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A narrative on the neurobiological roots of attachment-system functioning

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Attachment theory is one of the most comprehensive frameworks in social and developmental psychology. It describes how selective, enduring emotional bonds between infants and their caregivers are formed and maintained throughout life. These attachment bonds exhibit distinct characteristics that are intimately tied to fundamental aspects of mammalian life, including pregnancy, birth, lactation, and infant brain development. However, there is a lack of a cohesive biological narrative that explains the psychological forces shaping attachment behavior and the emergence and consolidation of attachment patterns at a neurobiological level. Here, we propose a theoretical narrative focusing on organized attachment patterns that systematically link the two primary purposes of the attachment behavioral system: the provision of tangible protection or support and the corresponding subjective feeling of safety or security. We aim for this detailed delineation of neurobiological circuits to foster more comprehensive and interdisciplinary future research.

Main

Attachment relationships represent the essence of mammalian existence across a vast array of species[1,2] (e.g., rodents, primates, ungulates, and humans), where they serve as a fundamental survival mechanism[3]. Accordingly, attachment relationship development and maintenance is intimately tied to all fundamental aspects of mammalian life, including pregnancy, birth, lactation, and their associated neurobiology[4]. Because attachment bonds are of critical importance for mammalian survival, they have been the focus of extensive human and nonhuman animal research for almost a century[5,6]. These combined research efforts have culminated in describing functional neuro-anatomical models of human attachment[7,8], associated learning theories[9,10], and the subcortical neural circuits and involved neurotransmitter systems in animals[11]. However, research is lacking a comprehensive narrative about the biological processes that can account for the psychological forces that shape attachment behavior and the consolidation and maintenance of attachment patterns. Therefore, understanding attachment relationships, whether human or across the diverse spectrum of mammalian life, demands a theory that recognizes the complex interplay between multiple biological and epigenetic processes and the nurturing environment.

Young mammals face two primary challenges in their early life: a brain that is not fully developed at birth and the imperative of maintaining closeness to their nursing mothers[12]. Consequently, the mother's body and her behaviors play a critical role in structuring the juvenile brain, guiding it towards social interactions through the intimate bond formed with her[13]. This bond also provides the context for developing neural networks supporting mammalian social behavior through caregiving[13,14]. For the small percentage (3-5%) of mammalian species exhibiting cooperative parental care, father involvement and paternal parenting behaviors also contribute to infant brain development[15].

Attachment bonds exhibit several distinct characteristics[1], the first being an infant's marked preference for specific individuals, their 'attachment figures'. The critical importance of these selective and irreplaceable bonds is revealed through the child's sustained efforts to stay near these figures, especially during times of distress and need[16]. Another critical aspect of attachment bonds is the infant's response to temporary separations and subsequent reunions with attachment figures, which both shed light on the quality of attachment relationships. Optimal attachment is usually associated with adaptive behaviors (e.g., crying) during separation and a joyous reunion[5,12,17]. Conversely, pronounced separation anxiety and distress or indifference upon reunion may point to potential attachment difficulties[18]. Finally, the degree to which infants use their attachment figures as a 'secure base' for exploration further indicates attachment quality. This is because infants can only confidently venture out from their caregivers to explore the world if they know and feel that their caregivers are available and responsive whenever needed[5].

Research has shown that in response to distinct infant-caregiver interaction patterns in times of need, infants develop different personality-like dispositions known as attachment patterns. These patterns are either characterized as organized (i.e., secure, insecure-avoidant, and

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insecure-anxious) or disorganized[3,5,19–21]. In humans[22], infants who establish a secure attachment relationship with their attachment figures generally show distress when separated from them. They seek comfort from their caregivers to cope with distress and utilize them as a stable base to explore their surroundings. Conversely, insecure-avoidant infants are often absorbed in exploring their surroundings and rarely seek physical comfort, sometimes even actively avoiding it (i.e., attachment system deactivation[5]). Insecure-anxious infants frequently become upset even when their attachment figures are present, and they typically cannot be appeased after separation, displaying either passivity or anger (i.e., attachment system hyperactivation[5]). Thus, insecure-anxious infants are less likely to venture and explore their surroundings, even when their attachment figures are present. Lastly, disorganized attachment characterizes infants with mixed, bewildered, or cautious behaviors toward their attachment figures, particularly in highly stressful situations often experienced as part of early adversity[23,24]. Attachment patterns remain relatively constant from infancy through adolescence[25,26] and even into late adulthood[27,28], according to studies conducted over periods as long as 59 years. Although the psychological processes relating to developing and maintaining attachment behaviors and interindividual patterns are well-studied[5,17], the exact neurobiological processes sustaining them are yet to be elucidated.

A major driving force of attachment pattern establishment and maintenance appears to be social allostasis-driven learning necessary for the dynamic adjustment of our physiological balance in an ever-changing environment. Social allostasis operates through external co-regulation of an individual's internal states by significant others, often their caregivers and attachment figures[29–31]. To date, research has suggested many neurobiological players in attachment, social learning, and social allostasis, the main ones being the endocrine hormones oxytocin[14,32] and arginine vasopressin[14,33,34], reward system neuromodulators by dopamine[14,35] and endogenous opioids[36], the monoamine neurotransmitter serotonin[37], stress hormones – particularly those of the Hypothalamic-Pituitary-Adrenal (HPA) axis[38] and the sympathetic nervous system[39] –, and neurotrophins such as Brain-Derived Neurotrophic Factor (BDNF)[40]. Here, we present a narrative that aims to comprehensively reconcile the action of these neurobiological players and link them to potential epigenetic mechanisms that may, in concert, contribute to attachment pattern formation and maintenance.

The Main Themes and Sequelae of Attachment Behavior

Bowlby[12,18,41], the founder of attachment theory, proposed that the mammalian attachment behavioral system most likely developed because it increased the chances of survival and eventual procreation for members of a species who are born with a lack of sufficient abilities for self-defense, movement, and nourishment (also see[3,21]). The system aims to provide tangible protection or support and the corresponding subjective feeling of safety or security ("felt security"[42]). This two-fold aim becomes prominent when an individual encounters real or symbolic stressors and perceives that their attachment figures are not adequately present, caring, or responsive[12]. In such scenarios, the behavioral attachment system is triggered, and the person is compelled to restore real or symbolic closeness to external or internalized attachment figures until a sense of security is regained. Under standard conditions, behavioral attachment system activation is thus demonstrated in seeking closeness to attachment figures.

As a complete sequence, attachment behavior begins with the sensory perception of a threat (e.g., a natural sign of danger[12]), which triggers proximity-seeking behavior to attachment figures, followed by a reunion that helps to remove the threat, alleviates distress and fosters felt security[7]. Following the acquisition of felt security, the behavioral attachment system is deactivated, and the person can return to their daily activities. Below, we theorized about the cascading sequence of neurobiological processes that could characterize the above-explained attachment behaviors, integrating knowledge from animal models and studies in humans. This sequence is portrayed in Fig. 1.

Attachment behavior initiation. Attachment behavior initiation begins with the sensory perception of a threat, its integration, and evaluation, as well as downstream signaling to and recruitment of output structures, mounting an appropriate physiological and behavioral response[3,21,43–48]. Extensive research in humans and animals—independent of any direct attachment theory considerations—delineates the underlying neural pathways and the involved neurotransmitter systems in detail[49]. Our perception of a real threat begins with sensory input converted into chemical-electrical signals and sent to the thalamus[50,51], which acts as a neuronal relay station. The thalamus subsequently forwards these signals through two primary routes: a "high road," where sensory information is processed in detail by the sensory cortices [the primary visual, auditory, somatosensory, and gustatory cortices, which respectively receive sensory information from the lateral geniculate nucleus (LGN), medial geniculate nucleus (MGN), ventral posterolateral nucleus (VPL) and ventral posteromedial nucleus (VPM)][52–54], and a "low, quick and dirty road", a more direct route to the amygdala via the thalamo-amygdala pathway, which allows a quick initial threat response[54]. The amygdala subsequently acts as a saliency detector[55,56] transferring the incoming sensory information directly or via the basal/lateral nucleus (BLA) to the central nucleus (CeA). From the central nucleus, neural projections to the hypothalamus and periaqueductal gray (PAG) mediate the behavioral and physiological threat response. The latter involves rapid sympathetic nervous system activation related to a "fight-or-flight" response via the locus coeruleus (LC) that produces and releases noradrenaline. Research in rhesus monkeys[57] has revealed that the locus coeruleus shows a bimodal activation pattern. Its first peak of activity is in response to threat cues, approximately 100 ms before any action is taken. The second peak begins at the initiation of the reaction to the threat. The initial locus coeruleus activation in response to threat cues thus likely facilitates the mobilization of sensory and attentional resources, while the subsequent activation supplies the necessary energy for the early stages of movement[57]. Accordingly, noradrenaline would provide the energy to appraise a threatening situation and sustain a "fight-or-flight" response.

Besides the initiation of a "fight-or-flight" response originating in the central nucleus and (in part) mediated by the locus coeruleus, neurons in the basal/lateral nucleus release glutamate (an excitatory neurotransmitter) to the ventral tegmental area (VTA) – a midbrain structure critical for a range of reward and motivation processes—stimulating dopamine release[58,59]. Furthermore, there are glutamatergic axonal pathways from the basal/lateral nucleus to various parts of the striatum, including the nucleus accumbens (NAc) as well as the globus pallidus within the basal ganglia[60], which further connect to the subthalamic nucleus and pedunculopontine nucleus via inhibitory the Gamma-Aminobutyric Acid-ergic, (GABAergic) axonal pathways[61] and to the substantia nigra pars compacta (SNc) to cause dopamine release[62]. Research in rhesus monkeys[57] has shown that dopamine release within the substantia nigra pars compacta is associated with both the decision and motivation to act and initiate movement.

Crucially, acquiring the energy, the decision, and the motivation for movement is sufficient for a general "fight-or-flight" response independent of attachment behavior but not for proximity-seeking towards attachment figures as an integral part of attachment behavior. Evidence shows that proximity-seeking could be seen as an extension of "fight-or-flight" behavior that is not only aimed at distancing oneself from a present threat but also at directing oneself toward a "safe haven" in the form of an attachment figure[18,48,63–65]. Bowlby[18] already stated that "the behavior that reduces the distance from persons or objects that are treated as though they provided protection is nothing other than attachment behavior. Viewed in this perspective, therefore, though not in others, attachment behavior appears as one component among the heterogeneous forms of behavior commonly grouped together as fear behavior" (pp. 89-90). After studying numerous incidents of natural and man-made emergency situations, Mawson[63–65] also observed that when attachment figures are absent, and the perceived danger is mild, a low-intensity "flight-and-affiliation" response is triggered, leading to an orderly evacuation away from the threat and toward familiar

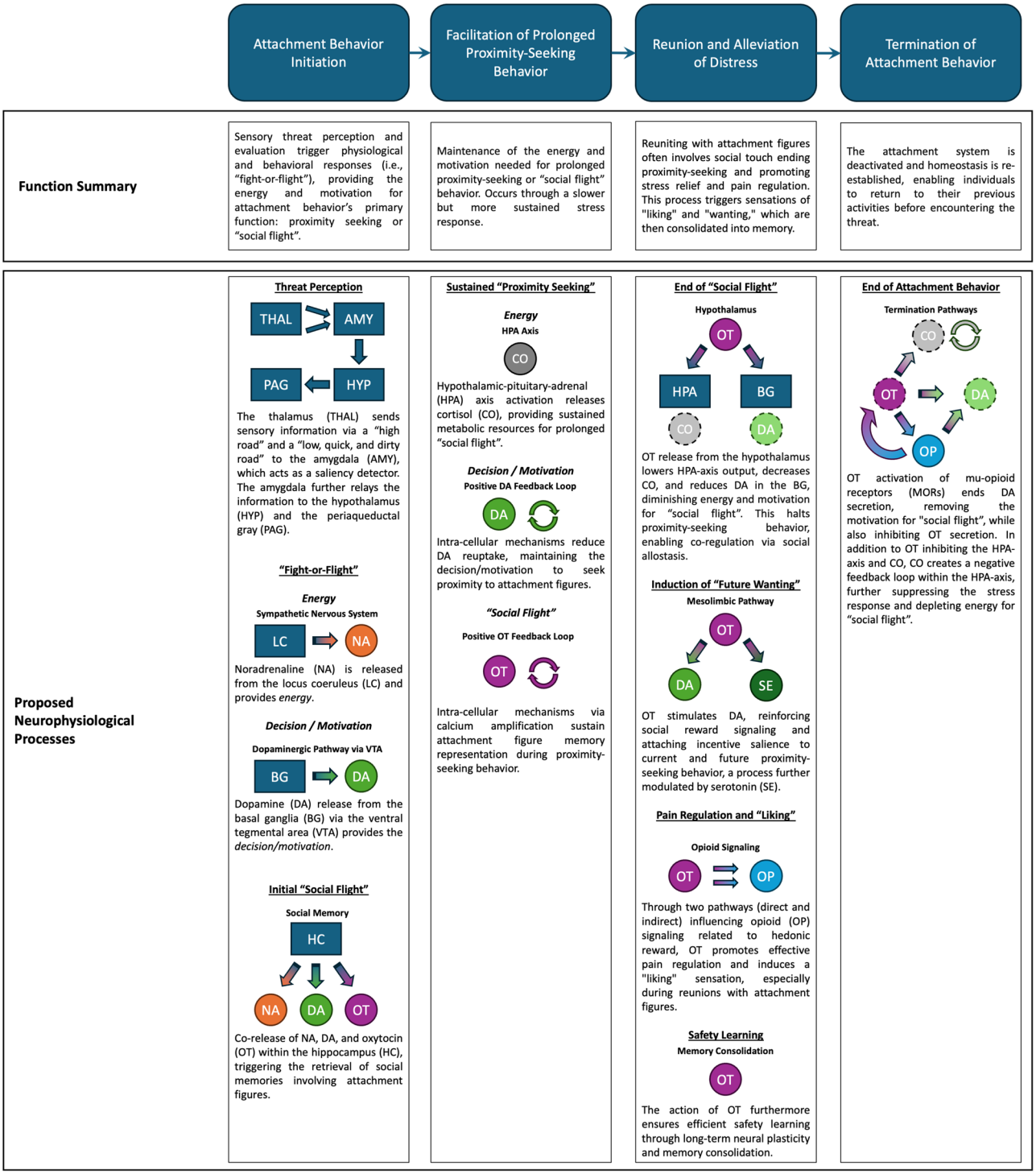

Fig. 1 | The proposed cascading sequence of neurobiological events in attachment behavior. THAL Thalamus, AMY Amygdala, PAG Periaqueductal gray, HYP Hypothalamus, LC ocus Coeruleus, NA Noradrenaline, BG Basal Ganglia, DA Dopamine, HC Hippocampus, OT Oxytocin, CO Cortisol, HAP Hypothalamic-Pituitary-Adrenal axis, SE Serotonin, OP Opioids.

surroundings and people (also see the extensive review on social attachment during crises[66] and studies on social defense theory[3,21,44–47]). Thus, this behavior could be named "social flight"[30], which is also in accordance with the "tend-and-befriend" hypothesis[67].

A potential neurobiological mechanism for such "social flight" behavior may be associated with the co-release of dopamine and noradrenaline from the locus coeruleus into the hippocampus, which was found to be critical for episodic memory[68–70], and the release of dopamine from the ventral tegmental area, which influences memories of rewarding, highly positively valenced events[71]. Noradrenaline release plays a key role in enhancing memory consolidation and retrieval for emotionally arousing events and stimuli[72], whereas dopamine release relates to the selectivity of these stimuli[72] and the formation of positive, rewarding experiences[71]. Attachment figures are individuals of whom we hold an extensive number of episodic memories, which began in high-arousal (i.e., negative and threatening) situations and ended as positive, rewarding, and soothing

co-regulation experiences (see below). Thus, the co-release of dopamine and noradrenaline might trigger the retrieval of social memories specifically involving our attachment figures. In addition, oxytocin, a peptide hormone and neurotransmitter, was found to be an important mediator of social memory in rodents, such that oxytocin release is enhanced during retrieval of social memory[73], which also facilitates memory processes associated with social recognition[74]. Altogether, these processes could retrieve our attachment figures' identity from memory, directing the "social flight" response specifically towards them. Here, we must stress that direct empirical evidence for this mechanism is still lacking, and further research is needed to validate these ideas.

More generally speaking, and in accordance with a learning theory of attachment[9,10], the association between safety and proximity to attachment figures is likely to follow classical and operant conditioning principles as part of an overall safety conditioning process. Thereby, an individual not only has the energy, the decision, and the motivation for movement, but has been conditioned to seek proximity to specific attachment figures, which means that directional attachment behavior can start to unfold.

Facilitation of prolonged proximity-seeking behavior. Noradrenaline secretion from the locus coeruleus as part of the sympathetic nervous system initiates a rapid "fight-or-flight" response that constitutes a quick yet short-lived physiological activation[75]. To maintain the energy needed for prolonged proximity-seeking behavior, a slower but more sustained stress reaction is manifested via the Hypothalamic-Pituitary-Adrenal (HPA) axis, resulting in the synthesis of glucocorticoids, predominantly cortisol. Following its production, often around fifteen to twenty minutes after the initial stressor, cortisol, a steroid hormone, is released into the bloodstream. The influence of cortisol on the body is multifaceted, encompassing an enhancement in glucose availability for energy and suppression of the immune response to prevent overreaction, among other functions[76]. Thus, we propose that the energy needed for prolonged "social flight" behavior can be sustained through Hypothalamic-Pituitary-Adrenal axis involvement. Studies in humans have shown that attachment behavior is linked to cortisol, not only in situations that provoke an attachment threat, such as a conflict discussion within a close relationship, but also more generally in terms of daily cortisol patterns and associations with depression[77].

Aside from the energy needed to sustain prolonged proximity-seeking behaviors, the target of the behavior—i.e., the mental image of attachment figures—needs to be sustained in memory, as does the motivation to reach attachment figures. Research has noted that oxytocin, essential for social recognition memory[74], and dopamine, which governs the motivation for movement[57], have positive feedback loops[78,79] critical for pro-social and approach behaviors towards rewards such as food or protective figures.

Oxytocin binding to the oxytocin receptor activates the inositol trisphosphate (IP3) pathway, producing inositol trisphosphate, which yields calcium release from the endoplasmic reticulum via inositol trisphosphate receptors[80]. The localized calcium increase activates ryanodine receptors (RyRs) on the endoplasmic reticulum, causing further calcium release through a calcium-induced release mechanism[79]. This cascade further amplifies the initial calcium signal[79]. The amplified calcium rise, in turn, stimulates additional oxytocin release from the soma and dendrites of oxytocin neurons, which can then bind back to its receptors on oxytocin neurons, restarting the positive feedback cycle of inositol trisphosphate production, calcium release via inositol trisphosphate and ryanodine receptors, and more oxytocin secretion[79]. This ryanodine-receptors-mediated calcium amplification is critical for generating the pulsatile bursting pattern of oxytocin release, important for maintaining various social behaviors such as lactation[79], and potentially also the sustained attachment figure memory representation during proximity-seeking behavior. Research in animals has shown that the latter process is especially pronounced in regions such as the supramammillary nuclei (SuM) of the hypothalamus[74], the anterior dentate gyrus (aDG), the anterior CA2/CA3 regions of the hippocampus[81], and the lateral septum[82].

Dopamine's positive feedback loop begins through the activation of protein kinase A (PKA) by dopamine D1-like receptor (D1 and D5) signaling[83]. Activated protein kinase A then phosphorylates and inhibits the dopamine transporter (DAT), reducing dopamine reuptake[84]. This results in higher extracellular dopamine levels, which can further activate D1-like receptors and protein kinase A[83]. The consequence is a positive feedback loop where dopamine release leads to activation of protein kinase A, inhibiting dopamine transporter to amplify dopamine signaling, which can trigger more dopamine release. Such a dopamine-driven positive feedback loop amplifies dopamine signaling, which is important for reinforcing reward learning and motivating approach behaviors toward rewards. This process could maintain the motivation to seek proximity to attachment figures, which will subside only after a reward is gained during the reunion phase with these attachment figures (see below).

Reunion and alleviation of distress. The next stage of attachment behavior is the individual's reunion with their attachment figures – i.e., proximity is achieved, often manifesting as a cradle or hug. It is well established that intimate skin-to-skin contact initiates a cascade of sensory responses starting at the skin surface[85]. Sensory information is subsequently relayed to the brain through specialized pathways like the dorsal column-medial-lemniscal pathway and the spinothalamic tract[86], which terminate in the somatosensory and insular cortices[87]. From there, neuronal and neurohormonal signals are transmitted to the hypothalamus, stimulating specific neurosecretory cells in its paraventricular and supraoptic nuclei[88]. These cells produce the hormone oxytocin and transport it along their axons to the posterior pituitary gland, where it is released into the bloodstream. Furthermore, the oxytocin-releasing neurons, especially parvocellular, also project to many other parts of the brain[89]. Oxytocin subsequently takes a leading role in stress alleviation by acting allostatically to promote stability through changing environments[90]. Oxytocin reduces Hypothalamic-Pituitary-Adrenal stress axis reactivity[91], mainly via the GABA signaling pathway, particularly by potentiating $GABA_A$ receptors[92]. As a result, corticotropin-releasing hormone (CRH) secretion will subside, followed by a decrease in the adrenocorticotropic hormone (ACTH) and cortisol[91]. Oxytocin also affects dopamine activity in a region-specific manner[93,94] by potentiating $GABA_A$ receptors on dopamine neurons in the substantia nigra pars compacta, whereby dopamine activity within the substantia nigra pars compacta is reduced by an average of 70%[94], which in turn yields a decrease in locomotion and the motivation to move. We suggest that such decreased locomotion and the motivation to move will ultimately bring proximity-seeking behavior to a halt, thereby allowing for co-regulation through social allostasis as one of the primary outcomes of attachment behavior to unfold[5].

Oxytocin furthermore increases dopaminergic activity in the ventral tegmental area by binding to Gαq-coupled receptors, which stimulates the phospholipase C pathway to enhance dopamine neuronal firing within the mesolimbic pathway involving the nucleus accumbens (NAc) and the mesocortical pathway leading to the prefrontal cortex (PFC) including the ventromedial PFC (vmPFC)[93,94]. Dopaminergic signaling enhances the salience of associated behaviors and induces a future "wanting" of these behaviors[95,96]. The consolidation of social reward signaling furthermore requires a third-order modulation[89] such that oxytocin promotes serotonin secretion, which activates serotonin 1B-receptors that are needed to facilitate long-term synaptic modulations (often long-term depression)[97]. In doing so, the mesocortical pathway facilitates adaptive behaviors and responses that aim to enhance the chances for survival under threat[98]. We propose that mesolimbic signaling may be associated with attaching an incentive salience to proximity-seeking behavior and, thereby, to attachment figures. This view aligns with the perspective that humans instinctively strive for closeness and support from others, which enhances their survival chances[12]. As shown previously in humans, ventromedial prefrontal cortex activation within such a context could signify a social safety cue[99], fostering the motivation to reconnect with one's attachment figures in the future[100,101].

Moreover, research in animals revealed a unique subpopulation of parvocellular oxytocin neurons in the paraventricular nucleus of the hypothalamus that project to magnocellular oxytocin neurons in the supraoptic nucleus (SN) and the deep layers of the spinal cord via neurons positive for neurokinin-1 and oxytocin receptors, known as wide dynamic range neurons[102]. This neuronal pathway plays a critical role in pain management, as it can inhibit spinal pain processing in two distinct ways, each with its own timeline[102]. Specifically, the transmission of pain signals from Aδ- and C-type primary afferent neurons to wide dynamic range neurons is efficiently suppressed by oxytocin projections to the deep layers of the spinal cord (the "fast route") and by oxytocin released into the bloodstream from magnocellular oxytocin neurons (the "slow route")[102]. We propose that through these direct and indirect pathways, oxytocin enables efficient pain regulation following a reunion with attachment figures. Indeed, there is ample evidence from human studies that being physically (i.e., through handholding) connected to attachment figures reduces both subjective (i.e., ratings of pain) and objective (i.e., brain activity) measures of threat and pain processing[103–105].

Oxytocin neurons from the hypothalamus also project to the nucleus accumbens, affecting opioid signaling in association with hedonic reward[95,96] and a "liking" sensation. In a rat model, it was shown that activation of the oxytocin receptor (OXTR) led to increased preproenkephalin gene expression, the precursor of enkephalin, an endogenous ligand for the mu-opioid receptor (MOR; associated with euphoria and analgesia)[106]. A different study observed that an oxytocin infusion into the nucleus accumbens (NAc) of female prairie voles resulted in enhanced preproenkephalin gene expression (with no discernible impact on preprodynorphin expression), which serves as a precursor for dynorphin, the ligand for the kappa-opioid receptor (KOR; associated with dysphoria and negative mood states)[107]. Likewise, mu-opioid receptor messenger RNA increase in the nucleus accumbens in prairie voles was observed during bond formation, a period characterized by heightened oxytocin release in the nucleus accumbens[108]. Because this indirect process takes a few minutes to manifest, the associated hedonic effect would only arise after the oxytocin-related stress and pain reductions, secession of movement, and increased "wanting" sensation. We thus propose that positive emotions and a "liking" sensation associated with attachment behavior, particularly the reunion with attachment figures, are tightly linked with the neurobiological association between oxytocin and endogenous opioids. Our considerations are based on earlier conjectures as part of the Brain Opioid Theory of Social Attachment (BOTSA[36]), providing significant evidence for the role of the endorphin system in mammalian bonding and attachment behaviors, particularly under distress.

Finally, oxytocin allows for long-term neural plasticity and memory consolidation by acting on the CA1 and CA2 subregions of the hippocampus via first-, second-, and third-order modulations (the latter involving serotonin)[89]. Animal research showed that oxytocin can lower the threshold for triggering depolarizing neuronal inputs and thereby initiate a long-term potentiation (LTP) process in specific brain regions such as the hippocampal CA2 and the olfactory bulb[89]. Furthermore, when CA2 neurons in the hippocampus are activated through oxytocin signaling and fire in bursts, this enhances CA1 pyramidal neuron activity, enabling plasticity in the CA1 region[89]. These rapid and enduring alterations to synaptic communication play a crucial role in consolidating changes in neural responses. Specifically, long-term synaptic plasticity enhances and stabilizes neural representations of essential sensory stimuli related to social interactions. As a result, responses to incoming social signals are identified and recognized more readily by oxytocin modulation, which acts as a social salience signal amplifying neural responses[89]. These responses are then consolidated via long-term plasticity mechanisms, ensuring that regions like the auditory and visual cortex remain responsive to relevant stimuli potentially for the individual's lifetime[89]. We suggest that such memory consolidation processes via the action of oxytocin ensure efficient safety learning, as already explained above in association with the learning theory of attachment[9].

In sum, we propose that following an individual's reunion with their attachment figures and modulated via the secretion of oxytocin, individuals may experience a reduction in distress and pain, a decrease in the motivation to move away from attachment figures, an increase in the "wanting" and "liking" of attachment figures, and the consolidation of these experiences in memory. These effects furthermore ensure the inclination to use proximity-seeking behavior in response to future threats.

Termination of attachment behavior. Additional processes are expected to complete the attachment behavioral cycle by deactivating the attachment system, enabling the individual to return to the activities they were engaged in before encountering a threat. Animal research has shown that activation of the mu-opioid receptors by oxytocin and the resulting positive hedonic effects facilitate the termination of dopamine secretion, returning it to pre-stress levels. Specifically, mu-opioid receptor's endogenous ligand, enkephalin, is expressed in D2-like neurons[109–111] – i.e., neurons harboring the D2-like dopamine receptors (D2, D3, and D4 receptors) – that have an inhibitory effect by diminishing the cyclic adenosine monophosphate (cAMP) messenger. In addition, animal and human studies showed that mu-opioid receptors inhibit oxytocin secretion[112–114]. Apart from the inhibitory effect of oxytocin on the Hypothalamic-Pituitary-Adrenal stress axis, it is also well established that cortisol promotes negative feedback by decreasing corticotropin-releasing hormone and adrenocorticotropic hormone secretion via the activation of glucocorticoid receptors (GRs)[115] in the hypothalamus. Notably, this negative feedback loop also depends on the prevalence of mineralocorticoid receptors as the latter dampens glucocorticoid receptors' sensitivity via regulation of FK506 binding protein 5 (FKBP5)[115]. As a whole, the above processes promote the re-establishment of homeostasis and thereby abolish the stress response initially triggered by a threat. We assume that similar processes mediated via oxytocin, mu-opioid receptors, dopamine, and cortisol eventually yield a deactivation of the attachment system.

Development of attachment patterns

Research in humans indicates that individual differences in attachment patterns (secure, insecure-avoidant, insecure-anxious, and disorganized) are consolidated in response to repeated and consistent interactions with attachment figures[9] – support and warmth for security, emotional and spatial distancing for avoidance, uncertainty of care for anxiety, and abuse and neglect in combination with other environmental factors for disorganization[5,17,23,24].

Studies across species conducted in the recent decade[40,116–128] suggest that the source of human attachment pattern consolidation may be the epigenetic code – a layer perceived as the dynamic interface between genes and the environment[129] – that directs changes from the cellular level to the psychological level. Epigenetics is the study of partly heritable molecular alterations in Deoxyribonucleic Acid (DNA) and histone proteins that can modify gene expression without changes in the underlying DNA sequence. DNA methylation is one of the most studied epigenetic processes, especially in cross-species attachment research, in which a methyl group attaches to a cytosine nucleotide next to guanine in the DNA at a so-called CpG (cytosine-phosphate-guanine) site[130]. Its function may be compared to that of a dimmer switch: the greater the methylation density on a specific DNA site within a particular cell type or tissue, the greater the repression of the regulatory construct of a related gene[131,132]. DNA methylation is thought to be influenced by prenatal[133] and postnatal life events[134] and genetic background[135,136], and its state is reversible[137]. Therefore, we predict that the manifestation of human attachment patterns would be directed by epigenetic changes in specific hubs discussed in the current narrative related to attachment behavior.

Animal studies reliably show that variations in maternal care, such as high versus low licking/grooming behavior in rats, can lead to differences in DNA methylation and gene expression in the offspring's brain, particularly in genes related to stress response and behavior. For example, the pioneering

research by Meaney and Szyf revealed that offspring of rat mothers exhibiting high levels of licking/grooming and arched-back nursing had reduced DNA methylation and increased expression of the glucocorticoid receptor gene in the hippocampus, leading to diminished stress responses and less fearful behavior[138]. Cross-fostering experiments further revealed that these epigenetic changes and associated stress responses were dictated by the rearing mother's behavior rather than genetics. Moreover, treatment with DNA methylation-removing agents in adulthood could potentially reverse the effects of low maternal care[137]. Extending their findings to humans, the authors discovered increased DNA methylation and reduced expression of the glucocorticoid receptor gene in the hippocampus of suicide victims with a history of childhood abuse or neglect, alongside genome-wide higher DNA methylation levels and reduced expression of protein synthesis-related genes[139]. A recent systematic review of research on the link between attachment and epigenetics in humans corroborates these initial findings[140]. It indicates that 6 out of 11 documented studies report an association between the quality of maternal caregiving and DNA methylation variations in infants and children, particularly in genes involved in socio-emotional development, and that maternal caregiving behavior can partially buffer the effects of early adversity on DNA methylation. Notably, another meta-analysis of epigenome-wide studies across the lifespan in humans found no significant associations between DNA methylation at birth (cord blood) and later childhood cognitive skills[141]. However, the authors suggest that methylation patterns may arise from gene-environment interactions later in life, which is the theoretical process suggested in attachment research.

Studies directly examining the epigenetic makeup of human attachment patterns are scarce, although the limited available findings refer to a few main players in this theoretical narrative[116,117]. Regarding the stress response, the Nuclear Receptor Subfamily 3, Group C, Member 1 (NR3C1) gene, which codes for the glucocorticoid receptor, has been a focal point of research[120,121]. Studies, such as those by Bosmans and colleagues, have shown that increased methylation of the glucocorticoid receptor gene, particularly in the context of low maternal support and high chronic stress, predicts higher levels of anxious attachment in children[121]. Prenatal exposure to maternal depression has also been linked to increased glucocorticoid receptor gene methylation in newborns, correlating with altered stress responses[142]. Furthermore, FK506 Binding Protein 5 methylation was found to affect the relationship between FK506 Binding Protein 5 genotype and anxious (resistant) attachment, associated with infants' cortisol reactivity in[122].

A second line of studies focused on oxytocin. For instance, Thaler and colleagues[143] found higher oxytocin receptor (OXTR) methylation in women with anorexia nervosa linked to insecure attachment and social avoidance, while Haas and colleagues[124] demonstrated that oxytocin (OXT) hypermethylation was associated with higher anxious attachment scores and impaired emotional recognition. Ein-Dor and colleagues[120] noted that higher oxytocin receptor promoter methylation was specifically linked to attachment avoidance. Additionally, studies like those by Fujisawa and colleagues[144] and Robakis and colleagues[118] connected increased oxytocin receptor methylation to early maltreatment and postpartum depression, respectively, highlighting its role as a potential biological correlate for social and emotional behaviors influenced by early adverse experiences. To date, no studies directly associate methylation in the dopamine and opioid system with human attachment patterns. We believe, however, that studies on the epigenetic makeup of human attachment behavior and patterns consolidation hold promise in revealing the biological depths of attachment. Longitudinal research endeavors on this topic are underway, such as "Project Alpha" (pre-registered at https://osf.io/kcns7/).

Concluding remarks

Attachment behavior and the consolidation of attachment patterns encapsulate complex, multifaceted processes that span the spectrum of animal and human experience. In the present manuscript, we aim to share a comprehensive theoretical framework that integrates the myriad of elements identified across various research domains into a cohesive narrative. This approach aims to deepen our insight into how attachment bonds are formed and maintained among humans and animals and highlight the significant role of epigenetic processes in influencing a wide array of life domains, from threat responses and romantic relationships to psychopathology. Nonetheless, it is essential to acknowledge that, despite its comprehensive scope, any theoretical argument represents a simplification of the many processes occurring across our 37 trillion cells. It nonetheless underscores the complexity of animal and human development and the ongoing challenge of capturing the full spectrum of attachment-related phenomena. Through its ambitious synthesis, we hope that the current work sets the stage for future explorations that promise to unravel further the mysteries of human attachment behavior and development, underscoring the profound impact of these processes on our lives.

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Competing interests

The authors declare no competing interests.

Additional information

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