What is resilience: an affiliative neuroscience approach

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Resilience – a key topic in clinical science and practice – still lacks a clear conceptualization that integrates its evolutionary and human-specific features, refrains from exclusive focus on fear physiology, incorporates a developmental approach, and, most importantly, is not based on the negation (i.e., absence of symptoms following trauma). Building on the initial condition of mammals, whose brain matures in the context of the mother's body and caregiving behavior, we argue that systems and processes that participate in tuning the brain to the social ecology and adapting to its hardships mark the construct of resilience. These include the oxytocin system, the affiliative brain, and biobehavioral synchrony, all characterized by great flexibility across phylogenesis and ontogenesis. Three core features of resilience are outlined: plasticity, sociality and meaning. Mechanisms of sociality by which coordinated action supports diversity, endurance and adaptation are described across animal evolution. Humans' biobehavioral synchrony matures from maternal attuned behavior in the postpartum to adult-adult relationships of empathy, perspective-taking and intimacy, and extends from the mother-child relationship to other affiliative bonds throughout life, charting a fundamental trajectory in the development of resilience. Findings from three high-risk cohorts, each tapping a distinct disruption to maternal-infant bonding (prematurity, maternal depression, and early life stress/trauma), and followed from birth to adolescence/young adulthood, demonstrate how components of the neurobiology of affiliation confer resilience and uniquely shape the social brain.

Key words: Resilience, oxytocin system, affiliative brain, biobehavioral synchrony, mother-child relationship, neurobiology of affiliation, sociality, plasticity, meaning

Resilience, usually defined as positive outcome despite adversity[1-3], is likely the ultimate goal of human maturity and the single most important target of prevention and intervention science. Individuals who are able to face life's hardships with courage and perseverance, maintain positive outlook under difficult circumstances, enjoy both intimate bonds and a wider social circle, express empathy and compassion to others' misfortune, foster industry and a sense of agency toward long-term autonomous goals, live a life of creativity, vitality and meaning, and are free of debilitating symptoms despite early adversity or current trauma, define the hallmark of human achievement and the main goal of clinical effort since Freud. It is thus surprising that, despite decades of research, a comprehensive biobehavioral perspective on resilience has not yet been formulated.

Current empirical work on resilience typically focuses on the neurobiology of stress and fear regulation, or employs epidemiological/clinical research in the aftermath of trauma. In both lines, resilience is conceptualized as the "absence of symptoms" or the "maintenance of mental health" following adversity or trauma[4]. A recent interdisciplinary panel[5], while emphasizing the urgent need to shift the focus from psychopathology to resilience in the field of mental health, and highlighting the immense economic burden and personal suffering caused by stress-related disorders, concluded that resilience can only be defined *ex post facto* after the trauma has passed and some individuals do not succumb and remain symptom-free.

From a scientific standpoint, such position is problematic. Without a clear definition of a construct, empirical evidence cannot accumulate nor can it guide intervention effort. In particular, it is critical to identify whether resilience involves processes that gate deterioration following physical or mental insult, or those that uniquely foster strength and stamina[6,7].

Positive psychology focused on resilience as a key component of well-being[8] and launched the well-known resiliency training in the US army[9]. Some aspects of resilience are also echoed in the writing of post-Freudian psychoanalysts who emphasized the functioning, growing and relating aspects of the self and its embeddedness in the social milieu, such as Sullivan[10], Fromm[11] and Erickson[12]; in the work of Maslow[13] on self-actualization; and in the formulations of humanistic psychology[14]. Yet, these authors did not focus on resilience *per se* but on personal growth, did not integrate systematic research into their models, and did not incorporate neurobiological findings into their conceptualizations, or even negated the relevance of any neuroscientific evidence[15,16]. A human-specific model of resilience, which on the one hand is attentive to internal reality and man's higher faculties, but on the other draws on evolutionary models and incorporates neuroscientific findings into its core concepts, has not been constructed.

Two major issues may further complicate the construction of a comprehensive biobehavioral model of human resilience. First, with most current effort directed toward understanding the neurobiological underpinnings of mental disorders, research in psychiatry has generally focused on features that can be readily tested from a cross-species perspective. This has led to an almost exclusive focus on the neurobiology of fear – the neural, endocrine, genetic and molecular processes that sustain the fear response and enable stress management[4,17-21]. Accordingly, studies often utilize cross-species stress-related paradigms, particularly fear conditioning, and this has resulted in a fear-focused view of resilience[22,23].

Second, a true focus on development as a core component in understanding mental health, particularly resilience, has often been missing, despite the fact that all models of the self are, in essence, developmental (that is, describe stage-like progression from immature to mature states). Resilient individuals are

not only born, but are (critically) raised. It has been advocated[24] that, in order to study resilience, we must follow children from infancy and over lengthy periods to detect age-specific biological, behavioral and social markers that tip children toward a resilient pathway. However, such longitudinal effort is extremely rare.

These two issues have led to a rather limited, one-sided view of resilience. When asked, in a discussion on resilience, "what have you changed your mind about...", a panel of leading researchers[25] all pinpointed the narrow focus on fear physiology and stress neurobiology in resilience theory and research as the main issue they had changed their mind about.

A new conceptualization of resilience must be evolutionary-based, enable a thorough cross-species research, and set the stage for meticulous data collection that tests its specific expression across developmental stages, contexts and psychopathological conditions. Most critical for science, it should be verifiable (i.e., open to proof and falsifiability).

In the following, we propose a model of resilience that is based on the neurobiology of affiliation and offers a biobehavioral, evolutionary-based and developmentally-sensitive conceptualization, which is not constructed on the neurobiology of fear on the one hand or on the pursuit of happiness on the other. Our model takes into account the fundamental condition of mammals, whose brain matures in the context of the mother's body and caregiving behavior, and contends that maturation of all neurobiological processes that foster resilience are embedded in the provisions afforded by the mother's body and species-typical caregiving.

Moreover, the model argues that any understanding of resilience must consider the initial dependence of the infant on its mother and the immense impact that this dependence has on brain structure and function. Mammalian young are born with an immature brain, and their brain is shaped by the mature maternal brain through physical proximity, lactation, and the assemblage of species-typical well-adapted caregiving via processes that provide external regulation from mother to young in a system-specific manner[26,27].

Such external regulation of the immature brain by the mature brain charts the core mechanism of brain development in mammals and functions to fine-tune the infant's neurobiological and behavioral systems to life within the social ecology and its unique features[28,29]. We argue that the tuning of the infant's brain to life within the ecological niche and its distinct hardships marks *the very essence of resilience* and that processes that participate in such tuning define what resilience "*is*", and should become the focus in resilience theory and research.

CORE COMPONENTS OF THE NEUROBIOLOGY OF AFFILIATION

Our model draws on three core components of the neurobiology of affiliation: the oxytocin system, the affiliative brain, and biobehavioral synchrony.

Oxytocin

The ancient oxytocin system, evolving approximately 500 million years ago, functioned to mediate organisms' response to environmental challenges by supporting the regulation of basic life functions, such as water conservation, thermoregulation and energy balance across the phylogenetic scale[31,32]. Hence, its initial involvement in endurance, organism-ecology adaptation, and resilience.

With the evolution of mammals, oxytocin has been incorporated into labor and lactation. For mammalian young, then, the mother-infant bond has become the key context for the maturation of systems that support stress reduction[32]. Life-sustaining functions no longer develop in the context of the group, like in fish or ants, but within the intimacy of the "nursing dyad", via provisions embedded in the mother's body.

In mammals, the oxytocin system became the key one supporting the resilience-by-affiliation mechanisms, where robustness, plasticity and tolerance of ecological hardship is achieved by social contact in processes that span a single cell to human cultural communities[29,33]. Overall, the role of oxytocin in resilience stems from three sources, associated with its involvement in neural plasticity, sociality and immunity.

Oxytocin is implicated in *neural plasticity* at the molecular, cellular and network-assembly levels[34-36]. Oxytocin neurons can co-express with various neurotransmitters, including dopamine, serotonin and opioids. Oxytocin-expressing neurons include a wide variety of cell types, such as GABAergic interneurons, glutamatergic pyramidal cells, and other peptidergic cells[34,37,38]. Oxytocin integrates brain and periphery, incorporates massive epigenetic inputs, and is particularly related to attachment experiences[39,40]. It increases plasticity in the hippocampal network to increase salience of the attachment target[41], and attachment experiences shape oxytocin receptors availability[42].

Oxytocin's pulsatile mode of release is particularly important for neural plasticity, by which it shapes environment-dependent neurobiological systems[43]. Its pulsatile release coordinates birth according to favorable environmental conditions, charting the first integration of brain and environment in human life[44]. Its surge during birth causes gamma-aminobutyric acid (GABA) signaling to change from excitatory to inhibitory, synchronizing the fetus' hippocampal neurons with the transition from prenatal to postnatal life[45,46], setting the lifelong excitation-to-inhibition balance. Optimal balance of excitation and inhibition is critical for adaptive functioning and buttresses the "sensitive period" effect, which is critical to the robustness of all living organisms[47].

Oxytocin plays a key role in *sociality*. The neural systems that enable attachment and bonding evolved through oxytocin's sensitivity to the recurring elements in the environment, imbuing mother and surrounding with incentive value[48-50]. Oxytocin availability at core limbic sites guides infants to prefer cues associated with their mother, leading to the formation of dyad-specific attachments[51,52]. During first post-birth days, oxytocin receptors become connected to specific social cues via oxytocin's links with the brain dopamine reward system[53-55], olfactory-amygdala pathways[56,57], innervation of sensory cortices[54], and sharp-

ening signal-to-noise ratio in hippocampal pyramidal cells[58]. These program the brain's social perception, preferences and memory, and connect them to the attachment target.

Oxytocin supports the integration of individuals into social groups[59,60]. Across evolution, it has been implicated in social functions: in courting rhythmic movement in nematodes[61], social processes in worms[62], mate selection and flocking in birds[63], exclusive bonding in herding animals[64], and social affiliation in rodents[65], primates[66] and humans[29,67]. Evolutionary constraints led this flexible environment-dependent system to direct young to bond with their parents, function within their social ecology, and engage in the social structure of their species[64]. Notably, greater social support and a sense of belonging to the social group have been repeatedly associated with greater resilience[68-70].

The infant's oxytocin system is shaped by caregiving. Animal studies indicate that maternal behavior programs oxytocin receptor availability in the brain[71], and longitudinal human studies show that peripheral oxytocin is programmed by sensitive parenting repeatedly experienced throughout childhood[72-74]. Oxytocin induces a physiological state of quiescence that affords participation in the world without fear and stimulates the desire for social contact through its links with dopamine in striatal neurons[75-77]. This unique state provides the basis for the individual's sense of security upon which resilience can develop.

Finally, oxytocin plays an important role in functionality of the *immune system*. Human studies show associations between oxytocin and immune biomarkers[78,79]. In cell culture, oxytocin reduces oxidative stress and interleukin-6 (IL-6) secretion from stimulated macrophages[80]. In vivo, it decreases inflammatory cytokines, IL-6 and tumor necrosis factor (TNF)-α[81]. During periods of bond formation, including the period of becoming a parent and falling in love, both oxytocin and IL-6, an immune biomarker, increase their activity[82], and oxytocin is implicated in quicker wound healing[83]. Recently, an oxytocin-producing gut bacterium (*Lactobacillus reuteri)* was found to play a role in resilience, stress management, and quicker wound healing in the host, suggesting not only an additional gut-brain axis of oxytocin production, but also a microbiome-host link that promotes resilience[84].

The affiliative brain

The "affiliative brain" charts the network of inter-connected structures that enable humans to form and maintain close relationships[85].

The human affiliative brain, which evolved from the rodent maternal brain, expanded to include several higher-order cortical networks that integrate the immediacy and subconscious motivation with the cognitive aspects of human parenting[30,86]. This global human caregiving network has been further repurposed to sustain human social affiliations with lovers, close friends, and fellow humans, all shaped in the infant's brain by maternal provisions during early sensitive periods[30,85].

Studies of the maternal brain in animal models date back to the 1950s, and describe the critical role of the medial pre-optic area of the hypothalamus in initiating the subcortical network that enables mammalian mothers (and fathers in bi-parental species) to care for their infants[87]. Primed by oxytocin release during pregnancy and labor, the medial pre-optic area sends projections to the amygdala, to increase maternal vigilance for infant safety, and to the ventral tegmental area, to increase maternal reward from infant stimuli, sensitizing a limbic network underpinning maternal care (also including the nucleus accumbens, lateral septum, ventral pallidum, bed nucleus of stria terminalis, and globus pallidus).

In humans, this subcortical network expanded to include higher-order networks that enable empathy, simulation, mentalization, and emotion regulation, forming a global network that supports attachments[30]. In the 3-5% of mammalian species that show bi-parental care, the same system underpins father care. However, recent molecular and system-level findings show that different neuronal populations underpin maternal and paternal caregiving[88], and, while the same network supports human mothering and fathering, the pathway to fatherhood is more cognitive and relies on concrete paternal childcare activities[87,89].

Oxytocin plays an important role in tuning and function of the affiliative brain. Humans are wired for social behavior via activity of the mammalian caregiving network, which contains abundant oxytocin receptors[90]. Oxytocin causes long-term depression in the amygdala[91] to attenuate amygdalar response to aversive social stimuli, increasing network connectivity and enabling response specificity to social targets[92,93].

Following the attenuation of social avoidance, oxytocin enhances motivation for social bonding through its crosstalk with dopamine receptors in striatum, particularly nucleus accumbens. Dopamine acts in nucleus accumbens to organize goal-directed reward-related behavior by inhibiting the output of GABAergic (inhibitory) neurons[94-97], which enables activation of glutamate (excitatory) inputs, leading to energetic, vigorous, goal-directed action[98,99].

Nucleus accumbens shell contains oxytocin receptors that form heteromers (neurons expressing for both oxytocin and dopamine[100]) and this enables dopamine neurons specifically suited to identify sensory-motor reward to encode the temporal patterns of social action[49,101]. This allows the brain to internalize the social partner, encode bond-specific patterns, and draw reward from social synchrony[96,101].

The tighter oxytocin-dopamine crosstalk during bond formation enables the flexible incorporation of the new bond into the self[102] and the formation of sensory-motor memories of attachment experiences[103]. Thus, while dopamine affords motivation and vigor, oxytocin provides the tranquility necessary for bond formation.

While this brain network sustains human parenting, it also provides the neural support for the formation of other affiliative bonds throughout life; hence the term "affiliative brain". Animal[104] and human[85] studies indicate that the mammalian paren-

tal brain also sustains pair-bonds in monogamous mammals[77], and romantic attachment and close friendships in humans[85]. This affiliative network develops in the infant's brain during early sensitive periods through attuned caregiving, and enables the child to form close relationships, fall in love, become a member in social groups from sports team to nations, and eventually nurture his/her own children.

It has long been noted by Darwin[105] that evolutionary adaptations take place at the parent-infant interface and its inherent plasticity enables the emergence of new behaviors which, over time, alter gene expression. Consistently, our model – which places the parent-child interface at its core – highlights how the affiliative brain utilizes its inherent plasticity for resilience, endurance and recalibration.

The affiliative brain confers resilience in multiple ways. Optimal activation of this network enables individuals to form and maintain social bonds throughout life, manage stress by relationships, and, through the crosstalk of oxytocin and dopamine, draw their deepest reward from affiliations, rather than non-social sources (e.g., drugs of abuse). Indeed, disruptions in the integration of oxytocin and dopamine is found in addiction, when reward disconnects from its social targets and disruptions are found in both oxytocin[106] and neural plasticity[107,108].

The parental brain shapes the child's social abilities. We found that parental brain activations in infancy predicted the child's emotion regulation, stress management, and symptom formation across the first seven years of life[109-111]. In parallel, sensitive and synchronous parenting longitudinally shaped the child's affiliative brain in adolescence[112,113]. Finally, humans' large associative cortex enables humans to find meaning through love to abstract ideas, such as homeland or God, and extend affiliations to fellow-humans, pets, or the Earth's flora and fauna, all supported by the same network[85].

Biobehavioral synchrony

Biobehavioral synchrony is the core mechanism sustaining human sociality and affiliation. It is defined as "the coordination of biological and behavioral signals between social partners during moments of social contact", and it describes the mechanism by which the parent's mature brain externally regulates the infant's immature brain and tunes it to social life[29,114,115].

Biobehavioral synchrony creates a template for the coordination of the biological with the social and mental; the merging of autonomous self with autonomous other; and the integration of moments of interpersonal match with moments of mismatch, alone states, and reparation, all within a secure dialogue.

In multiple studies spanning infancy to adulthood, and across a wide range of healthy and high-risk populations in various cultures, we showed that these "precious social moments", when parent and child coordinate their non-verbal behavior, frame moments of biological coordination. For instance, only during these episodes there was synchrony between mother and infant's heart rhythms[116], coordinated release of oxytocin[117], and

brain-to-brain synchrony in the social brain[118].

Synchrony links with better stress management[73], higher respiratory sinus arrhythmia[119], and better immune functions[120], depicting a mechanism by which coordinated social behaviors reduce stress and enhance resilience.

The linkage of behavioral and biological synchrony originates *in utero*[121], incorporating the infant's biological rhythms into a social dialogue that transforms the biological into relational and the intra-individual into interpersonal. Patterns of non-verbal synchrony reverberate in the dyadic relationship across time, while expanding in symbolic and interpersonal complexity[122], and such increased diversity of repertoire amidst a core order charts a mechanism of resilience, as suggested by dynamic systems' theory[123]. Notably, all forms of physiological synchrony (neural, endocrine and autonomic) are embedded within behavioral coordination, supporting our main hypothesis that behavioral synchrony frames physiological connection and that resilience is behavior-based[29,124,125].

Biobehavioral synchrony experienced in the first months of life marks a critical experience during a sensitive period that predicts a host of resilience-related outcomes from birth to young adulthood, including emotion regulation, symbolic competence, stress management, lower externalizing and internalizing symptoms, and social brain development[30,114,126,127].

Across development, the non-verbal affect matching of infancy morphs into reciprocal exchanges that incorporate, like expanding ripples, the child's growing symbolic, linguistic and social competencies and evolves to include empathy, perspective taking, and intimacy, all built upon the rhythmic non-verbal core in the service of resilience (see below). This echoes Maslow's notions[13] that the "self" includes both what the person is and what the person can become. Furthermore, while charting a human-specific mechanism that develops across human life, biobehavioral synchrony draws on a long evolutionary line of socially-based survival-related mechanisms in mammals and other eusocial (hyper-social) species that sustain endurance and resilience.

Across evolution, from bacteria to human, synchrony builds on processes that bind two organisms (or entities) into a coupled biology. Recent advances in quantum physics suggest that such coupling began even before the emergence of life, as seen in the phenomenon of "quantum entanglement", the connection of particles across time and space that locks two units together, giving their union immeasurable strength and endurance.

THE THREE TENETS OF RESILIENCE

Taking into consideration the aforementioned foundations of affiliative neuroscience (oxytocin, the affiliative brain, and biobehavioral synchrony), our model highlights three tenets that define what resilience *is*. While all three are required for the making of the resilient individual, they come in different combinations across individuals and cultures, and express differently across ages and stages (Figure 1).
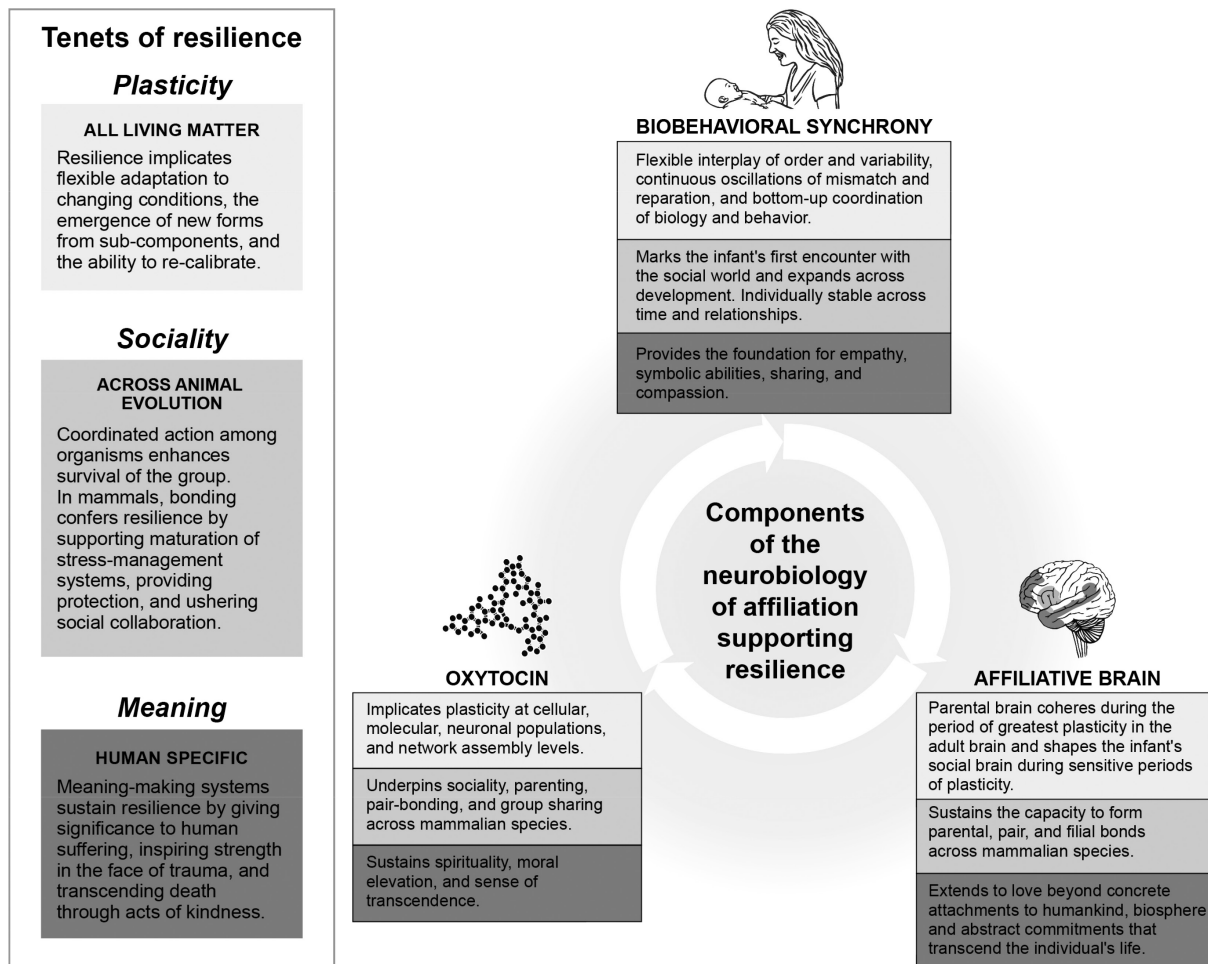
Tenets of resilience

Plasticity

ALL LIVING MATTER

Resilience implicates flexible adaptation to changing conditions, the emergence of new forms from sub-components, and the ability to re-calibrate.

Sociality

ACROSS ANIMAL EVOLUTION

Coordinated action among organisms enhances survival of the group. In mammals, bonding confers resilience by supporting maturation of stress-management systems, providing protection, and ushering social collaboration.

Meaning

HUMAN SPECIFIC

Meaning-making systems sustain resilience by giving significance to human suffering, inspiring strength in the face of trauma, and transcending death through acts of kindness.

BIOBEHAVIORAL SYNCHRONY

Flexible interplay of order and variability, continuous oscillations of mismatch and reparation, and bottom-up coordination of biology and behavior.

Marks the infant's first encounter with the social world and expands across development. Individually stable across time and relationships.

Provides the foundation for empathy, symbolic abilities, sharing, and compassion.

Components of the neurobiology of affiliation supporting resilience

OXYTOCIN

Implicates plasticity at cellular, molecular, neuronal populations, and network assembly levels.

Underpins sociality, parenting, pair-bonding, and group sharing across mammalian species.

Sustains spirituality, moral elevation, and sense of transcendence.

AFFILIATIVE BRAIN

Parental brain coheres during the period of greatest plasticity in the adult brain and shapes the infant's social brain during sensitive periods of plasticity.

Sustains the capacity to form parental, pair, and filial bonds across mammalian species.

Extends to love beyond concrete attachments to humankind, biosphere, and abstract commitments that transcend the individual's life.

Figure 1 The three tenets of resilience as integrated into the core components of the neurobiology of affiliation

Resilience implicates plasticity

At the outset, resilience involves mechanisms that promote flexible adaptation to changing conditions, resourceful use of contextual provisions in the service of personal growth, and the capacity to persist toward long-term goals tempered by the ability to modify and recalibrate. That is, resilience implies plasticity.

Plasticity relies on neurobiological systems that underpin social fittedness, physical stamina and endurance as they flexibly adapt to diverse conditions[128,129]. Bonding is likely the process exuding the greatest plasticity in mammals. Great neural plasticity has led to the evolution of viviparity (internal gestation) and to physiological reorganization in mother and young that enabled the maturation of the fetus within the maternal body[130]. Immense neural plasticity is also required to make that newborn the most salient object to its mother to the exclusion of all other focus[131].

As noted, the oxytocin system plays a key role in neural plasticity, which is critical to the formation of attachments, and the period after childbirth marks the time of greatest plasticity in the

adult brain[132].

The "plasticity" component of resilience comprises two features: a) resilience is integrative and regulatory; b) resilience is time-based.

Resilience is integrative and regulatory

Regulation promotes flexible integration of system components into a functional whole, shaping self, individuality, agency and well-being through the formation of new, person-specific, dyad-specific and culture-specific configurations. Much developmental research has been directed to the construct of "regulation", with some suggesting that this is the single most important concept in understanding developmental disruptions[133,134].

Across multiple fields, "regulation" adopts a system perspective. It describes how various components of the system dynamically coalesce into a functional whole; how higher and lower elements hierarchically organize over time; and how components from within the system integrate online with those in the

immediate environment[123,135-137]. Conceptual models suggest that regulatory processes mature on top of each other from biological to emotional to attentional to self-regulatory processes[138], and parent-child co-regulation (synchrony) supports maturation of higher-order regulatory skills, such as attention modulation and self-control[139-141].

Resilience is time-based

Resilience is time-bound and process-based, and develops from simple to complex and from biological to mental. The "timeness" component of resilience is critical not only across evolution (phylogenesis) and from infancy to adulthood (ontogenesis), but also at the level of concrete social experiences.

Social moments always unfold in time when two or more participants create a novel "dance" of matched and mismatched moments that coordinate behavior, physiology and mental states. The timeness of these encounters enables the formation of new forms from existing units. Time, therefore, is an indispensable component of resilience (the ability to re-calibrate) and this is captured by "synchrony", a time-based construct.

Resilience is social

Sociality underpins survival and adaptation, and species that can better utilize social mechanisms of coordinated action have a significant survival advantage. This is elegantly described by the entomologist E. Wilson[142] in *The social conquest of earth*, where he argues that humans achieved supremacy among vertebrates and ants among invertebrates, in terms of population size, spread across earth, and durability, due to their eusociality (hyper-sociality), which involves the capacity for collaborated action among group members and social organization across generations.

Primitive mechanisms of synchrony are found in ants, fish and birds, and are underpinned by the coordination of biology and behavior through vasotocin, the parent molecule of the mammalian oxytocin and vasopressin[32,62,143]. Humans' biobehavioral synchrony, therefore, relies on a long history of social mechanisms that promoted resilience via action coordination. Consistent with the behavior-based principle of affiliative neuroscience, these mechanisms were selected with a focus on behavior: social behavior in the group in non-mammalian species and affiliative bonds in mammals. Notably, however, while loneliness is hazardous to the well-being of any living organism[144], the "social" component of resilience is highly variable, and wide variability is observed across the animal kingdom, paralleled by great variability in the density and localization of oxytocin receptors[145,146].

Social monogamy

Social monogamy marks the first extension of the mother-infant bond to other attachments within the family, specifically mating and fathering. Studies on social monogamy utilized several primate species (cotton-top tamarins, marmosets and lamurs)[147], and five rodent species, all originating from a single rodent lineage (prairie voles, mandarin voles, California mice, Campbell's dwarf hamsters, and Mongolian gerbils)[148].

Monogamy provides the basis for fatherhood. Direct paternal care is found mainly in socially monogamous species[149], where fathering occurs in the context of maternal care and parents coordinate their caregiving in relation to each other[150]. Paternal care contributes to confer resilience to mammalian young, increasing offspring survival, litter size, and growth rates[151-156].

While the specific ecological pressures that led to bi-parental caregiving and to humans' cooperative breeding are unknown, paternal caregiving stabilized monogamous mating systems. Once social monogamy has been established in a species, it fosters the emergence of complex social behaviors, that foster resilience[154,157].

Both father care and pair bonds involve the extension of the mother-infant bond, repurposing the same neural networks and molecular processes and providing the first expression of both consistency and diversity in the neurobiology of affiliation. Monogamy also necessitates coordination of the three intra-family attachments (mothering, fathering, and the pair-bond) in the formation of a family unit, and such coordination paved the way for the evolution of the human family and, eventually, of complex socio-cultural organizations, leading to humans' supreme resilience in the animal kingdom.

In humans, involved fatherhood confers substantial resilience. Throughout human history, fathers have been the main source of indirect care, controlling the material resources, physical conditions, and social status with which infants develop[158,159]. Historical accounts point to close associations between paternal provisioning and child mortality in pre-industrial US and Europe[160], and anthropological studies indicate that men with more land or higher social status show greater reproductive success[161,162].

In modern societies, greater father involvement enhances child resilience, in terms of better mental health, higher academic achievement and professional attainment, and better self-regulatory abilities[163,164]. Children of involved fathers are less aggressive and resolve conflicts with more respect and dialogue[165], and epidemiological studies show that fatherless children are more prone to aggression, law-breaking, and conduct problems[166,167].

Complex social organizations

While social monogamy marks the first extension of the mother-infant bond to the family unit, complex and hierarchical social organization was thought to evolve only in hominins and expand in parallel to the increase in brain size[168]. Recent research in Western gorillas discovered hierarchical social modularity, defining not only complex affiliative behavior within extended groups of kin, but also reciprocity and cooperation among non-

kin groups toward goal-directed seasonal coalitions, in ways that mirror the social structure of a small human village[169].

Such behavior-based organizations enable the joint gathering of widely-dispersed foods and protection from predators, enhancing resilience through collaborated actions outside the family. Among primates living in groups, such as chimpanzees, post-conflict reconciliation behaviors were observed, which enable group members to amicably resolve conflict and maintain social ties, and these affiliative post-aggression acts involve increase in urinary oxytocin[170].

A study in marmosets showed that the greater the bonding among an affiliative pair (of same or opposite sex), measured in terms of relationship duration, time spent together, and amount of affiliative behavior, the greater the endocrine synchrony of urinary oxytocin fluctuation[171], pointing to biobehavioral links in non-human primates that preceded humans' biobehavioral synchrony.

Biobehavioral synchrony – a human-specific mechanism

Building on these mechanisms of sociality that sustain stress management, group cohesion, and sensory-motor coordination, biobehavioral synchrony is a human-specific mechanism through which two individuals can mutually impact each other's physiology without physical contact, but via the coordination of facial socio-affective signals, which is not found in non-human primates and rodents[29].

Human synchrony develops throughout life into an increasingly complex human social exchange that involves the co-construction of a joint narrative, the capacity to assume multiple perspectives, and the ability to empathize with others' pain, actions, emotions, and mental states. The development of synchrony begins with the mother's recognition of the infant's biological rhythms *in utero* and culminates in adult-adult relationship of mutual care and intimacy.

Resilience involves meaning

While the first two tenets of resilience build on species-general foundations and add a human dimension, the meaning-making element is exclusively human. For a conceptualization of human resilience, we must integrate the species-general foundations of endurance, diversity, adaptation and stress-management with the human ability to give meaning to hardship, adversity and trauma.

Humans' ability to give meaning to trauma often utilizes collective cultural or religious myths and, at other times, builds on forming personal meaning through actions, typically those that involve the strengthening of affiliative bonds or acts of altruism that extend beyond the individual.

Much research has underscored the role of spirituality in the capacity to bounce back from trouble or in the ability to use trauma for growth[172-174]. Studies have also pointed to the importance of generosity in resilience[175], and to the consoling function of religious affiliations that give collective meanings but also generate community support[176,177]. W. James, in *The will to believe*[178], considered belief as an intentional choice that confers resilience and enables the individual to create a personally-meaningful view of reality that gives significance to trauma and hardship. His famous metaphor of turning discrete experiences into a meaningful whole as resembling "alive electrical wires" that light and shine versus "dead wires" that remain diffuse and unlit, elegantly describes this resilience-promoting function of belief.

Meaning-making introduces a future dimension into the concept of resilience, adding a temporal horizon beyond the "remembered presence"[179] of other primates. This underscores the goal-directed function by which humans create cultural myths that transcend the individual's life and fuel internal reserves of resilience in the face of hardship.

The attribution of meaning that transcends the individual's life is not only a core feature of resilience, but also relies on the two systems of the neurobiology of affiliation. Carter[76] suggested that the oxytocin system provides the neurobiological substrate for spirituality, via its role in sustaining love, caring, empathy, and moral elevation, and, specifically, as the oxytocin system enables mammals to experience "a state of vigilance without fear", that is, to be fully aware of the present moment without vigilance of potential danger. Similarly, the neural structures that cohere into the "affiliative brain" and are formed during early sensitive periods enable humans to extend love to unfamiliar strangers, social groups, and abstract ideas, bestowing generosity beyond the individual's immediate bonds.

However, intense cross-generational cultural myths, meaning systems, and religious beliefs run the risk of overlooking the first tenet of resilience – flexibility – by tightening habits, obligations, and submissive attitudes and increasing surveillance and rigidity. Such close-knit groups often function through tight in-group cohesion, achieved by tightening the neural and behavioral synchrony among in-group members to a hyper-social level in the face of real or perceived danger. For instance, throughout human history, soldiers receive intense training for coordinated action, and this motor synchrony enables the removal of cognitive empathy during battle in order to fight and destroy out-group members. The social component of resilience becomes significantly tighter for the in-group and is abolished for the out-group.

Notably, both oxytocin and neural synchrony participate in such in-group/out-group division, built on ancient mechanisms that immediately distinguish friend from foe to protect loved ones. For instance, we studied the neural response of Israeli and Palestinian youth using magnetoencephalography (MEG) while viewing in-group and out-group protagonists in pain. For the first 500 ms, representing the brain's automatic response to vicarious pain, youth responded to the pain of both in-group and out-group members. However, after this half-second of grace, top-down processes blocked the brain's natural empathic response to the out-group, displaying only response to the pain of in-group[180].

Two processes assisted in shutting down the evolutionary-ancient empathic response to a conspecific in distress: increase in

oxytocin levels and tightening brain-to-brain synchrony among group members. Thus, oxytocin and neural synchrony functioned in the service of a superordinate meaning system not supporting empathy, but out-group derogation.

Studies on the involvement of oxytocin in out-group derogation[181] open the question of how to integrate the role of meaning systems which, on the one hand, can increase resilience by building communities and giving cross-generational meaning to trauma, while, on the other, induce out-group aggression and prejudice. Perhaps one solution should focus on directing constant effort to imbue ancient meaning systems with flexibility and humanity, so that old rituals do not become rigid and extend to all fellow humans.

SYNCHRONY FROM INFANCY TO ADULTHOOD: THE UNFOLDING OF RESILIENCE

Synchrony does not only mature across animal evolution, but also throughout the lives of individuals. Synchrony's main development occurs within the mother-child relationship, the primary mammalian bond, and from there it expands to other social bonds, including fathers, mentors, close friends, and romantic partners, to humankind, and to a sense of synchrony with nature, art, and sacred experiences.

These notions provide biological and scientific evidence to Winnicott's conceptualization in *Playing and Reality*[182] on the mother's non-impinging presence as the basis for symbol formation, play, creativity, and spiritual experiences. Synchrony increases in complexity, diversity of repertoire, symbolic level, and degree of mutuality across childhood and adolescence, tuning the experience-dependent social brain to understanding others' mind, showing empathy to others' distress, and participating in relationships[183]. The rootedness of synchrony in evolutionary-ancient patterns and in the fetus' biological rhythms grounds this experience in the physical and the concrete and enables the entire history of the relationship to resonate within a human moment of meeting.

While philosophical perspectives on "embodiment" suggest that the "self" constructs from micro-identities that unfold during concrete daily experiences, synchrony adds the element that the self assembles from concrete patterns *with a significant human*. Our model details the maturation of this phenomenon across both evolution and human life, and charts its contribution to resilience in the face of condition-specific adversity.

Mother-infant synchrony originates from the mother's recognition of the infant's first biological rhythms *in utero*, such as heart rhythms and sleep-wake cycles, which send signals to the placenta and the maternal brain[184-186]. Following birth, mothers entrain these familiar rhythms into the dyadic exchange.

Studies from the 1970s described how mother-infant face-to-face interactions build on the "burst-pause" pattern of biological periodicities, such as sucking or crying[187,188]. From the entrainment of these biological rhythms, synchrony progresses through distinct stages into an empathic, adult-adult relationship that is dialogical and empathic.

We followed mother-child synchrony from birth up to age 25 and observed how interactions maintained the same non-verbal rhythmic patterns, arousal fluctuations, and positive peaks across a quarter of a century. For instance, some dyads cycle steadily between low and medium arousal, while others engage in quick peaks of positive arousal. Such stability gives order while complex and creative patterns are incorporated into the dialogue and form a familiar and unified event.

Apart from providing the "rhythm of safety", two additional features of synchrony are particularly important in fostering resilience. First, the micro-structure of the synchronous experiences is that of a constant shift between rupture and repair. According to Tronick[189], mothers synchronize with the infant only about 30% of the time; thus, dyads spend more time in mis-coordinated states that are framed by precious moments of synchrony. Psychoanalytic and developmental authors[189,190] emphasize the importance of such match-mismatch cycles for teaching infants how to tolerate moments of non-attunement and how to repair the misunderstanding inherent in human dialogue.

Two types of deviations from the long-mismatch-shorter-match pattern are described. The first, hypersynchrony, is found in anxious mothers and expresses in heightened episodes of matching (above 45% of the time); the second, withdrawal, observed in depressed mothers, involves a near total lack of attunement. Both result in regulatory difficulties in infants[191,192]. Synchrony, therefore, creates a series of micro-events consisting of constant rupture and repair, training infants for social frustrations within a safe context. At around 9 months of age, infants begin to assume responsibility for interactive "repair"[193], which prepares them for the equal relationships with friends and partners.

A second resilience-promoting feature of synchrony is its role as the first context for the development of predictions in the brain. Recent models on "predictive coding"[194,195] view the brain as a computational device whose main role is to increase adaptation by minimizing entropy and augmenting certainty. Neural oscillations play an important role in predictive coding: alpha oscillations participate in building predictions, beta oscillations in assessing the accuracy of these predictions, and gamma oscillations in prediction error, the constant pitting of the brain's predictions with incoming information[196,197]. Synchronous experiences provide a template for polyrhythmic coherence that enables multisensory representation of the body in the world[197] and involves the integration of alpha, beta and gamma rhythms in formation of social predictions during real-life events[112].

Using ecological paradigm and hyperscanning techniques, we found brain-to-brain coupling of gamma rhythms between both mothers and children[118] and romantic partners[198] during moments of behavioral synchrony. Gamma rhythms have been shown in both animal[199,200] and human[201,202] studies to index brain maturity, highlighting the role of synchrony in fine-tuning this maturity. Gamma rhythms and prediction error in viscero-motor cortex and motivation areas amplify feelings but blur the distinction of self and other, due to the agranularity of these re-

gions[203]. Thus, the experience of synchrony can provide a new vantage point on social brain maturation in real-life contexts.

Developmental stages of synchrony

In multiple longitudinal and cross-sectional studies, we detected five distinct stages in the development of synchrony from pregnancy to young adulthood, and showed individual stability among these stages and sensitivity to specific adverse conditions.

Preparation for synchrony relates to the mother's increasing familiarity with the fetus' biological rhythms: the sleep-wake cycle, consolidating at around 31-32 weeks of gestation[204,205], followed by the organization of heart rhythms at around 33 weeks of gestation[206,207]. These cycles coordinate with placenta response[208], and better organization of these biological rhythms predicted greater mother-infant synchrony at 3 months[121].

Neonatal period: maternal postpartum behavior

Immediately after birth and across the first 6 weeks of life, human mothers – like any mammalian mothers – express the species-specific repertoire of maternal behavior, which in humans involve gaze at the infant's face and body, expression of positive affect, "motherese" high-pitched vocalizations, and affectionate touch. However, unlike other mammals, human mothers coordinate their behavior with the neonate's scant moments of alertness. Thus, in health, the human infant experiences at birth a coordination between his/her inner state and the response of the social world.

The expression of maternal postpartum behavior in the neonatal period provides the foundation for the development of symbolic competence in the toddler years[209], and better cognitive development and less externalizing and internalizing symptoms across early childhood[210], and correlates with parental oxytocin[211].

Infancy: affect synchrony

During the third month of life, mothers and infants begin to engage in an interactive "dance", where they coordinate their gaze, affective expressions, co-vocalizations, and touch patterns into a dyad-specific rhythmic dialogue. This non-verbal experience plays a key role in social, emotional, cognitive, and brain development[114]. Mothers and fathers engage in parent-specific forms of synchrony, more rhythmic in mothers and object-focused in fathers[212].

Parent-child affect synchrony is associated with multiple hormones that support bonding, such as oxytocin, vasopressin, beta-endorphin, prolactin, cortisol and salivary alpha amylase, as well as immune biomarkers, including salivary IgA and IL-6[213]. Similarly, it is linked with activation of the affiliative brain in both mothers[214] and fathers[89]. Non-verbal synchrony is also found during triadic mother-father-infant interaction[215], setting the stage for children's social participation in cultural and group activities.

Toddler/preschool: symbolic play sequences and co-construction of imaginary narratives

At the second and third years of life, toddlers begin to engage in symbolic play and start to imbue objects with symbolic meaning and "story-like" symbolic sequences. Children's symbolic complexity is not only predicted by synchrony with mother and father in infancy[216], but the temporal contour of the infant's rhythmic exchange with mother and father predicts the organization of symbolic play sequences – brief, random and numerous with father, and longer, slower-to-build and fewer with mother[126].

During the preschool years, children begin to co-construct a dialogue that contain future and past events, imaginary scenarios, and alternate reality, in which they can immerse themselves. These playful creative abilities draw on the non-verbal synchrony of the first months of life[210] and transform the synchronous dialogue into a social event involving creativity, language and emerging theory-of-mind skills, that express inner reality. Preschoolers' reciprocal interactions with mother and father predict children's theory-of-mind abilities and the development of a moral stance across childhood and adolescence[114].

At this stage, children begin to have "best friends" and enter into social institutions built by the culture. The experience of affect synchrony shapes the child's social competencies with peers in culture-specific ways[217]. Parental oxytocin levels, OXTR genes, and early synchrony predict children's synchrony with their first best friend[72].

Later-childhood/adolescence: empathic dialogue

Beginning at around 9-10 years, and continuing into adolescence, children markedly reduce the amount of "play" interactions with their parents, and the dialogue becomes a verbal one: interactions that require the resolution of conflicts, exchange of information, and, in health, parent-child discussion of experiences, ideas, feelings, opinions, and plans for the future.

The synchronous dialogue at this stage incorporates the child's emerging capacity for behavioral, emotional and cognitive empathy; the ability to plan ahead, elaborate, cooperate, and show motivation; and the capacity to see the other person's point of view. Such social abilities, particularly at this stage when the attachment focus shifts from parents to friends, are crucial for children's well-being, and are associated with resilience in the face of adversity and with maturation of the social brain[113,218-220].

Adulthood: mutuality, intimacy and perspective-taking

When the mother-child bond was "good enough" and synchrony progressed along developmental lines, creating space for

both resonance and reparation, mother and young adult are able to face each other as two adults who still maintain their roles, but are able to incorporate them into a dialogue that respect their maturity yet reverberates their entire relationship. It rests on the early familiar rhythms and echoes all developmental stages, but it is a dialogue that is mutual and respectful, intimate and autonomous, familiar and secure, and still differs from a couple.

Such dependable synchrony enables individuals to enter with trust and mutuality other relationships and build the bridge to the next generation, that can transcend the parent's life through the adult child's ability to evoke the dyadic experiences with the parent in his/her own brain in the parent's absence.

Overall, synchrony, which gradually enriches the infant's social repertoire with the maturation of more complex mental abilities, enables variability within order, diversity within familiarity, and creativity within stability. Synchrony bears on the "stuff" of life, where the biological integrates with the social to give meaning, form bonds, and withstand hardship.

THE MAKING OF THE RESILIENT CHILD: THREE LONGITUDINAL HIGH-RISK COHORTS

Our model suggests that biological and social provisions embedded in the mother-infant bond provide the foundation for life-long resilience. For many children across the globe, however, these provisions are compromised. To make progress in understanding resilience, we must tease apart one adverse condition from the next, examine the specific provisions impaired by each, and test how these omissions affect outcome.

We have suggested that human studies must begin at birth or as close to it as possible, employ longitudinal designs, and examine the "missing component" in the maternal provisions on the basis of specific research programs in animal models, that manipulate these provisions and test their sequalae on offspring brain and behavior[30].

There are three main sources of disruptions to maternal-infant bonding, stemming from mother, child and context, each affecting millions of children worldwide.

Maternal postpartum depression impacts 15-18% of parturient mothers in industrial societies, and up to 30% in the developing world[221]. We have suggested that Meaney's work[222] on the long-term effects of low maternal licking-and-grooming on the brain oxytocin and stress response in rat pups may provide insights into the long-term consequences of maternal depression.

Premature birth occurs in 10.5% of live birth in industrial societies[223], and its well-known negative impact relates, in part, to maternal separation following incubation, and its effects on environment-dependent life-sustaining systems, resonating Hofer's "maternal proximity" model[27].

Early life stress bears long-term negative consequences on development. One in five children worldwide are growing up in the context of chaos, immigration, food or shelter insecurity, tribal or ethnic war, poverty, and violence. The animal model that may parallel these disruptions is the "varying foraging de-

mands"[224,225], in which bonnet macaque mothers are exposed to episodes of available food versus unavailable and difficult to find food, alternating unpredictably between times when mother is available and periods of minimal caregiving. Such conditions were found to carry the worst effect on offspring – in terms of brain growth, stress response, and behavior – compared to the high or low conditions, suggesting that the inconsistency embedded in early life stress is the most detrimental to children's resilience.

To understand resilience from a developmental neuroscience perspective, we followed three cohorts of mothers and infants from birth (or infancy) up to adolescence/young adulthood, focusing on how the components of the neurobiology of affiliation differentiated children on a risk versus resilient trajectory. Each cohort tapped one of the aforementioned disruptions to maternal-infant bonding, and hypotheses were based on the parallel animal models.

The *postpartum depression* cohort utilized a community birth-cohort to tease out mothers who were chronically depressed across the child's first years. The *war-exposed* cohort involved mothers and children living in a zone of continuous war-related trauma, and the *premature cohort* included low-birthweight but neurologically intact premature infants, half of whom received maternal-infant skin-to-skin contact ("kangaroo care") in the neonatal period. Repeated assessments of synchrony, regulatory skills, oxytocin, stress hormones, and psychopathology were conducted across childhood, and at the final time-point we imaged the social brain.

Maternal postpartum depression

Our birth cohort included only physically healthy, cohabitating mothers who were above 21 years and above poverty line, to tease apart the effects of depression *per se* from frequently co-occurring conditions (single parenthood, teenage mothers, poverty). Women were assessed for depression repeatedly across the first year, and again at 6 and 10 years. We formed two cohorts: children growing up in the context of chronic maternal depression from birth to 6 years, and healthy controls.

Maternal depression increases psychopathology

Exposure to early and chronic maternal depression markedly increased child propensity for psychopathology, even when families were at low risk. At six years, 60% of children to mothers who were diagnosed with major depression at both 9 months and 6 years, and reported being generally depressed throughout the child's early years, received a full-blown Axis I psychiatric diagnosis (compared with 15% of controls), with the most prevalent disorders being anxiety and conduct disorders[226]. At 10 years and pre-adolescence, more than 50% of these children still received a psychiatric diagnosis, even when mothers remitted, highlighting the long-term effect of early exposure. Higher externalizing and internalizing symptoms were also reported in children of de-

pressed mothers[227].

Synchrony fosters resilience

Depressed mothers failed to provide the age-appropriate co-regulatory caregiving required to support development. At 9 months, micro-analysis of non-verbal behavior indicated that depressed mothers showed minimal social gaze, positive affect, and affectionate touch, and engaged in minimal synchrony with their infant[191]. As synchrony extended over time, depressed mothers were unable to develop more mature forms of reciprocal dialogue.

Synchrony was individually stable from birth to adolescence, and the lower synchrony in children of depressed mothers predicted increased psychopathology and greater social withdrawal. At 6 years, children of depressed mothers showed little behavioral empathy[228]. At 10 years, they showed lower executive functions and reduced emotion understanding. These aberrant socio-emotional outcomes were predicted by the lower synchrony.

At the same time, synchrony functioned as a resilience component. Among children of depressed mothers who still received more synchrony (either from their fathers, due to greater functionality of the oxytocin system, or because of the child's inborn sociability), it served as a protective factor.

Children's ability to function more adequately in the social world, form friendships, and engage in peer activity, all triggered by synchrony, markedly reduced the effects of early maternal depression on the propensity for mental disorders, executive abilities, and emotion knowledge. This effect was particularly salient in late childhood, a period when peer relationships begin to assume a greater impact on children's lives, lending support to our argument that resilience components function differently at various stages and that development should become a focus in the conceptualization and research of resilience.

Altered stress response is mediated by mothers' negative parenting

Effects of maternal depression on children's stress response were complex, depending on developmental stage, type of measurement, and resilience indicators. At 9 months, infants of depressed mothers showed greater cortisol reactivity to a social stressor and diminished recovery[229]. At 6 years, maternal depression impacted cortisol variability, but this was found only among children who received tense, critical and negative parenting[228]. These findings highlight the importance of the plasticity/flexibility component of resilience for stress reactivity. At 10 years, only children of depressed mothers who received more negative parenting exhibited higher cortisol, and such over-activation of the hypothalamic-pituitary-adrenal (HPA) axis mediated the effects of depression on psychopathology[221].

We also measured salivary IgA, a biomarker of the immune system, and found higher levels in children of depressed mothers in late childhood, indicating greater stress, but this was found only among children receiving minimal synchrony, attesting to the resilience role of synchrony on the stress and immune systems.

Fathers enhance resilience

In the context of the minimal synchrony provided by the depressed mother, a synchronous father-child relationship served an important resilience function. When fathers showed sensitive and reciprocal parenting, the propensity for psychopathology among children of depressed mothers markedly decreased[230]. It appears that one mechanism by which sensitive fathering promotes resilience is by altering the family atmosphere, making family interactions more cohesive, harmonious and involved even when mothers are depressed[231]. These findings echo the "social monogamy" mechanism described above, and suggest that opening the maternal-infant bond to other affiliative bonds within the family confers resilience.

In another study, we followed parents and their first-born child in the Israeli and Palestinian societies from infancy to preschool. We found that maternal depression carried a less toxic effect on child psychopathology and symbolic competencies in the Palestinian society, and this was related to the extended-family living arrangements in this culture, which enabled children ample opportunities for synchronous interactions with other adults of kin relationship[232].

Oxytocin promotes resilience

At both 6 and 10 years, depressed mothers and their children had lower oxytocin production, as measured in both saliva[226] and urine[233]. Both mothers and children had greater prevalence of the GG genotype on the OXTR gene (rs2254298), associated with greater vulnerability for mental disorders[234]. When mothers had the A allele on the OXTR gene, the child's propensity to receive an Axis I diagnosis at 6 years was reduced by half[226]. At 10 years, when children's salivary oxytocin was high, this attenuated the effects of maternal depression on child externalizing and internalizing symptoms[227].

Adolescents' affiliative brain

In early adolescence, we measured children's neural empathic response to others' pain and the brain basis of attachment using MEG. Among children of depressed mothers, we found disruptions to the neural empathic response in the superior temporal sulcus, a hub of the social brain, which showed diminished alpha activation and quicker abortion of neural response at around 900-1100 ms post-stimulus. Such aborted response was predicted by the augmented intrusive and negative parenting and diminished synchrony that these adolescents experienced in infancy, highlighting the detrimental effects of the depressed

mother's style on brain development over time[219].

To assess the brain basis of attachment, we employed the typical paradigm of exposing children to videos of their own interaction with their mother at an earlier stage as compared to unfamiliar interaction. The typical neural activation to attachment cues involved a multi-rhythmic response of alpha, beta and gamma, including alpha suppression in posterior region, and beta and gamma activations in a large right cluster including the superior temporal sulcus, fusiform gyrus, and insula. However, children of depressed mothers, but *only* those who developed an affective disorder themselves, showed an aberrant response involving both reduced response to social cues and attenuation of the differentiation between attachment and non-attachment stimuli. These disruptions were predicted by the lower functionality of the oxytocin system and the reduced mother-child synchrony across childhood.

While these findings specify the risk for later attachments in children of depressed mothers, they also show that some children growing up in the context of chronic maternal depression are more resilient, and that components of the neurobiology of affiliation are markers of resilience.

Early life stress and trauma

Our early life stress and trauma cohort included children and their mothers living in a zone of continuous war who were exposed to repeated and unpredictable missile and rocket attacks for nearly 20 years. We assessed children in infancy, middle childhood (5-7 years) and late childhood (10 years), and imaged the social brain in early adolescence.

Comorbid mental disorders following chronic early trauma

Children growing in such a traumatic and chaotic environment exhibited a 3 to 4-fold increase in the prevalence of Axis I mental disorders and a marked increase in internalizing and externalizing symptoms. In comparison with the depressed mothers cohort, a special feature of this cohort was that two thirds of the diagnosed children showed more than one diagnosis, with some presenting three or even four mental disorders, suggesting that trauma expresses in multiple dysfunctions across the entire psychopathological spectrum[235].

Assessing the trajectories of risk and resilience across the first decade of life in trauma-exposed children, we found that children who never exhibited mental disorders or remitted after early psychopathology had mothers who were less symptomatic, experienced more synchrony, and showed greater social competence at late childhood (10 years)[236].

Oxytocin buffers stress

In this cohort, oxytocin functionality was associated with resilience in the face of trauma. Greater functionality in the oxytocin

receptor gene in child, mother and father differentiated children who developed chronic post-traumatic stress disorder (PTSD) from those who remitted by middle childhood[235].

At 10 years, unlike the children of depressed mothers, we found no group differences in children's oxytocin levels, indicating that not all children growing up within a war zone show fundamental disruptions to the biological basis of affiliation, and that some mothers are able, by recruiting significant effort, to buffer the hazardous effects of war on their child. Oxytocin levels in war-exposed mothers, however, were lower, attesting to the immense burden of raising a child in the context of unpredictability and trauma, and such burden was found across multiple maternal hormonal and neural systems.

Endocrine synchrony was found between mother and child. When maternal oxytocin was low and synchronous parenting reduced, children exhibited significantly more symptoms. But this was not the case when mothers maintained high oxytocin levels and exhibited sensitive, non-intrusive parenting[120].

The stress response

We measured mothers' and children's chronic and phasic cortisol in early childhood, late childhood, and early adolescence, by assessing both hair and salivary levels of the hormone. In early childhood, cortisol and salivary alpha amylase, a marker of the sympathetic arm of the stress response, differentiated exposed children with and without PTSD. The exposed no-PTSD children had significantly higher levels, while the PTSD children had low and flat levels[236]. These findings suggest that, in the context of chronic trauma and during early childhood, greater activation of the HPA axis marks resilience, not risk.

At 10 years, again, both chronic and phasic markers of the HPA axis were elevated only in war-exposed children who developed psychopathology, and those were children of mothers with higher HPA axis activation and lower synchrony[73]. We suggest that "mothers stand between war and the child" and that, when mothers are able to contain their own stress and protect the child from the external trauma, they are capable to buffer the child's stress response.

In early adolescence, however, exposed children as a group, as well as their mothers, showed higher and less variable cortisol levels, suggesting that chronic exposure to unpredictable stress marks a risk factor in itself, regardless of the relationship. Possibly, such vulnerability is expressed during key developmental periods, such as the transition to adolescence[237]. Immune biomarkers were higher in war-exposed mothers and children, highlighting the great wear-and-tear on the immune system in the context of chronic adversity and supporting models on allostatic load and the stress response[238].

Children's and mothers' brain

In this cohort, unlike the other two, we imaged both mother's and child's brain in identical paradigms, in an attempt to assess

how chronic stress impacts neural systems in both sides of the caregiving dyad. Across paradigms, we found that alterations in brain functioning were predicted by the history of the relationship, differentiating children on risk or resilience trajectories for maturation of the social brain.

We assessed connectivity and power of the default mode network (DMN), the neural system that sustains the sense of self, switch of internal and external attention, and autobiographical memory[239-241]. In both mothers and children, disruptions were found to DMN connectivity, not power, highlighting again the role of the plasticity component in resilience and the reduced ability of the discrete structures to cohere into a unified system that provides a foundation for the sense of self.

Disruptions to maternal DMN were found in alpha rhythms, the main rhythm of the awake mature brain, whereas disruptions to children's DMN occurred in the theta band, a biomarker of the developing brain[242]. Children with PTSD showed the greatest disruption to theta connectivity. Disruption in theta connectivity patterns were predicted by maternal intrusive, anxiety-provoking parenting across childhood and by higher cortisol production in later childhood, underscoring the long-term effects of unpredictable rearing combined with uncontained parenting on the core system sustaining neural functions[243].

We found no group differences between exposed and non-exposed children in the neural empathic response to others' distress. This response involved alpha activation in a large cluster including the supplementary motor area, part of the embodied-simulation network, and the middle cingulate cortex, a node of the DMN. Synchrony, which was diminished in the war-exposed cohort, mediated the effects of early trauma on the neural empathic response, and children receiving more synchrony across childhood showed greater activation to others' distress[244]. Mothers' neural empathic response similarly showed disruptions, but those were specific to the adult brain[245].

Prematurity

Our "kangaroo care" project is the only existing study testing the effects of maternal separation and structured contact on the maturation of life-sustaining functions over time in human infants. Mothers of low-birthweight premature infants (<1,750 g) were randomized to the experimental intervention (skin-to-skin contact for at least one hour per day for at least 14 consecutive days during the incubation period) or to standard incubation care.

Dyads were followed seven times across the first decade (before the intervention, at discharge, at 3, 6, 12 and 24 months corrected age, and at 5 and 10 years). In young adulthood (18-20 years), we home-visited young adults and observed their relationship with their mothers, assessed hormonal indices and executive functions, and within the next month imaged the social brain using functional magnetic resonance imaging.

We found that provision of maternal bodily contact impacted the same systems in humans as it did in young mammals. Kangaroo care improved autonomic functioning and organized the

sleep-wake cycle, and improved newborn orientation and information processing. At the same time, it improved mothering and the provision of maternal behavior in the neonatal period[246].

Consistent with our model of the staged development of regulatory functions[138], these improvements in physiological regulation and mothering enhanced resilience and dynamically impacted development. Neonates showed better arousal modulation in the processing of highly-aroused stimuli at 3 months, better exploratory behavior at 6 months, and better abilities for self-control at 1 and 2 years. Mental, but not motor, abilities were improved in the experimental group at 6, 12 and 24 months[247,248]. At the same time, mother-infant synchrony improved, and mothers also expressed more breast milk, triggering an oxytocin response[249]. Following kangaroo contact, synchrony was greater at any observation across the first years, and the higher social reciprocity linked with better cognitive and regulatory abilities[210].

At 10 years, we found that the improved regulatory capacities of the kangaroo care subjects persisted. We found higher respiratory sinus arrhythmia and better responsivity of this arrhythmia to emotional stress, indicating more adaptive functioning of the autonomic nervous system. Sleep was measured by actigraphy worn across five consecutive nights, and children who received kangaroo care as neonates showed better sleep organization and shorter wake bouts. Furthermore, the kangaroo children's HPA axis response to social stressor exhibited diminished cortisol stress response and quicker recovery[250]. As to cognitive abilities, by 5 years there were no longer differences in general IQ, but kangaroo care subjects had improved executive abilities, working memory, and cognitive flexibility at 5 and 10 years.

Overall, our findings underscore the systems impacted by the resilience components embedded in the maternal body and well-adapted caregiving, as those related to the management of stress, flexible response to environmental conditions, modulation of arousal and attention, and the capacity to engage in reciprocal dialogue.

In young adulthood, we imaged the brain's empathic response to others' emotions in the kangaroo care group and the controls, assessing how the brain sustains "empathic accuracy", an important determinant of the empathic response[251,252], and differentiates response to others' distress, sadness and joy. Using complex analysis, we detected three structures that showed highly dissimilar activations across emotions: the amygdala, anterior insula, and temporal pole. Synchrony measured across development, from infancy to young adulthood, mediated the links between group membership and social brain's flexible empathic response to others' emotions. Thus, the kangaroo care increased synchrony provided a pathway by which early attachment experiences shaped the flexible neural response to others' affective states.

CONCLUSIONS

Resilience is a core construct in clinical theory and research that is yet to receive a comprehensive, biobehavioral conceptualization. Two main lacunas in current models on resilience in-

volve the exclusive focus on the neurobiology of fear and the lack of empirical attention to development. Moreover, most models define resilience on the negation (i.e., absence of symptoms following trauma) rather than addressing what resilience *is*.

We argue that the initial condition of mammals should be taken into consideration in understanding resilience. Mammalian young are born with two important constrains: their brain is immature at birth, and young maintain close proximity to a nursing mother. As such, all systems that support resilience, stress management, adaptation and endurance mature in mammals in relation to the provisions afforded by mother's body and caregiving behavior.

We propose a model of resilience based on the neurobiology of affiliation, the emerging scientific field that describes the neural, endocrine, genetic and molecular processes which underpin our capacity to bond, love, care, empathize and belong to social groups.

Our model highlights three core components of the neurobiology of affiliation that sustain resilience. These include the oxytocin system, the affiliative brain, and biobehavioral synchrony.

The oxytocin system is implicated in plasticity at the cellular, molecular and network assembly levels, wires the brain toward attachments, underpins the mammalian capacity to manage hardships through relationships, and plays a role in the immune system.

The affiliative brain evolved in humans from the rodent maternal brain, expanded to include higher-order structures that enable empathy, simulation and mentalization, and extended to support all other affiliative bonds, including romantic attachment, close friendship and mentorship. It is marked by great plasticity, cross-generationally transmits to infant during early sensitive periods, and shapes socio-emotional competencies.

Biobehavioral synchrony involves the coordination of biological and behavioral processes during social interaction, and it is the mechanism by which the maternal mature brain externally regulates the infant's immature brain and tunes it to social life. Humans' biobehavioral synchrony draws on mechanisms by which coordinated social behavior fosters diversity and adaptation across animal evolution, and develops within the mother-infant bond on the basis of the fetus' biological rhythms *in utero*, upon which the mother builds a social non-verbal "dance" during the first months of life. This synchronous exchange expands across development into a dialogue of mutuality, intimacy, and acknowledgement of multiple perspectives, and transfers from the mother-child relationship to other human affiliation and encounters throughout life, charting a key trajectory in the development of resilience.

Our model proposes three tenets that address what resilience *is*. These include plasticity, sociality and meaning. While the first two are animal-general, the latter is human-specific. All three tenets are supported by oxytocin, the affiliative brain, and biobehavioral synchrony, due to their involvement in neural and behavioral plasticity, their role in attachment and sociality, and their support of the capacity to attribute meaning to trauma through cultural and spiritual systems and affiliative acts that transcend the individual.

This model is supported by evidence from three longitudinal cohorts, each followed from birth/infancy up to adolescence/young adulthood. Each cohort addressed one type of disruption to maternal-infant bonding, originating in mother, child or context (maternal depression, premature birth, and chronic exposure to war-related trauma), which bears long-term impact on the child's brain, behavior and well-being. In each cohort, hypotheses were built on a specific research program in animal models that describes the "missing component" in each condition (liking-and-grooming, variable foraging demands, and maternal proximity). We repeatedly measured psychopathology, parenting, synchrony, oxytocin and stress hormones, cognition and regulatory functions, particularly looking for factors that separate children on risk versus resilient trajectories. In adolescence/young adulthood, we imaged the social brain.

Disruptions to development emerged across conditions; yet, outcomes were condition-specific and mainly expressed in interaction effects, with some children showing significant resilience. Components of the neurobiology of affiliation – synchrony and oxytocin – functioned as resilience factors across development in condition-specific ways. Endocrine synchrony (the hormonal concordance between mother and child oxytocin and stress hormones) functioned to increase risk or resilience, attesting to the mother's continuous biological external-regulatory impact on risk and resilient trajectories. In late childhood, children's social competencies, buttressed by synchrony, functioned as important resilience markers. Regulatory functions matured on top of one another, and greater regulation improved later functioning, particularly alterations during early sensitive periods, as, for instance, resulted from mother-infant skin-to-skin contact to premature infants.

In imaging the social brain, we found alterations pending on risk and resilience status. While children reared by chronically depressed mothers aborted the neural empathic response, not all children growing in traumatic contexts showed disruptions; *only* those who received minimal synchrony. The brain basis of attachment was disrupted in children of depressed mothers, but *only* among those who developed affective disorder. Similarly, when assessing the brain basis of empathic accuracy, premature infants who received synchrony showed an adequate social neural response.

In sum, drawing on 20th century philosophical and neuroscientific models that formulated a concrete, behavior-based approach to cognition and action and blurred the distinction of brain and mind, our model aims to direct attention to systems that sustain our capacity to form affiliative bonds, enter into social groups, and use relationships to manage stress, as core features of the human capacity to withstand, even thrive, in the face of trauma.

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