disruption of needed neural processes is very significant and potentially lasts a life time."

Normal physiology at birth also includes the acquisition of a healthy microbiome (Mueller, Bakacs, Combellick, Grigoryan, & Dominguez-Bello, 2015). The mother's fecal flora is necessary and vital to the newborns health and well-being. The more species and the greater diversity the better, "dysbiosis" refers to adversely altered microbiota (Zhang et al., 2015). The microbiome impacts immunity (Di Mauro et al., 2013), metabolism, brain growth (Douglas-Escobar et al., 2013) and subsequent health and development (Diaz Heijtz et al., 2011). Neonates born by caesarean bypass the vaginal canal and the perineum (Shin et al., 2015), where they would pick up maternal gut flora (Dominguez-Bello et al., 2010), instead the "race for the surface" is won by hospital organisms (Dominguez-Bello et al., 2010). Such altered microbiota puts preterm neonates at risk for necrotizing enterocolitis and severe infections (Madan et al., 2012). Dominguez-Bello et al. (2016) was able to partially restore the healthy microbiome by vaginal microbial transfer. Artificial formula and antibiotic administration are identified as further major contributors to dysbiosis (Bokulich et al., 2016; Mueller et al., 2015). A healthy microbiota may also be protective against hospital acquired infections (Kim, Covington, & Pamer, 2017). Ongoing studies are examining whether immediate SSC would have a better effect. In terms of life history theory, SSC with "zero separation" contact would have ensured that the neonate shared the mother's full microbiota.

7 | NORMAL NEONATAL PHYSIOLOGY AND BEHAVIOR

James McKenna has stated "Nothing an infant can or cannot do makes sense, except in the light of mother's body" (personal communication). This applies not only to observable behaviors, but also to the underlying physiology. John Bowlby (1969) attributed later "secure attachment" to early physiological support provided by the mother or primary caregiver, in the form of sensory inputs, and that physiological process he labeled "bonding." Hofer (2006) conducted detailed studies on this, elaborating on the model. When observed experimentally, bonding is not the best term, but rather "regulation." The regulation refers to physiological control of all systems, in the present but also in terms of establishing set-points for healthy physiological functioning for future independent regulation. All sensory inputs from the mother are necessary, each has unique impact on a specific physiological aspect, collectively over different periods of time this creates an "umbrella under which the infant development can unfold" (Hofer, 1994). However, the sensory input is rather a sensory exchange between mother and infant, Hofer (2006) uses the term "interaction" at this sensory level. The term interaction is generally used at a behavioral and social level. The infant's capacity for socio-behavioral interaction is, however, built on, has grown out of, the early platform of mother-infant sensory and physiological interaction. This is a highly sophisticated neural construct and takes a long time. The mother's constant and uninterrupted physical presence is necessary throughout the period of infancy, and even beyond (Hofer, 1994). For the neonate and the infant mother-regulation is necessary, self-regulation should never be the goal.

In the neonatal period, there are three essential occupations (Alberts, 1994) or primary behaviors, namely sleeping, feeding, and connecting. None rank higher than any other, and all of them are managed by the same limbic and ANS. Those systems orchestrate also the *state organization*, the appropriate control of the level of arousal of the organism. State ranges from deep sleep through to drowsiness to alertness through to extreme arousal during hard crying. The lowest levels of state organization include several sleep states. It is not immediately evident on superficial observation that healthy sleep is cyclical, with cycles of ~1 hr, made of Quiet Sleep, Active Sleep, and REM sleep (Scher, Johnson, & Holditch-Davis, 2005). Fetal, neonatal, infant, and adult sleep differ, with a distinct pattern of maturation to adult sleep architecture usually established at 1 year (Doussard-Rossevelt, Porges, & McClenny, 1996). One-hour interval sleep cycles remain through life. Adults have blocked such cycles together at night while neonates sleep in one-hour intervals day and night (Born & Wagner, 2009). And neonates *should* sleep that way! It is during healthy sleep cycles that memories are consolidated in adults (Born & Wagner, 2009), but in neonates and infants this is when the basic neural architecture of neural circuits and networks are laid down (Graven, 2006; Peirano & Algarin, 2007).

When they wake in a safe environment, neonates will spend some time in a state organization period referred to as *quiet awake*. I suggest the purpose of this state is emotion connection. It is characterized by eye-to-eye contact, mutual vocalizations, with sensitive reciprocity in dyadic interactions. It does not need to last for long, some connection epochs last for some seconds, some minutes. During maturation, the connection time gets longer. It has been shown that mothers hold their babies more on the left side (laterality; Todd & Banerjee, 2016), recent evidence suggest this supports the right brain development described by Schore (2001). Mothers in harsh and stressful environments do not show left laterality (Morgan, Hunt, Sieratzki, Woll, & Tomlinson, 2018)!

Breastfeeding requires a higher level of state organization, measures of ANS activity show surprisingly high autonomic activation during early suckling until the start of the milk ejection reflex, after that follows a calm and regulated vagal state maintained for some minutes by nonnutritive suckling. The neonate that has never been separated will swallow the contents of a single milk ejection reflex, which is around 20 mL for a term infant (Prime, Geddes, & Hartmann, 2007). That is also the maximum capacity of the stomach of a term neonate (Bergman, 2013). The neonate has "food security," it does not experience hunger, it knows when it wakes up it will have immediate availability of mother, of mother's breasts and of mother's milk. The nonnutritive suckling engenders a lowering of state and leads to another sleep cycle.

After some weeks, the infant grows and needs more than the 20 mL. The frugal and time efficient way to feed is to provide the ejection contents from the other side. An equally possible option is to spend some extra effort and elicit a second milk ejection reflex. The latter also allows the choice of blocking together two sleep cycles, and taking larger volumes, this usually occurs between 2 and 10 months. This wide variability is normal, and it is linked also to time spent in connection. Infant personality and temperament begin to be expressed, influencing the maturation. As infancy progresses a fourth basic biological behavior is added to the repertoire, namely play (Panksepp, 1998). Play begins with eye-to-eye contact and gaze aversion with peek-a-boo being a later expression of this (Greenspan, 2004). Play here is entirely social and emotional, it seems to arise out of emotional connection; toys are only meaningful if they support interaction.

The same ANS and the same emotional brain coordinate and orchestrate these behaviors. Our need to study and describe the behaviors as I have attempted to do is necessarily reductionistic, but it needs re-emphasizing that the behaviors work in symphonic harmony to achieve optimal development of the neonate.

The above may not seem familiar to the reader. I venture that this is because neonates have not been cared for according to life history theory. Neonates that are separated from their mothers and fed according to a schedule cannot and do not behave as described above. Modern society has disrupted the expected pattern of behavior that best supported development. James McKenna has described this expected pattern of behavior in great detail, suggesting the term *breastsleeping* (McKenna & Gettler, 2016), which conveys also the higher level ANS control of feeding and sleeping (and implicitly: connecting).

8 | SEPARATION PHYSIOLOGY AND BEHAVIOR

The above descriptions intend to convey the ecology aspect, that the mother and neonate are relating to each other, and that the mother is the expected environment for the neonate. None of the processes described can occur during separation. If the harm of separation was entirely a matter of delaying development, it would have no major consequence. There is, however, no "pause button," development continues. In the absence of mother, an alternative physiology and behavior kick in, resulting in an altered developmental trajectory.

In the section above, I described state organization as a higher determinant of neonatal and infant behavior. State organization is in turn determined by higher order systems. The highest order system is a "threat appraisal system," or as described before, neuroception (Porges, 2003). The most fundamental determinant of every aspect of behavior and state organization and physiology is determined by the question "Am I safe?." Depending on the answer, entirely different neural programs determine physiology and behavior (Despopoulos & Silbernagl, 1986).

Threat appraisal is functional in the fetus and observable in very preterm neonates. Stress neurobiology is still undergoing development, along with the ANS described above. The neonate is as developmentally vulnerable to future disorders as the immaturity of the physiological stress systems. It is therefore reliant on caregiving, which is defined as the regulatory and buffering system provided by the mother (or caregiver; Loman & Gunnar, 2010). The emotion regulatory system is distinct but intricately connected to the stress regulation system, both require buffering. The stronger the emotion regulation and stress management systems, the less the vulnerability to emotional and behavioral disorders, both current and future (Loman & Gunnar, 2010). Figure 2 depicts the above, adapted from Loman and Gunnar (2010).

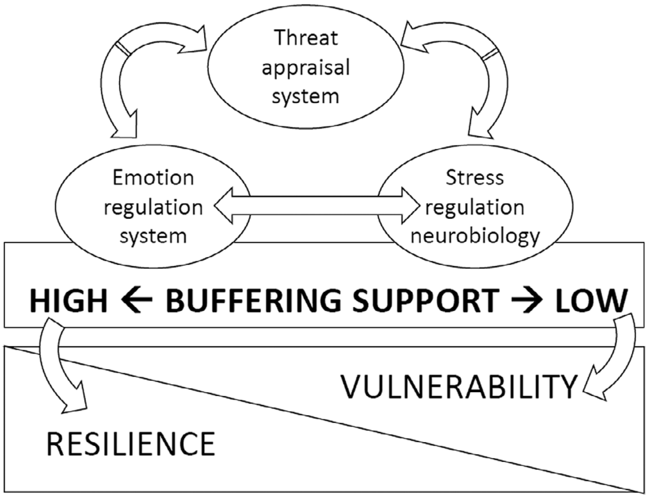

FIGURE 2 Toxic stress is the absence of buffering protection of adult support. Threat appraisal requires buffering, and the degree of buffering determines emotion regulation systems and stress regulation systems that determine future resilience or vulnerability

The amygdala is regarded as the center for emotional system processing, responding to both safe/positive and unsafe/negative stimuli. To the highest point of the neuraxis, the frontal cortex, the amygdala sends a warning signal that activates an avoid orientation (Amodio et al., 2008), initiating a defense mode that influences or determines every aspect of neurological function (Despopoulos & Silbernagl, 1986). The entire cortex and limbic system are fully and completely occupied in appraising the threat, and all resources diverted to respond appropriately. The unsafe environment has various dimension to consider. A distal threat does not elicit the same response as a proximal or overwhelming threat (Graeff, 1994). The severity, nature, and source of the threat, as well as previous experience and stage of maturation may be factored in (Graeff, 2004). The greater the threat, the deeper the brain structures involved, the more "primitive" the defense mechanism (Graeff, 2004). An important dimension of threat appraisal is interoception (internal body senses), not elaborated here (Graeff, 1994). The following table summarizes details of these processes, specifically as applies to the neonate. It is adapted primarily from Perry, Pollard, Blakely, Baker, and Vigilante (1995), with elements from Porges (1997), and Graeff (1994). (Table 1).

Focusing on the behavioral response of the neonate, and elaborating on the phylogeny of the ANS above: a "far distal" threat can simply be avoided by the mother. The neonate cannot actively avoid so crying is therefore necessary to make the mother aware of the threat and ensure immediate retrieval. Infant crying elicits responses from particular circuits in mother and father brains, leading to the compulsion to approach and rescue infants (Swain, Lorberbaum, Kose, & Strathearn, 2007). Should the threat (such as a predator) be

TABLE 1 Stages of threat appraisal and underlying anatomy and physiology, applicable to neonates

Appraisal	SAFE	ALARMING	DANGEROUS	LIFE THREAT	DEADLY
Threat	Absent	Distal	Proximal	Close	
Response options	REST	VIGILANCE CRYING	FREEZE	DISSOCIATION	FAINTING "Mini-psychosis"
Primary brain activity	NEOCORTEX Subcortex	SUBCORTEX Limbic	LIMBIC Midbrain	MIDBRAIN Brainstem	BRAINSTEM Autonomic
Analysis	Cortex, frontal lobe	Basolateral n, amygdala	Hippocampus		
Outflow	Amygdala	Hypothalamus	Hypothalamus	Periaqueductal gray matter	Periaqueductal gray matter
ANS	PSNS low	Vagal brake, SNS high	SNS and PSNS both very high	PSNS only, high	
Cognition	ABSTRACT	CONCRETE	"EMOTIONAL"	REACTIVE	REFLEXIVE
Emotion	CALM	AROUSAL	FEAR	TERROR	TUNED OUT

closer than the mother is, or if the threat includes the mother, crying would be a poor survival strategy. Instead, freeze is achieved by intense SNS and PSNS activation where the neonate lies absolutely still and pretends to be dead. Maternal defense can consist of distracting a predator or hiding. Should the threat be prolonged, the neonate is unable to maintain this intense and energy requiring autonomic state so enters the next deeper level response which is dissociation. This is a low energy state, in which there is active lowering of heart rate and temperature with relatively high parasympathetic tone, the reptilian defense is to conserve energy so as to be able to outlast the attention span of the predator until mother returns. Reviews of clinical studies report that during SSC core temperature is 0.5°C higher than "normal" as in incubator care. The biological interpretation is that the incubator temperature is unphysiologically lower, evidence of dissociation defense.

With the above insights, careful scrutiny of separated infants does allow for distinguishing freeze and dissociation states from quiet sleep and REM sleep states, to a degree. The biological default is nonseparation, directly comparing infants in SSC to separated neonates makes the difference more apparent (Morgan, Horn, & Bergman, 2011). We have, however, used heart rate variability (a measure of PSNS activity) with concomitant impedance cardiography (ICG, a measure of SNS activity), to draw the interpretations I have presented. Broadly, there is also correlation between autonomic state and frontal lobe laterality on EEG (unpublished). The frontal lobe represents areas responsible for the approach or avoid activity described above.

That a predator is a threat is obvious, but the most severe threat imaginable to a neonate is something more subtle: it is maternal absence, or mother-neonate separation. The sensory cue for her absence is even more subtle: it is the absence of mother's smell. Olfactory cues from mother are primary drivers for sleep cycling (Doucet & Schaal, 2006), and for breastfeeding behaviors (Doucet & Schaal, 2006; Porter & Winberg, 1999). Absence of maternal smell results in cessation of sleep and feeding intentions, replaced by the threat appraisal and responses described above.

Earlier I described the work of Hofer (Hofer, 2006), describing how mother–infant interactions is the mechanism that achieves regulation of the neonate. Hofer went on to study separation. The immediate physiological response is dysregulation, of all measurable physiological systems. The dysregulation may not be outwardly severe, but it is acutely alarming for the neonate. The immediate response to separation in almost all mammals is a distress signal, or crying in the human (Christensson, Cabrera, Christensson, Uvnas-Moberg, & Winberg, 1995). The purpose of this is to elicit re-union with mother (Hofer, 2006; Swain et al., 2007), and restoration of regulation. The infant knows that the mother will certainly respond to the crying, if she is at all able (Swain et al., 2007). If there is no re-union, the neonate's interpretation may be that the mother is in danger herself. Distress calls are therefore seldom prolonged. Once the appraisal has been reached that maternal absence is ongoing, the next stress response mechanism kicks in. Growth hormone is switched off, and the adrenal gland activated. There is quiescence and degrees of freeze, with worsening dysregulation. However, within 10 min or so the dysregulation begins to abate, as cortisol is released into the blood stream. Cortisol is a stress "rescue hormone" and is able to restore homeostasis. All resources have been diverted from growth and development, for example, calories are being used for thermogenesis. Our modern culture has interpreted the quietening as calming down, while in fact the infant is experiencing the very opposite.

The capacity to evoke a high cortisol response is a sign of good health, and an appropriate response to threat. Cortisol restores regulation, but it is intended to do so as a stopgap temporary measure. However, lowering that cortisol is the second part of the healthy response, and for this the buffering protection of adult support is necessary. The separated human neonate has "stable vital signs," which we interpret positively. But the separated neonate has cortisol Level 2–4 times higher than normal (Anderson, Change, Behnke, Eyler, & Conlan, 1996), the separated preterm neonate 10 times higher cortisol than normal (Modi & Glover, 1998). High levels of glucocorticoids are neurotoxic when studied in primates (Uno et al., 1994) and pigs (Kanitz, Tuchscherer, Puppe, Tuchscherer, & Stabenow, 2004). Homeostasis sounds like a good thing, but for a developing organism it is homeorhesis that is required (De la Fuente et al., 2014). In conditions of "changing energy dynamics" homeorhesis protects the developmental trajectory, in contrast to homeostasis with high cortisol and absent growth hormone. For the human neonate, self-regulation is a state of stress.

9 | CLINICAL EVIDENCE—HUMAN STUDIES ON SEPARATION

I have described the physiology of the separated neonate, noting that this is the usual condition of neonates in our current culture, and the standard of care for low birth weight infants (LBWI). There are in fact randomized controlled clinical trials (RCTs) on human LBWI where the standard of care is compared to an intervention from life history theory, namely SSC. We conducted the first such study on 35 babies between 1,200 and 2,200 g (Bergman et al., 2004). In order to ensure "zero separation" mothers had to give consent before birth; and all potential subjects were kept on mother's chest without separation until weighed, at which point they were randomized and those allocated to standard of care were immediately separated and placed in incubator. Those allocated to SSC were immediately placed back on mother's chest. Normal routine care, and the additional measures taken to collect research data were done exactly the same in both groups for the first 6 hr of life. A list of objective criteria defining physiological instability severe enough to require medical intervention was used as the primary outcome. The parameters were set so as to provide a measure defining instability with high specificity. In the incubator group, 15/18 (83%) neonates needed medical attention, in the SSC group only 1/13 (8%). Further, the neonates had heart rate, respiration and oxygen saturation monitored continuously for the 6 hr, computed to a composite measure of physiological transition with high sensitivity (SCRIP: Stability of the CardioRespiratory system In Preterms (Fischer, Sontheimer, Scheffer, Bauer, & Linderkamp, 1998)). At 6 hr all SSC subjects were fully stable while only half the separated babies were stable. Separated babies less than 1,800 g were more unstable at 6 hr than at 2 hr. This study has been replicated in Vietnam on 100 babies between 1,500 and 2,500 g, with similar results (Chi Luong, Long Nguyen, Huynh Thi, Carrara, & Bergman, 2016). Note the paradigm for ethics approval and publication in a journal: SSC is the novel intervention being compared to standard of care; to our biology it is separation that is the intervention.

A Cochrane review on "Early skin-to-skin contact for mothers and their healthy newborn infants" (Moore, Bergman, Anderson, & Medley, 2016), focusing on studies on full term neonates, does identify the paradox of intervention and control, the forest plots are annotated to indicate "favors intervention" on the right, rather than the customary left. Apart from the physiological outcome, the primary finding is that breastfeeding outcomes are significantly improved. The physiology underlying this finding is described above. Kangaroo Mother Care is a composite strategy including SSC and breastfeeding with early discharge (WHO, 2003). A Cochrane review on this, "Kangaroo mother care to reduce morbidity and mortality in low birthweight infants" (Conde-Agudelo & Díaz-Rossello, 2016), concludes there is a significant lowering of mortality. Note, however, that the term KMC as endorsed by the WHO is for LBWI that have stabilized, "in order to tolerate" SSC. The accepted "standard of care" that newly born infants should be separated remains. Susan Ludington maintains a bibliography of all material published on Kangaroo Care (USIKC; hrrp://www.kangaroocareusa.org). This includes some 120 tables, one for every separately identified outcome. For every known outcome, SSC is superior to separation, our current standard of care.

From these studies and reviews, if the practice of SSC (nonseparation) had been standard of care, the conclusion would be that the intervention (maternal-neonate separation) was worse for the baby. It would not be possible to change the standard of care to something provenly worse. But it seems not be necessary to change the standard of care to something provenly better. The RCTs conclude that the intervention is better than the control, but since the standard of care is the standard of care, there is no need to change it.

With very few exceptions, the above findings have had no impact on care of LBWI.

10 | SEPARATION PHYSIOLOGY AND TOXIC STRESS

In the short term, high cortisol is protective, in the long term it may lead to harm. Meaney and Szyf (2005) studied the effect of early life experiences in rats. Cortisol receptors are predominantly found in the hippocampus. Cortisol is picked up by such receptors, and the result is a negative feedback signal to the hypothalamic–pituitary–adrenal gland (HPA) axis, stopping cortisol production (Meaney & Szyf, 2005). Meaney observed that some mother rats did a lot of "licking and grooming (LG)," others did much less. The pups that had a lot of LG were healthier, and when they became mothers they did a lot of LG to their pups. Conversely, offspring from low LG mothers were less healthy, and did less LG on their pups. In an iconic experiment Meaney and his team swapped newly born pups between high and low LG mothers. The pup of a high LG mother, when reared by a low LG mother became unhealthy, and when having its own pup behaved like its low LG foster mother. Conversely, offspring from a low LG mother reared by a high LG mother were healthy and high LG later. Meaney could then show that the quality of early maternal care influenced the number of hippocampal cortisol receptors that were expressed. Epigenes were discovered in this way (Meaney & Szyf, 2005). They can be regarded as switches, and in this particular case methylation switches on the DNA were being activated to switch off the gene that made the protein for the receptor, or acetylation switches were turning them on. The more licking and grooming the pup received, the more acetylation was taking place, the more cortisol receptors were being expressed on the hippocampus, which then became more efficient in removing cortisol from the bloodstream on one hand, and signaling the HPA axis to stop making it on the other. Low grooming pups have higher proportion of methylated genes, with fewer receptors. Any stress results in cortisol elevation, which then takes much longer to remove from the blood stream, and production of cortisol continues since the negative feedback loop is weaker. The permanently elevated cortisol is a contributor to poor health, both physical and socio-emotional. Further, the switches are inherited from parent and even grandparent.

Early maternal care matters. The immediate responses to threat (Table 1) translate over time to alterations in the neural stress circuitry with adverse impact on development. A life history theory perspective always has a speculative side, but the following interpretation has support from research. The newborn has sophisticated sensory capacities, as does the genome in the form of signals picked up by epigenes. The epigenes of a low LG mother "know" that she is absolutely the best, and that she would be doing high LG if she could. The reason that she does not, is because the world outside is poor and impoverished, dangerous and difficult. The mother is obviously working hard to defend and feed herself first, that is why she cannot spend as much time with offspring. The mother is good, the environment is bad. As stated above, maternal absence is the greatest threat. The epigene therefore makes a prediction about the adult world, thereby providing the best preparation possible for the offspring. In a dangerous world, it is highly beneficial for survival and reproductive fitness to maintain a high cortisol level. This is the substrate also of the fast life history strategy described above (Ellis & Del Giudice, 2019). In a benign environment with lots of resources, the mother has much more time to spend with her offspring, and does lots of licking and grooming, her offspring have more receptors, and over the lifespan suffer less harmful effects of high cortisol. The reproductive strategy changes, the benign environment is safe, longer is spent on offspring with more spaced pregnancies, and infant mortality is lower. If mortality is high, the fast life history theory reproductive strategy is to have more children with shorter intervals. For the species, both strategies are necessary, as environmental changes are inevitable (Ellis & Del Giudice, 2019).

The epigenetic phenomenon was first described for cortisol, but occurs widely. This is elaborated in a book "The Fetal Matrix," which introduces the concept of predictive adaptive responses (PARs) (Gluckman & Hanson, 2005). Some genes change their output constantly, for example insulin production in response to glucose levels. But there are other genes that are essential to development, it is to these that PARs apply. Complex systems need irreversible building blocks and tools, and for such the PAR leads to a "very early, once off and forever" setting of the gene expression (Morgan, 2013). The resulting behavioral neural circuitry becomes "canalized," and resistant to change.

The cortisol receptor genes in the rat are almost identical to those of the human, and in most species there are several kinds of cortisol receptor. In a study on 215 psychiatric subjects, the degree of methylation was measured, and analyzed according to how much "severe abuse or neglect" had been experienced in childhood (Perroud et al., 2011). Where there had been no abuse at all, there was no methylation. One episode of abuse did not increase methylation either. However, once there were two events of abuse (a second knock), methylation increased, thereafter with a dose response effect of more increase proportional to more neglect. From a life history perspective, the epigenes "know" that a single bad event does not necessarily predict the nature of the environment. However, if a bad thing repeats itself, and if it does so in the short space of time that the gene is being expressed, then it is highly likely that the PAR is an appropriate response to the environment.

Our early understanding of neurodevelopment comes from animal and primate studies. While modern human neonatal care accepts maternal-neonate separation as a norm, in all animal studies such separation is universally accepted as a severe stressor, perhaps the most severe possible (Kaufman & Rosenblum, 1967). A small rodent, *Octodon degus*, is used as an animal model to test human anti-depressant medications. The pup is separated in the first 3 days of life, for 6 min twice a day (Ziabreva, Poeggel, Schnabel, & Braun, 2003). That is enough to make alterations to dopamine and serotonin receptors in the hippocampus and amygdala such that a "depression model" is created. Early weaning and social isolation of piglets produces cortisol receptor changes in the hippocampus and the frontal lobe (Poletto, Steibel, Siegford, & Zanella, 2006). In a monkey study, separation at 1 week resulted in an amygdala-specific gene change (GUYC1A3), with an enlarged but less functional amygdala, with anxiety and depression when adult (Sabatini et al., 2007). In another monkey study, 1–2 hr episodes of separation took place daily during the first month of life (daily separation dose less than 10%). There was reduced cortisol receptor expression in the hippocampus, prefrontal and temporal cortex, and the hippocampus was 10% smaller in size, with subsequent adult depression (Arabadzisz et al., 2010). Following animal studies, it has been shown that human adults with depression have a smaller hippocampus, by about 10% also (Driessen et al., 2000). Joan Luby studied a group of preschool children, with a careful history of the degree of maternal support provided to the children. Hippocampal size of children whose mothers gave low support was 10% smaller than from high support, with increases in depression scores (Luby et al., 2012). McGowan et al. (2009) reports that in adult suicide victims that were abused in childhood, hippocampal cortisol receptors were 40% methylated, compared to 10% in control victims.

The adaptation following the PAR prepares the organism for the predicted environment. The change is always adaptive, and adaptation in itself is not the problem. The problem arises when the prediction is wrong, this is "maladaptation" (Cicchetti, 2010; Gluckman & Hanson, 2005). Rats reared in environments with very low glucose adapt, and in some subspecies even live longer than normal. When such rats are placed in a glucose rich environment, they are maladapted, and fare very poorly (Panksepp, 1998). The key issue is not whether glucose is good or bad, or the environment is good or bad, it is the (epigenetic) maladaptation that predicts poor outcome. The genome is prepared for a diversity of environments but takes millennia to change. The epigenes are able to adjust to change in environments on a generational time scale.

It is difficult to imagine (and previously rejected) that some seemingly small effect in early life can impact the individual over the lifespan. This is nevertheless the platform for a rapidly expanding body of science, called Developmental Origins of Health and Disease (DOHaD) (Hochberg et al., 2011). Originally "fetal origins of health and adult disease" or "fetal programming" was described by David Barker, from careful epidemiological studies of birth weight and placentas reflecting cardiovascular disease in adults. Later early life events were implicated. For example, the amount of weight gain in formula fed American men in the first week of life predicts their obesity after 30 years (Stettler et al., 2005). Very briefly, at any time window that a developmental gene is being expressed, unexpected events or toxic stress leads to adaptation (Hochberg et al., 2011). The adaptedness is limited to the potential embedded in the genome, as we can interpret from life history theory. In so far as the early life event was able to mislead the epigene concerning the future environment, the subsequent maladaptation may lead to disease—DOHaD. Conditions implicated include obesity, diabetes, cardiovascular disorders, psychiatric disorders (Heindel & Vandenberg, 2015), and some cancers (Heindel, Skalla, Joubert, Dilworth, & Gray, 2017).

There is a subtle difference with respect to what I have described here as maladaptation, and the "toxic stress" as widely understood in Early Childhood Development (Ellis & Del Giudice, 2019). Adverse childhood events lead to toxic stress, and a build-up of allostatic load (McEwen, 1998; McEwen & Gianaros, 2011) leading to the methylation described. However, when separated at birth, the methylation and adaptation is a primary change, with more pervasive and more profound impact to the life history strategy (Ellis & Del Giudice, 2019). The world in which the neonate and infant is born in may in fact be as predicted, such an infant may "thrive" due to its adaptation to a harsh environment. The "thrive" is in the short-term, as it is being traded off for long term health. Later trauma can produce the same methylation and harm, but may be ameliorated by earlier positive maternal buffering care.

11 | RESILIENCE—STRESS RESISTANCE

Thus far, I have described the nonseparated infant according to the expected life history, and contrasted this with the separated infant, with respect to physiology and behavior, and the underlying science. For any developing infant, the primary developmental objective should be resilience, or stress resistance. This has been defined as the "capacity to maintain healthy emotional functioning in the aftermath of stressful experiences" (Parker, Buckmaster, Sundlass, Schatzberg, & Lyons, 2006). An illustrative primate study compared mother-reared monkeys with peer-reared monkeys. At 18 months of age they were all free ranging in normal social life, and underwent a stress test. Mother reared monkeys had a peak of cortisol with 15 min, which returned to normal within 30 min, the peer-reared had a delayed and prolonged peak (Feng et al., 2011).

"Healthy emotional functioning" we have already identified as a function of the amygdala and the frontal lobe, as in the approach orientation described above. These are oxytocin rich circuits. Oxytocin is the hormone of reproduction (uterine contractions, milk ejection reflex), but it also the social hormone, often called the affiliation hormone (Nissen et al., 1996; Ross & Young, 2009; Uvnas-Moberg, 1998). During labor, maternal oxytocin blood levels are extremely high, and these reach the fetus to the extent that after vaginal birth, the neonate has very high circulating levels (Ross & Young, 2009). These may preactivate the amygdala and prefrontal lobe.

Physiological hormones very seldom work in isolation, rather in an orchestral kind of way with other hormones. The two key hormones involved in resilience are oxytocin and dopamine. Dopamine is the hormone for drive and purpose and will to live, and with that also identified as the hormone for joy. It is also responsible for forming and maintain habitual behaviors. It is involved in sexual and reproductive behaviors (Baskerville & Douglas, 2010). It is perhaps best known as the reward hormone. Parts of the brain that produce dopamine have also been called addiction centers, cocaine fits perfectly onto the dopamine receptor. Lastly, it may be less well known that such centers are in fact parenting centers rather than addiction centers. A key element of parenting is the compulsion of ensuring constant wellbeing of offspring, nothing gives greater reward. Thus, at birth, the essential neurological accomplishment is the connection of oxytocin centers and dopamine centers in the brain (Strathearn, Fonagy, Amico, & Montague, 2009).

This connection is dyadic, it occurs in parallel in the infant and the maternal brain. For the infant the salient cues are maternal smell, warmth and contact, and possibly colostrum. For the mother the cues are suckling, vocalization and tactile stimulation. In the mother, the connection of the dopaminergic and oxytocinergic systems enable her to correctly process the sensory cues she received from the infant, and respond accordingly (Strathearn, 2011). The capacity or potential for this connection is only optimal in the minutes and hours after birth, when oxytocin levels are high and there is time for emotional connection. Swain et al. (2008) studied maternal fMRI after vaginal birth and caesarean birth, looking at what brain areas responded to own-baby cry stimuli. Different brain areas responded to the crying, with vaginal birth mothers showing increased activity in "sensory processing, empathy, arousal, motivation, reward, and habit-regulation circuits." I venture that the relevant difference in these two groups was not the mode of delivery as such, but the subsequent period of separation that likely followed the caesarean birth. Ruth Feldman selected (a priori) two groups of mothers, some that were "synchronous" having good emotional connection with their infants, and others she termed "intrusive." The two groups showed the same changes Swain described, with these changes being interpreted as being evidence of "anxious and high-risk parenting" (Atzil, Hendler, & Feldman, 2011).

The neonate requires immediate and continuous buffering for its regulation. Any stress is "tolerable" with adult buffering, note that "adult" means a father or primary caregiver can provide adequate buffering. For the newly born, however, the default in life history theory is mother. The oxytocin and dopamine connection allows for emotional and social connection (oxytocin) being the most joyous and rewarding experience possible (dopamine), a positive or virtuous cycle is created. Numerous developmental and adult behavior disorders have been implicated when these systems fail to work together (Baskerville & Douglas, 2010). However, this connection is also the defining circuitry for resilience. Charney (2004) describes the neuroscience of individuals who despite external adversity display resilience. The circuits of the brain where oxytocin and dopamine work, are the same as those of cortisol. Oxytocin and cortisol are antagonists, but when oxytocin is connected to dopamine it has the upper hand, and cortisol is lowered rapidly. This is the mechanism for resilience, the "capacity to achieve healthy emotional functioning in the aftermath of stressful experiences." The window of opportunity (critical period) for this connection is in the first day of life. Over days and perhaps weeks the final number of cortisol receptors will be expressed, augmenting the humoral arm of the neural arm of resilience.

12 | MATERNAL NEUROBEHAVIOR AND SENSITIZATION

A description of the parenting brain interacting with the infant brain is provided by Swain and colleagues in a detailed review of parent infant interactions including functional neuroimaging studies (Swain et al., 2007). An important detail from this review for the purpose of this article and resilience, is "reciprocity," also described as contingent behavior. The closeness and strength of the mother–infant interactions are measured in terms of how well the mother can read the baby's messages, and how she can convey that understanding back to the baby. This creates a positive feedback loop that enhances infant development. This same close interaction reinforces circuits for oxytocin (sociality) and dopamine (reward), engendering ever increasing resilience. The article identifies many factors that in subtle or dramatic ways contribute to decreasing the quality of maternal care, creating a "spectrum" of quality of care. Resilience and vulnerability mirror this spectrum, they are a result of quality of maternal care.

Protecting and promoting this connection should therefore be the overriding priority. In this way doula support (ACOG, 2014), and "natural birth" (Mercer, Erickson-Owens, Graves, & Haley, 2007; Smith, Plaat, & Fiska, 2008) improve outcomes, and are consistent with life history theory, a birth companion is a universal factor in non-Western cultures that are closer to our roots. A common (but misguided) approach is to coerce or encourage the mother "to rest and be alone," that this is good for her, and that it is "best and safest for her baby to be in the nursery". Reproductive biology affirms that there are critical periods that operate in the newborn (Lee & Cheng, 2003), but equally in the mother. Separation immediately after birth, and for the hours and days that follow, should be avoided at all costs. The window of opportunity, critical or sensitive period, in the maternal brain is less than the usual time for reunion after caesarean birth (Swain et al., 2008). Very high dose oxytocin inhibits the anterior cingulate gyrus (Uvnas-Moberg, 2003), leading to "ferocity of defence of young" (Hahn-Holbrook, Holt-Lunstad, Holbrook, Coyne, & Lawson, 2011; Leng, Meddle, & Douglas, 2008). The window for this effect is only some hours (Uvnas-Moberg, 2003). Early suckling produces prolactin, which ensures mammogenesis is optimal (Uvnas-Moberg, Widstrom, Nissen, & Bjorvell, 1990). The window for this is 2 days: successful breastfeeding requires "zero separation."

Another piece of evidence comes from an RCT in which SSC was given immediately after birth for 6 hr to the intervention only (described above), after that both groups could do SSC by clinical indication or choice, the dose of SSC was measured during the hospital stay (Bergman et al., 2004). The time required for low birth weight neonates to physiologically stabilize was 6 hr, but we do not know what effects this has on neonatal neural circuitry, nor the time required. Ann Bigelow followed up 12 of these subjects in their homes some months later, and filmed mother–infant interactions. The maternal dimension of interaction was analyzed by QSORT, predictive of later infant secure attachment; and by NCATS (teaching scale in mother), predictive of later child Bayley score for cognitive development. The dose of SSC in the first 6 hr (random allocation) did not differ in the groups, though it did predict subsequent higher SSC dose. However, the higher the dose of SSC given in the first 24 hr, the higher was the maternal score both in the QSORT and the NCATS. The inference could be that a 6-hr dose is not enough sensitization period for the mother. The neuronal changes to sensitize the maternal brain to mothering involve several complex systems. We have earlier discussed the oxytocinergic and the dopaminergic systems, but there are also endorphin systems, prolactin and mammary physiology, serotonin systems (Suarez-Trujillo & Casey, 2016), and epinephrine and stress-related systems (Buckley, 2015). Animal parenting has been extensively studied (Kinsley & Lambert, 2008), allowing also a life history interpretation of what is involved for the human mother and family. On plausibility, I would suggest that 24 hr is a minimum length of time required for maternal sensitization, during which separation of mothers and babies should be strenuously avoided.

Life history theory emphasizes the role of the mother in the neonatal period (Cook, 2008), but does in no way exclude the father (Lozoff & Brittenham, 1979). Fathers and mothers have identical circuits for parenting (Fleming, Corter, Stallings, & Steiner, 2002; Swain, 2011), which is quite rare in the mammal kingdom (Fleming et al., 2002). However, neural circuits function according to neurotransmitters and hormones that are messengers from higher and deeper circuitry, and the hormones differ between mothers and fathers (Fleming et al., 2002). In an ongoing study (unpublished) we have found evidence for a dopamine surge in fathers within 30 min of experiencing SSC in the first few hours of their neonate's birth, this is not the same as when SSC is done after 2–3 days. Their behavior and feelings toward their infants have also been shown to be stronger (Gloppestad, 1994, 1998). They can effectively warm their babies in SSC (Christensson, 1996), in life history terms this means they do not replace mothers, but must have at least a supportive role in neonatal care. Fathers should be included in the birth experience.

13 | THOUGHTS ON THE FUTURE OF NEONATAL CARE

This special edition of the journal addresses the role SSC (Kangaroo Care) may have "in preventing and minimizing preterm and term infants' likelihood of developing developmental problems." I have presented a counter-argument, in so far as defining neonatal SSC as a biologically expected place and state of nonseparation from mother. From this perspective, I posit that maternal-neonate separation is responsible for increasing the likelihood of developmental problems.

The arguments presented apply to all full-term *H. sapiens* new-borns. It is the reproductive biology of our life science theory, our evolutionary biology. The fact that we separate babies is not disputed, that we may be doing harm to them because of separation is something we do not contemplate. Life history theory does explain why not all separated neonates have developmental problems. They do have resilience to cope, but they may be adapting their life history strategy in the process.

However, for the preterm and LBW neonate, their resilience is much less, and their dysregulation the more pronounced. Developmental outcomes are also proportional to their prematurity (Aylward, 2005). Kangaroo Care is a term usually reserved for preterm and LBWI. Life history theory does seem to have regard for prematurity. The small brain size at birth is the result of an "obstetrical dilemma" (Rosenberg & Trevathan, 1995), of a narrow pelvis from bipedalism, (walking on two legs), and a very large final brain size. In mammalian terms, a full-term human is extremely immature. Immaturity and early birth are necessary adaptations that the human species has acquired. Every baby is born with physiological and behavioral changes that have taken place to ensure that the immature organism survives and thrives. If that baby human is now born premature over and above immature, those very mechanisms can be relied on even more. There is other evidence that life history is prepared for such premature birth events: maternal milk of preterm mothers has higher concentrations of protein in the first 3 weeks, regardless of gestational age at birth (Charpak & Ruiz, 2007). At 28 weeks gestation newborns without other pathology and kept in SSC are able to suckle (Nyqvist, 2008), and to swallow safely (Nyqvist, 2008; Sase et al., 2005), and with help the majority can exclusively breastfeed at 34 weeks (Nyqvist, 2008). Current medical dogma is that infants cannot safely swallow until 34 or 36 weeks. This may be true for separated babies, and for babies feeding on bottles (Chen, Wang, Chang, & Chi, 2000; Meier, 1988).

What is required to change the philosophy of care for small infants? A new philosophy of care derived from life history theory could help. Identifying SSC and "zero separation" as the expected environmental requirement for better physiological outcomes, would be a first step. There is a current global focus to improve survival of the "small and sick neonate" (Moxon et al., 2018). One step in shifting the paradigm is to recognize that being "born small" (preterm and or low birth weight) does not equate to being "born sick." Many small babies are born small for purely maternal reasons, and do not have any pathology. The paradigm shift required is to recognize them as being otherwise healthy but requiring first the right environment and place of care, and then additional support for their immaturity. Overriding principle: they have less resilience to tolerate separation, so all additional support must be combined with "zero separation," that is, be provided while in SSC on a primary caregiver.

Some small neonates are born small because they are sick, they have a pathology. Their basic physiology requires the buffering protection of adult support as much as ever. Secondly, they require the additional support for their immaturity, and thirdly they now need the specific medical and nursing care appropriate to their diagnosis. Only in exceptional circumstances would such care be impossible to combine with SSC, but then parents should remain in maximal sensory proximity throughout. Practically, this requires profound change at a systems level: infrastructure, space, equipment, and staff training. Achieving this also requires that father or an other family member is included (Ortenstrand et al., 2010), and help with doing SSC (Erlandsson, Dsilna, Fagerberg, & Christensson, 2007; Gloppestad, 1998), for this space and amenities need to be provided. Broader social support is needed, and not the "one size fits all," and "no space for father" that institutional and impersonal services often codify so rigidly. Daunting as this may seem, we have no choice but to begin: we are able to change our care systems, we cannot change our biology.

At Karolinska Institute, such changes have been initiated, and the above philosophy is currently being tested in an RCT called IPISTOSS (Immediate Parent-Infant Skin-To-Skin Study). There is also a Bill and Melinda Gates Foundation funded multi-country RCT called iKMC (immediate KMC study), sponsored by WHO, taking place in Ghana, India, Malawi, Nigeria and Tanzania. The intervention is the same in both studies. The primary outcome in the iKMC study is lowering of mortality, 4,200 babies weighing between 1,000 and 1,800 g will be enrolled. The intervention group will receive immediate and continuous SSC with support for breastfeeding, the control group will receive SSC as soon as stable according to objective monitoring criteria. Results are expected in 2020. However, even if a substantial mortality lowering in low- and middle-income countries was found, this may have no impact on high-income countries. The IPISTOSS study is taking place in two high-income countries, with very good neonatal outcomes: Karolinska in Stockholm, and Stavanger, Norway. Essentially, the life history theory perspective and arguments that are presented in this article are the background for this protocol. Subjects are enrolled and randomized before birth, according to gestational age between 28 + 0 and 32 + 6 weeks. (Standard of care in these hospitals already includes immediate SSC to neonates 33 weeks and above, ethically they cannot be randomized). Outcome measures include transition physiology, epigenetics and telomeres, microbiota, stress neurobiology, breastfeeding and growth, maternal and neonatal MRI studies, maternal-infant interaction with emotional and cognitive development. We believe (or hope) that an understanding of, and evidence for, the underlying physiology and neurobiology of separation as a cause for harm would make it mandatory to change the current standard of care that separates newborns from their mothers. Thus, a second step in changing the philosophy of care for small neonates is to pre-empt the Semmelweis reflex, and provide not just evidence of efficacy (IPISTOSS) and effectiveness (iKMC), but validated scientific explanations for these findings.

The imperative for change requires a third level of endeavor. We do not question that when admitting a toddler to hospital we also admit a parent. Why do we treat the neonate differently? There is an ethics and human rights aspect to this. *Autonomy* is one of four ethical pillars, but the child does not have autonomy, it cannot communicate what it wants, nor make choices in difficult situations. So, instead of "autonomy of the child," the principle applied is "the best interests of the child." This comes from the 1989 United Nations Convention on the Rights of the Child (CRC), ratified by most countries. This states "A child's best interests are of *paramount importance* in every matter concerning the child." The choice for the child is the one with the highest net benefit among the available options.

At the time this was codified, we did not understand the needs of the newborn. It was believed that *surviving* required only that the heart and lungs and body organs worked normally, and that development would catch up later. It is, however, the development of the brain and subsequent mental health, which defines *thriving*. The importance of this very early quality care is recognized by the World Association for Infant Mental Health, who have written the "WAIMH Position Paper on the Rights of Infants" to complement the Convention of the Rights of the Child (WAIMH, 2016). The following are extracts from the Paper:

> Caregiving relationships that are sensitive and responsive to infant needs are critical to human development and thereby constitute a basic right of infancy.
>
> The infant therefore has the right to have his/her most important primary caregiver relationships recognized and understood, with the continuity of attachment valued and protected—especially in circumstances of parental separation and loss.
>
> The infant has the right to be given nurturance that includes love, physical and emotional safety, adequate nutrition and sleep, in order to promote normal development (WAIMH, 2016).

This resonates fully with the arguments I have presented. For all babies, and small and sick babies in particular, our vision of the future neonatal care must be one with immediate and continuous "*presence of the buffering protection of adult support*." Therefore the third step is "advocacy"—to be a voice for the needs of the child.

Finally, it may be the matter of choice. A current advocacy or policy mantra is "survive and thrive." In the context of my arguments, survival was never really the big issue, but the quality of survival, as in "thrive." Life history theory provides two choices: a fast and a slow life strategy. Both are equally good to "mother nature," the choice depends on the changing environment. But the fast life history strategy does not value "thrive." The trade-offs being made are at the expense of the individual specimen, in favor of the species. And the fundamental issue is the nature of the environment.

However, if we do not understand the communication mechanisms of the life history choice regarding the nature of the environment, we may mislead the genome. The signals we provide in modern obstetric and neonatal care (absence of parent) may inadvertently tell the genome to choose the fast life strategy (survive in a bad world). The subsequent neurobehavior of the individual is then maladapted to the benign or good world we imagine we live in, or wish to live in. If our birthing practices are such that the majority of individuals born are programmed into making the fast life history choice, our birthing practices may be to blame for the deteriorating state of the world. For example, we regard teen-age pregnancy as a public health problem. That we regard it as a problem is proof that we are in "slow life strategy" and that we think our environment is benign. The pregnant teenager does not understand our values, perhaps cortically she knows we think it is bad, but she does not feel that. Her genome has responded to early life signals (e.g., separated for 3 days at birth, sleeping alone at night, multiple caregivers with working mother) that have programmed her behavior. That she may be overweight, smoke cigarettes, and lead an unhealthy lifestyle is part of the fast life strategy package. The irony is that we who blame her for her conduct and condition are actually responsible for it, she did not choose it, our birthing and childcare culture did. Epidemics of noncommunicable diseases drain economic and human resources. Developmental disorders along with other mental health problems are estimated to affect a third of the world's population. They may likely originate in maternal-neonate separation, leading to a fast life strategy.

In terms of public health, it behooves us to understand, respect, and abide by the underlying biology governing life history strategy. Creating an early environment that supports the expression of a slow life history strategy is of paramount importance. It may not only improve the health and lifespan of the individual, but also make a better, more long-lasting and thriving civilization.

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