Appendices

THE PHYSIOLOGY OF BONDING

A CLOSER LOOK

The author's perspective

As mentioned in Chapter 2, humans can form very diverse and very complex bonds. In other words, the quantity and quality of co-regulation can vary substantially. The mechanisms through which these co-regulative processes are established are potentially even more complex. Many articles and reviews have been written about psychological, physiological or environmental factors influencing co-regulation. Most of those reviews focus on one or two factors: on one or two key instruments of an orchestra if you will. However, if, hypothetically, we would be able to describe all the instruments of the orchestra and the way they are related, new (design) opportunities for (technological) interventions to enhance bonding might be discovered. Regarding the consequences of suboptimal bonding, interventions enhancing bonding seem very important to society. Throughout my project, I have therefore attempted to analyze the physiology of bonding as thoroughly as possible and to capture that analysis in an image

In this appendix, I present both the analysis of the concept of bonding as well as the image reflecting that analysis. The aim of the latter is to visualize the physiology of bonding in a simplified but plausible overarching framework, in the form of a regulation scheme meant to function as a brainstorm tool, which can save designers, engineers and researchers time when thinking about interventions to enhance bonding.

As described in the thesis, bonding is defined as an organism's capacity to (co-) regulate not only his own internal environment, but also the internal environment of other organisms. Regulation is "the act of balancing the energy budget of the body in action", in order to survive. In other words, to maintain homeostasis. Co-regulation therefore is assisting another organism in maintaining homeostasis. Furthermore, mechanisms for maintaining homeostasis, i.e. for balancing the internal environment have been built in during evolution. Even a single-celled organism is equipped with several mechanisms to optimally adapt to the composition or physical state of the media in which the cell lives [1]. Moreover, even for a single-celled organism the most efficient, or in other words the optimal way to adapt to the environment is by working together. Therefore, evolution built in (and probably keeps building in) a mechanism for "working together": a mechanism for co-regulation, or bonding [2,3]. Before zooming in on this mechanism, closely related words or concepts need to be defined first.

A bond, *attachment, relationship, affiliation, love, emotions, sociality, interaction, social behavior* and *cognitive behavior* are all examples of words related to the word bonding. I consider an attachment (as defined by Bowlby [45]) and a relationship the result of a specific type of bonding or co-regulation. An a*ffiliation,* or even more intuitive, the word *love* refers to a very special bond. Relationships, attachments and love experienced throughout life influence the process of bonding, thereby creating a feedback loop.

Emotions, which I will come to later, are very important for the process of bonding and they are therefore building blocks of sociality. *Sociality* is the degree to which individuals of certain species tend to associate in social groups and form cooperative societies, the degree to which a specie is evolutionarily designed to form bonds [6]. As was described in the thesis, and as will be described later in this appendix, this bond formation is achieved through *interaction*, for instance *social behaviors*.

Interaction is when two organisms have an effect on each other (co-regulation). Even the slightest effect is an interaction; even the slightest interaction has an effect. When this interaction takes place in the form of (voluntary) behaviors, these behaviors are called *social behaviors.* However, not all behaviors

are social behaviors. For example, talking to someone is both cognitive and social behavior. Social behavior is always an expression of bonding. *Cognitive behavior* on the other hand does not necessarily have to be an expression of bonding. Sitting at home, calculating how much money you have earned for example is neither social behavior, nor does it include bonding, since it does not include co-regulation. It does however involve self-regulation.

These concepts will play a role in the second part of this chapter, but first I will describe how researchers came to define bonding as co-regulation.

Lorenz's work

Professor Lorenz in particular shifted the field of ethology from generally studying behavior to the biological study of behavior; looking at behavior through the eyes of biologists [7]. Lorenz studied the attachment behavior of young ducks and geese. He discovered that newborn chicks, ducks or geese would typically learn to follow and thereby bond to the first moving object they had encountered, even when that object was a human. The capacity to bond was thus present immediately after birth in these animals. For behavior to be present immediately after birth, brain circuitry needs to already be in place [8]. Around the same time, clinicians were making observations of the negative effects on personality development due to maternal deprivation or inadequate maternal care during the early years of life [9]. Informed by Lorenz's work and led by clinical observations, Bowlby and his colleague Ainsworth formed the "attachment theory".

Bowlby's work

"Attachment behavior is any form of behavior that results in a person attaining or maintaining proximity to some other clearly identified individual who is conceived as better able to cope with the world". These behaviors increase due to distress and decrease when distress lessens because care is being given [9]. Bowlby et al. state that there is a genetically programmed repertoire of such behaviors, which explains the behaviors of the poultry present immediately after birth as observed by Lorenz [10]. Moreover, as stated in Chapter 2, children can be categorized by the way they are attached, as judged by their behaviors. They can be securely or insecurely attached. Insecure attachment can be further divided into several categories [11]. For these categories and a more elaborate explanation of the attachment theory, we refer to Bowlby, Ainsworth, Bretherton, Homes and Waters [5,12,13]. According to psychoanalysts such as Bowlby, the child's first relations are the foundation for their future personality and for these relationships there is a critical age-window [4]. They opposed the, at the time widely believed reason for a child to attach to his mother to be "because she feeds him or her". They reasoned this could not be true, as many young animals are not even dependent of their mother for food, they can find food for themselves. Instead, they concluded that attachment is driven by the need to be protected, to have a sense of safety [5,12,13]. Strong support for this soon came from Harlow's work.

Harlow's work

Starting his research on neonatal and infant macaque monkeys, Harlow also seemed to question food as the primary reason to attach to a caregiver. One of his arguments was that human affection does not extinguish when the infant is no longer food dependent of the mother. Human affection usually lasts a lifetime. He found out that monkeys that were separated from their mothers 6 to 12 hours after birth started showing strong attachment to cloth pads that were used to cover the floors of their cages. Removing the cloths led to angry and violent behavior. Human infants can display similar contact-need to pillows, blankets, music, and teddy bears when separated from their mothers. This finding led to a study design using two surrogate mothers: one made from soft fabric, with maximal comforting capacity, the other made from wire-mesh. The mothers differed only in the contact comfort they were able to supply, not in temperature or food provision. It turned out that infant monkeys preferred the soft fabric mother, even when a bottle of milk was attached to the wire-meshed mother and not to the

soft mother [14]. Together, Harlow and Bowlby drew attention to the role of bonding for the well-being of the young [15]. What are the mechanisms responsible for this mother-infant bonding?

Hofer's work

Research by Hofer et al. demonstrated elements of the physiological mechanism regulating bonding. Experimentally controlled maternal separation revealed the existence of a deeper layer of physiological processes beneath the attachment behavior of infants and the care-giving behavior of mothers. Hofer demonstrated that a mother is instrumented with a set of "hidden regulators" such as her touch, odor and warmth. Each of those maternal physical properties regulates a specific physiological system in the rat pup [16]. For instance, separating mother and infant, but providing warmth, maintained the pup's level of general activity, but had no effect on other systems; the cardiac rate continued to fall [17,18]. On the other hand, during maternal separation, heart rate was regulated by the provision of milk to neural receptors in the lining of the pup's stomach [19]. The pups in their turn demonstrated care-eliciting behavior, or infant cues such as separation cries, or ultrasonic vocalizations (USV), directing the mother with her "hidden regulators" toward the pups when they needed assistance for their regulation [16]. In other words, a set of species-specific caregiving and care-eliciting behaviors were described, which was elaborated on by Fleming et al. and Trevarthen et al.

Fleming and Trevarthen's work

Fleming et al. observed that mothers of a variety of species (e.g. rat, sheep, voles) acted differently with their second infant than with their first [20,21]. They hypothesized a neurohormonal cause and therefore studied hormonal changes at the time of parturition. They demonstrated that activation of maternal responsiveness was indeed accompanied by changes in parturition hormones (particularly estrogen, oxytocin and prolactin) in the investigated mammalian species [22]. It took time to adapt to these hormonal changes after the first labor, but during the second pregnancy, adaptation had already taken place, which could explain the difference in behavior toward a second infant. Another, more important difference was the fact that mothers acted differently toward their own infant as opposed to other infants. This superior maternal responsiveness appeared to be caused by cues from the infants (such as pup specific odor, tactile characteristics and cries) causing neurohormonal alterations in the mother leading to recognition of, and enhanced bonding to (i.e. better co-regulation of) the mother's own infant. By building in such a signaling system (through cues) and the capacity to (unconsciously) imprint the cues of specific organisms (e.g. one's own mother or infant) [3,8], a bond can be established between organisms. Trevarthen placed this process in an evolutionary 'survival of the fittest' perspective. He stated that: "Social animals sense one another's internal states through external changes in the appearance of the body and from the quality or expression of movements made to regulate vital activities" [1]. This enables maximally efficient use of energy and optimal functioning within the ever changing environment [10,22]. As such, both Fleming and Trevarthen contributed to defining bonding as an evolutionarily developed, cue-based process of co-regulation. Meaney et al. subscribed the evolutionary perspective by addressing the neurohormonal consequences of suboptimal co-regulation.

Meaney's work

The experiments in the laboratory of Meaney et al. were set up somewhat similar to Harlow's experiments: exposing a group of animal subjects (mainly rats) to better or more caregiving and comparing them to a group with less caregiving or no caregiving. In these studies, care was (mostly) defined as the licking and grooming (LG) behavior of parental rats. For more detailed facts about the methodologies and findings of these studies I refer to both Chapter 7, as well as Liu, Francis, Caldji and Anisman amongst others [23–27]. In summary, differences in early life LG-experiences significantly alter the hypothalamic-pituitary-adrenal-axis (HPA-axis), otherwise known as the stress-axis [28,29]. In addition, differences in patterns of parental care alter the oxytocinergic system and other hormonal systems [30]. Such patterns of care giving, specifically the synchrony of caregiving, is investigated by Feldman et al.

Feldman's work

Synchrony is a temporal relationship between events, occurring all around the world: ant colonies carrying twigs together, bees collecting honey, and birds flying in a flock [31]. Chemical messengers that cause synchrony and reciprocity have been identified [32,33]. "A bee queen feeds her first young larvae not because of a 'maternal-care instinct', but because of larval secretions which effectively attract her to the larvae and which she licks up readily" [32].

These examples of synchrony and reciprocity were the basis of the research by Feldman et al, reporting that physiological factors showing both synchrony and reciprocity can also be found in humans:

- Eye contact is mostly based on mutual, synchronous gazing
- Menstrual periods tend to synchronize in female sharing households
- When a child drinks from the mother's breast, the uncomfortable pressure in the breast drops
- Warm, tactile stimulation is given back and forth
- Motherly sensory gratification insures maternal orientation toward the infant, etcetera.

Over the past years Feldman et al. performed studies demonstrating that such biosocial facilitation, defined as mutual biological and (microsocial) behavioral influences (cues, such as cries and temperature) that synchronize to a certain degree, significantly strengthens the formation of affiliative bonds. Regarding the serious consequences of suboptimal bonding described in part one of this thesis it seems valuable to add synchronization to the concept of bonding as a sort of "super feature".

In her articles, Feldman cites studies noting synchrony in human behavioral interactions such as gaze, vocalizations and body movements [34–36]. Yet, as Feldman herself states, "research on parent-infant synchrony in humans left many questions untouched and did not follow the rigorous empirical methods used with other mammals. No information was available on the development of synchrony from prenatal life to the end of the first year, a period parallel to the gestation-to-weaning period of other mammals" [37]. Feldman et al. tried to fill this gap, and here I will provide a summary of their discoveries [31,37–39]:

- Co-occurrences in behavior (coordination) are already observed during the first hours after birth, suggesting that humans are biologically prepared to engage in coordinated interaction
- In fact, synchronizing of biological rhythms already starts during pregnancy
- The brains of infants and parents are sensitized to mutual influences
- During postpartum playful episodes heart rhythm-synchrony has been observed
- Typical chains of behaviors coalesce into repetitive 'configurations'
- A momentary lack of coordination is normally followed by interactive repair the next second
- A patterned relationship develops, in which there is familiarity with the partner's rhythms
- Several biological rhythms such as the sleep-wake cycle and heart rhythm are responsible for social rhythmicity and synchronization in families

As previously stated, the sensitivity and reliability in other words, the quality of the co-regulation process reflects the strength of bonding between organisms [40]. Obviously, synchrony is a facilitator for sensitivity; therefore, the term 'super feature' seems justified. The amount (or quantity) of co-regulation is not a measurement for the strength of bonding; different stages in life require different amounts of co-regulation. From the moment of conception, co-regulation refers to the mastery of tasks accomplished in concert with the mother's body when the child is in the womb. Postpartum these tasks include everything from maintaining a normal body temperature to orchestrating physiology and behavior to the day-night rhythm of human existence, to learning to soothe and settle once basic needs are met. Later, it means developing the capacity to manage powerful emotions constructively and keep one's attention focused [41,42]. Throughout all these phases, the capacity for self-regulation grows and

therefore the dependency of co-regulation reduces. The content of the co-regulative processes thus change throughout life, but humans are social beings until the end and therefore not the quantity but the quality of co-regulation remains equally important from birth until death.
So, to summarize:

- Bonding is innate; it starts from the moment of conception (e.g. Lorenz).
- Bonding is not food-driven; it is an overall protection mechanism for the survival of species (e.g. Bowlby, Harlow).
- Bonding is an evolutionarily built-in, cue-based process of co-regulation (e.g. Hofer, Fleming, and Trevarthen).
- The way bonding increases chances of survival is by optimizing the adaptation of the internal environment to the external environment, suboptimal bonding leads to suboptimal adaptation (e.g. Meaney).
- Synchrony is a "super feature" optimizing co-regulation from conception until death (e.g. Feldman).

As stated in Chapter 2, this theory on bonding implies that the foundation of the underlying physiological mechanisms for all types of bonding – parental, pair, and filial – is the same [15], as they serve a common and crucial evolutionary purpose; "the maintenance and perpetuation of the species". It does not imply that there are no differences in the functioning of the bonding-mechanism, or in the content of the co-regulative processes as I formulated it above, but due to the shared purpose the efficiency of evolution will have caused much overlap [43]. In my view, the mechanism of bonding can be seen as a huge stage on which an orchestra is playing Mozart. In the beginning, the violins and a cello are playing, sometime later, all instruments are playing, but at the end, there is a piano-only part even though it is still the same song. In the next part, I describe the biological factors involved in the bonding mechanism as instruments of the bonding orchestra.

THE INSTRUMENTS OF THE BONDING ORCHESTRA

Senses

The regulation of all bodily processes is driven by sensorial information; the sleep-wake cycle, blood pressure, gene transcription, memory formation, cuddling, eating, conversing and so on [44]. The information can be external or internal, either way; some sort of sensorial signal is needed to initiate homeostatic processes. The brain can be seen as the command center for handling sensorial information and weighing that information [45].

The brain: higher brain functions

The brain processes sensorial information and then consciously or unconsciously responds to that information, with an instant or long-term reaction or a plan. The brain also takes care of that plan's execution through actors (such as the autonomic nervous system (ANS), hormones and muscles). At the same time, the reaction or plan is evaluated and possibly adjusted. The human brain with its cortex, in contrast to any other species' brain, contains many higher cognitive functions, enabling social reasoning, decision making in moral dilemmas, and a "theory of mind" [46].

For instance, mirror neurons facilitate social learning during synchronized interaction [47]. Mirror neurons are present in the parietal lobe and orbitofrontal cortex. These neurons (unconsciously) fire when an individual performs a motor act, but also when that individual observes another individual performing a similar motor act [48]. The hippocampal regions can subsequently memorize the motor act. These regions are the main storage areas for all formed memories. Memories are very useful for bonding, i.e. for parenting [23].

Memories, but also other higher cognitive functions enable the cortex to deal with societal challenges in increasingly complex ways [49]. "From the briefest glance to a nuance in someone's tone of voice, once primitive systems are aroused, higher brain functions are also energized to evaluate" [2]. Panksepp adds that higher brain functions allow self-discipline and emotion regulation. For instance, language contributes greatly to the regulation of emotions and to learning how to regulate emotions, by creating a means to ventilate them [2]. Emotional education and will power create the opportunity to choose which stimuli trigger full-blown emotional reactions. Cognitions (especially memories) can also trigger emotional circuits [2].

Social learning increases the chance of reproducing and aids teamwork and child rearing, and thus the likelihood of species' survival. Language, self-consciousness and planning are all higher brain functions supporting social functioning. In addition, social understanding can be formed, observations and predictions about people's current behavior can be made, and knowledge of the world based on past experiences can be applied to new situations [50].

Nevertheless, the cognitive apparatus relies on the underlying, primitive system. In young animals, emotional-limbic area lesions are much more devastating than neocortical lesions. Decorticated animals effectively compete with normal animals during rough-and-tumble play. Students asked to observe two animals and then choose which one was decorticated, typically chose the decorticated one to be the one with an intact cortex. Decorticates are generally more active, in contrast to the more timid ones with cortex [2]. "The essential 'core of being' is subcortical". Primordial circuits probably project a fundamental sense of 'self' within the brain. "Not a very skilled and intelligent self, but it allows animals to develop into the intentional, volitional, and cognitively selective creatures that they are" [2,51]. These findings are also supported by Bartels et al. [43], showing that mother-infant bonding behavior caused deactivation of cortical areas for cognitive social judgement, and activation of other, more primitive, subcortical brain areas.

The brain: subcortical brain areas

After more than 30 years of brain research, world-renowned brain scientist and professor in neurobiology Dick Swaab arguments that "we are our brain". "Everything we think, do and don't do is because of our brain" [45]. This is a central assumption to modern neuroscience. This theory yields many implications about controversial issues such as sexuality, psychiatric disease, the afterlife and freedom of choice. Can there be freedom of choice when choices are made by the brain; an organ? A discussion on these issues is beyond the scope of this review, but I would like to point out Swaab's opinion about the plasticity of the brain; the brain is not a fixed organ. The central nervous system consists of the cortex, the primitive brain areas including the brain stem and the spine and thus a part of the autonomic nervous system. All these areas are dynamic. They change during development. Especially the early life (post- but definitely also pre-natal) environment is crucial to the optimal development of the brain. Many factors influence it's molding [45,52] and keep influencing it across the lifespan [50,53,54].

Such influences are important to the nature-nurture debate: is there really a distinction between nature and nurture, seeing that the one is never independent of the other [2,41,45]. This discussion too is beyond the scope of this review, but the implication that "everything is connected" is important for the rest of the chapter. Brain functioning depends on the environment. In fact, Swaab et al. demonstrate that the female brain is already programmed for motherhood during pregnancy. It is pre-programmed to nurture, to feed and to sensitively read infant cues [45]. In addition, Sullivan emphasizes that infant brains are not simply immature brains, but brains exactly suitable for the infant stage of life. Features of the infant brain improve learning about the caregiver and cause immediate behaviors that ensure maternal proximity [52], which underlines Lorenz' findings of bonding-oriented brain circuitry present at birth.

In their review Seso-simic et al. [46] describe how reproduction and immediate post-partum survival are influenced by and guided by the circuitry of the midbrain, hypothalamic structures and limbic regions. Furthermore, Leckman et al. report on the hypothalamus, medial preoptic area (MPOA), bed nucleus of the stria terminalis (BNST), substantia nigra, midbrain-pons and superior colliculus [55]. The MPOA appears to be the master control region that senses the timing of parturition through the dynamic changes in estrogen, progesterone, oxytocin and prolactin. Immediately after parturition, oxytocin release in the MPOA activates the ventral tegmental area (VTA) directly and indirectly in response to pup stimuli, leading to elevated dopamine in the nucleus accumbens and activated dopamine receptors. This releases the inhibitory control of the ventral pallidum by the nucleus accumbens, allowing excitatory input from the basolateral amygdala to activate the ventral pallidum. The ventral pallidum is a major output relay of the nucleus accumbens and it modulates motor output in response to reinforcing stimuli via projections to the thalamus and cortical and mesencephalic motor nuclei, culminating in the expression of maternal nurturing responses toward pups [55].

This is only a limited summary of the brain's bonding networks. For specific overviews and in depth theories on brain circuitry, in addition to Hruby et al. [10,48] and Seso-Simic et al. [46] I especially refer to Swain et al. [47,56]. However, the extremely complex interplay of all involved brain regions, varying from ancient areas to more newly developed, cortical areas is still not understood completely. Either way, important to note is that, despite a shift to greater cortical involvement, evidence suggests that similar to in other mammals, old brain regions and brainstem areas drive human parenting to a great extent [57]. This once again seems to underline that the instruments of the orchestra play their music in harmony. For instance, the ancient brain systems not only demonstrate a continuous interplay with the cortex, but they also function via hormonal pathways that are part of the autonomic nervous system.

The Autonomic Nervous System (ANS)

Even though the ANS is part of the peripheral nervous system, it is mainly controlled by the centrally located hypothalamus and vagal nerve. The latter originates at the site of the medulla oblongata, a part of the brain stem. The brainstem is the oldest part of our brain; our ancestors had it long before they had cortices [58]. The ANS can thus be seen as a primitive subsystem of the brain, a part of the command center. It constantly communicates with other parts, even though the name implies autonomy. Like other parts of the nervous system, the ANS too weighs sensory information, values the environment and (unconsciously) regulates the individual's internal state [59].

The ANS is a balancing part of the nervous system, keeping vital parameters in their necessary ranges. It can have an enormous influence on hormonal systems [60]. It mainly consists of two counteractive subsystems: the sympathetic and the parasympathetic nervous system. To put it simply, the sympathetic system prepares all organs for activity and uses energy resources, for instance to hunt for food or to flee from bears. As was stated in Chapter 5, the parasympathetic system, with its key player, the vagal nerve, brings the body into a state of rest, restores energy resources and enables damage repair [61]. As opposed to the sympathetic "fight or flight" state, such a state of rest is obviously more appropriate for socializing, nurturing and bonding, as described in the polyvagal theory put forward by Porges et al. and described in Chapter 5 [62].

Porges argues that the ANS is a hierarchal neural organization, which has evolved through phylogenetic stages. In mammals, the ANS responds to challenges following a phylogenetic hierarchy, starting with activating the newest structures and, when all else fails, reverting to the most primitive structural system. Safety of the environment is sensed, and if an individual feels safe, the ANS switches to dominance of the newest structures: the myelinated parasympathetic branches. Heart rate and breathing slow down, blood pressure decreases. A relaxed state is experienced, enabling social engagement. This social engagement is aided by several cranial nerves that are responsible for movements such as eyelid opening (e.g. looking); facial muscles (e.g. emotional expression, smiling);

middle-ear muscles (e.g. extracting the human voice from background noise); muscles of mastication (e.g. ingestion); laryngeal and pharyngeal muscles (e.g. vocalization and language); and head-turning muscles (e.g. social gesture and orientation) [62]. Interestingly, these cranial nerves have developed from the same embryological structures during the same embryological phase as the myelinated branches of the vagus nerve.

In their research, Porges et al. demonstrate that these phylogenetically different neuroregulatory systems allow mammals to slow the heart rate by increasing the inhibitory vagal control of the heart (the vagal brake), but also to speed their heart rate by decreasing the inhibitory vagal control of the heart. This lessens the metabolic requirements for mobilization and communication behaviors. Not every mobilization has to be "fleeing from a bear", and cost as much energy [63]. This vagal brake enables more rapid and subtle changes in the regulation of visceral states (enabling higher complexity of bonding) [64]. Such changes in visceral state form the basis for the definition of emotions.

Emotions

Panksepp states "Emotions are consequences of the arousal of emotional operating systems or circuits that actually exist in the brain". Such arousal occurs by neural firing due to (rhythmic / diurnal / spontaneous / experience driven) sensorial information from the environment. When one or more of these systems are aroused, the internal state is adjusted according to the sensorial information that caused the arousal. If an organism becomes aware of this change in internal state it is called an emotion [2]. Emotions (changes in internal state) are thus important elements of the process of bonding.

Indeed, for instance becoming a mother is described as intensely emotional, or overwhelming even [65]. The reason that emotions can be overwhelming is because emotional circuits are each composed of an anatomical network of interconnected neurons and endocrine, paracrine and immune influences and they can therefore have enormous (co-) regulatory effects. The link between emotions and the ANS is thus very strong; in fact, the ANS has long been recognized as the only output system for emotions. Certainly, the ANS is part of many of the emotional circuits, but it is now appreciated that several other brain regions, including a separate enteric nervous system, contribute to the internal state shifts that are experienced as emotions as well [2].

Emotional circuits

Emotional circuits are evolutionarily built-in neural circuitries that lead to inherited (pre-programmed) cascades of responses of the internal state, to changes in the environment. Arousal in these circuitries cause 'reflexive' visceral reactions, such as an increase in heart rate caused by fear, but reflexive behavioral reactions can also be caused by these circuitries, for instance 'freezing' when seeing eye to eye with a bear. Depending on the neural complexity of the species, there are also inherited reactions on a non-reflexive level, e.g. a spider building a web, or the following behavior of poultry when they have just hatched from their eggs [2]. Panksepp states, "Emotional circuits thereby allow newborn animals to begin responding coherently to the environments in which they find themselves. Without such inherited behavioral potentials, no creature could survive" [2]. He furthermore hypothesizes that when such neural activities continue at low levels for extended periods of time, they can generate moods and ultimately personality dimensions [2]. Various personality dimensions can be addressed by this theory, because there are various emotional circuits. Activity in every such circuit normally leads to a survival-increasing reaction.

An important circuit for survival is called the SEEKING circuit. By providing an inner drive to explore the world and to find resources to survive, this circuit explains how animals regulate their energy and fluid metabolism. Another important circuit is termed the LUST circuit, this was already present within the reptilian brain, albeit much simpler than in the human brain. When aroused, this circuitry leads to reproductive states or behavior, necessary for the species' survival. The FEAR and RAGE circuits are

foundations for the “fight and flight” system. These mechanisms increase survival when facing danger. Even though there is some overlap in circuitry and purpose, a distinct and equally necessary PANIC system has been identified. This system assures that – especially when the SEEKING, FEAR, and RAGE circuits are still immature – organisms are maximally assisted by other organisms to survive. It signals separation and loneliness and assures that offspring are able to indicate that they are in need of care, e.g. by vocalizations. It therefore increases the chance that parents take care of their offspring. Even when the SEEKING, FEAR and RAGE circuits have matured, the PANIC system remains operative and the behaviors that result from arousal of a normally functioning PANIC system optimize family life. The core of the social emotions and of social bonding belong to the PANIC circuit. However, additional bonding-related circuits like LUST and PLAY have also been identified. Moreover, all of this neural circuitry functions through signaling molecules like neuromodulators, neurotransmitters and hormones.

Panksepp describes neuromodulators such as oxytocin, vasopressin, glutamate, dopamine and serotonin in a detailed way. For instance, he addresses neurochemical changes caused by circuitry activation due to pleasurable pro-social activities. When an individual becomes aware of this altered internal state, he or she experiences emotions of love, lust or happiness. The hormone oxytocin is one of the key players involved in these circuitries and therefore in generating these emotions.

Oxytocin

Many articles or reviews on bonding, of which I only refer to some frequently cited articles, either start with a section on oxytocin (OT), or dedicate their main part to it [3,15,66–71]. Neurons with OT receptors are widely spread throughout the central and peripheral nervous system [72]. In addition, most – if not all – visceral target organs of the ANS contain receptors for OT [72,73]. The extensiveness and complexity of the oxytocinergic system enables endless variation in the effect of OT on its receptors per different location within one individual organism and within different organisms. In addition, the fact that the biological properties of the sulfur bonds that create the ring in OT are dynamic also contribute to the various methods of acting of OT. Those sulfur bonds allow formation of both temporary and long-lasting unions with other chemical entities throughout the entire body, including neuromodulation within the central nervous system [67]. Neuromodulation is the regulation of a diverse population of neurons, as opposed to classical one on one synaptic transmission by neurotransmitters [74]. When acting through neuromodulation, OT is called a neuromodulator instead of a hormone.

As previously stated, genes responsible for OT-like peptides evolved more than 700 million years ago. The processes that were influenced by the OT precursor 700 million years ago (water balance, immunity, metabolic processes) are still regulated by OT and its structurally related molecule vasopressin (AVP). AVP is responsible for controlling urine dilution [61]. OT is found to increase wound healing and to improve the immune system functioning [75–77]. The OT and AVP molecules appear to have been repurposed repeatedly while maintaining former purposes, suggesting that they have been one of the important tools helping evolution drive organisms towards optimal efficiency. In humans, optimizing efficiency led to sociality and a growing neocortex. Indeed, OT is important for social behaviors, but it also supports cortical growth [67,78]. Besides its role in inflammatory processes, OT can stimulate cellular growth, death or motility. It influences differentiation, including stimulating stem cells to differentiate into cortical cells [79]. OT increases cortical plasticity [80]. In addition, OT receptors are found in bones, where they appear to induce bone growth and bone remodeling [81–85]. OT is therefore also linked to skull enlargement, but a direct relation has not yet been reported. Nonetheless, the nurturing effects of OT indirectly encourage encephalization by ensuring infant care and thus permitting slow maturation of the nervous system [67].

Furthermore, parallels between the evolution of mammalian physical traits and the evolution of the OT molecule, circuitry and functions have been discovered. For instance, the phylogenetic shift in the myelination of the vagus (described in the Polyvagal theory) is paralleled by a modification in the

hypothalamic regulation of the dorsal vagal complex via both OT and AVP [62]. It seems that in addition to the interplay between the sympathetic and parasympathetic system, the interplay between OT and AVP is also important. In a human study by Apter-Levi et al. parents with high OT levels displayed more affectionate contact compared to parents with low OT and those parents responded to infant social gaze with increasing social salience. In that same study, parents with high AVP engaged in stimulatory contact and tended to increase object-salience when infants showed bids for social engagement [86].

Vasopressin

Similar to in Apter-Levi's study, AVP has been demonstrated to stimulate paternal behavior (e.g. time spent grooming) in male prairie voles [87,88]. Other studies on human males show similar pro-social effects by AVP [89]. Also, brain regions that are part of the AVP circuitry are involved in socio-cognitive processes in humans and in rodents [90]. Similar to OT, AVP has been found to promote social recognition in rodents [91]. AVP probably prompts different, gender related social strategies. In men, the AVP-brain associations may support the ability to read the intention of others, in order to defend mother and young resulting in aggressive behaviors in certain contexts, while in women, AVP might support the ability to befriend to others [92,93]. Just as the effect of OT on the onset of maternal behavior is highly dependent on estrogen, the effect of AVP is highly dependent on testosterone levels in males [94].

Gonadal hormones

Testosterone amplifies the genetic expression of AVP receptors throughout the body and the AVP production in the hypothalamus. Accordingly, males have more extensive vasopressonergic circuits than females. The genetic blueprint of OT and OT receptors are under the control of the ovarian hormone estrogen [95]. Nonetheless, testosterone can have influences on OT concentrations as well [96]. Recent data from Feldman's laboratory show that "during the early stages of romantic attachment, levels of plasma OT and testosterone are inter-related and are associated with respiratory sinus arrhythmia (RSA), an index of parasympathetic influences over heart rate variability. Such hormonal-autonomic interactions were found to predict observed social reciprocity between new lovers, expressed in mutual gazing, matched affect, positive arousal, and affectionate touch" [15].

Estrogen, which remains at modest levels throughout pregnancy, rapidly increases as parturition nears. Progesterone, which has been high throughout pregnancy, begins to decrease [2,61,97]. In many species, the cocktail of these hormones leads to nesting behavior several days before the baby is due. Rat mothers literally start building nests, while human mothers color the room for the baby and shop for clothes and equipment [2]. Unfortunately, too little is known about the exact hormonal shifts and the interplay between OT, AVP, the gonadal, and other relevant hormones such as prolactin during pregnancy.

OT appears to stimulate prolactin release [75]. Fathers' prolactin levels correlated with OT and with paternal coordination of joint exploration with the infant [98]. Fathers with higher levels of prolactin tended to be more watchful and displayed more positive reactions to the infant's crying. Moreover, skilled fathers showed a higher increase in prolactin [99]. Prolactin administration facilitates maternal behavior in a steroid-primed non-pregnant rat. In sheep, steroid-priming is necessary for vaginocervical stimulation (causing OT release) to induce immediate maternal behavior in a non-pregnant ewe [97].

Opioids

Similar to OT, opioids are a part of the PANIC-system circuitry. To recall, the PANIC-system is the main contributing emotional operating system to bonding. An increase in opioid concentration has been reported to fade out arousal in the PANIC-system. Similarly, when exceeding a threshold, OT also fades out PANIC-system arousal. On the other hand initial PANIC-system arousal results in an increase in OT, but not opioids. For example, separation distress would result in increased OT facilitating social behaviors asking for parental attention (crying, vocalizations), but not in increased opioid levels. When

a parent responds to the distress behaviors, both opioids and OT are released to exceed a threshold (positive feedback loop) fading out the PANIC-system activity. The brain opioid system was the first neurochemical system found to exert a powerful inhibitory effect on separation distress [100]. Re-uniting the infant with social familiars causes separation distress vocalizations to stop and restores pre-separation levels of both opioids and OT [101]. Moreover, increases in opioid concentrations reduce the need for gregariousness [102]. In addition, touch has been demonstrated to activate both the opioid system [103] and the OT system [15], and an injection of opioids in the absence of social behaviors possibly stimulate an OT increase as well [104]. On the other hand, a sudden decrease in opioids might also increase OT just as acutely stressful experiences do. Either way, an increase in OT appears to increase the sensitivity of the brain to opioids [105]. All these examples once again indicate the complexity of human physiology and thus the physiology of bonding.

Currently, OT, AVP and opioid systems appear to be very important players in the construction and maintenance of social bonds in mammals. However, the main function of opioids is modulating pain. This might explain that to lose someone you love can actually feel painful, because, especially when we lose those in whom we have invested a great deal of genetic effort (our children) or those who have helped us to thrive (parents, siblings), the brain opioid level would plummet [2]. Such reductions in opioid activity increase the desire for social companionship. This opioid contribution to experiencing desire can also influence sexual reward and place preference. However, most of the experiencing of reward, including a rewarding feeling (and thus a motivation) for bonding comes from connectivity with the dopaminergic system.

Dopamine

Arousal of the dopaminergic system provides an intuitive reinforcement and increases the incentive value of experiences; the system is often called the reward system. By elaborately connecting such a reward-system to the OT-system, the infant's incentive value of the mother increases [15]. It leads to a very pleasant or satisfied feeling when dopamine synapses are active in abundance, a feeling that we eagerly want to activate and which thus feels as a reward once we experience the feeling [2]. However, interference of the systems or inappropriate arousal somewhere in the network can cause unwanted tendencies, such as addiction [106]. Bos et al. suggested a mutual influence between gonadal steroids, OT and dopamine interactions for most addictive behaviors [107]. Regarding monogamous rodents' studies, Young et al. [108] suggested the following model for pair-bond formation: OT and AVP contribute to memorizing social cues and individual recognition. Mesolimbic dopamine is involved in reinforcement and reward learning. Concurrent activation of neuropeptide and dopamine receptors in the reward centers of the brain during mating results in a conditioned partner preference, observed as a pair bond [108]. Champagne et al. showed that minute-by-minute dopamine release in the nucleus accumbens correlates with licking and grooming behavior [109], and not only does dopamine appear to be a significant modulator of social behavior, the specific type of dopamine receptor seems to be just as important. Facilitation of maternal behavior occurs through activation of the adenylyl-cyclase linked D1 receptor, but not with the phospholipase C-linked D1 receptor [110,111]. Nonetheless, since several other factors (including opioids) have been described to influence bonding, this seems to be a simplified version of the entire bonding network. For instance, Welch et al. published an article based on their theory that emotions and emotional behavior stem from dysregulations of a unified brain-gut network [112].

The brain-gut network: enteral hormones

Welch et al. provide evidence that two neuropeptides, secretin and OT, are critical in the conditioning of infant adaptive behavioral patterns, and that peptidergic mechanisms are abnormal in developmental disorders such as autism. In addition, cholecystokinin (CKK), a hormone especially involved in signaling hunger or satiety, has been shown to increase to 200% from before to after feeding during skin-to-skin contact, in comparison to feeding by nasogastric tube where CCK levels did not change [113]. "CCK may mediate part of the naturally soothing, calming aspects of milk and touch and

take part in the neuropeptide basis of early learning of discriminative maternal aspects" [114]. OT levels correlated with cholecystokinin. CCK appears to play a role in maternal-infant bonding [115,116].

Others

As previously stated, arousal in the PANIC- FEAR- and RAGE-circuit appears to be reduced by OT and vice versa. A threatening situation resulting in a release of for instance glutamate, cortisol, adrenalin and AVP, is the main reason for arousal of those circuits. When those circuits are aroused, stress is induced in the form of panic, fear or rage. In an adequately functioning system – depending on an individual's history – separation stress (panic) will increase OT release and thereby initiate vocalizations and social behaviors in order to start restoring the internal state balance [2]. When social behaviors are answered and a caregiver provides comfort and warmth, OT will continue to increase (the positive feedback loop) and the arousal in the PANIC- FEAR and/or RAGE-circuits generated mostly by glutamate, cortisol and adrenalin will cease [2].

Gamma-aminobutyric acid (GABA), is another neurotransmitter described to influence attachment in animal studies [48]. GABA and glutamate appear to participate in every behavioral, physiological and cognitive process that has ever been studied [2]. GABA is described as the overall inhibitor of the central nervous system (CNS). Thus, when GABA is secreted at the site of a dendrite belonging to an OT producing neuron, OT production will normally be inhibited. Since GABA is a substance functioning very broadly throughout the CNS, further details are beyond the scope of this review [61,75], nonetheless GABA has been implicated in many psychiatric disorders. Secretin and OT inhibit GABA activity [112].

Adrenocorticotropic hormone (ACTH) is a pituitary hormone of which the production is increased by the hypothalamic hormone corticotrophin-releasing hormone (CRH) under influence of stressful situations. The main function of ACTH is then to stimulate the adrenals to produce the stress hormone cortisol. The CRH to cortisol chain is called the HPA-axis or "stress axis". The stress-induced rise in plasma ACTH causes a rise in OT, OT then attenuates or inhibits the stress response (depending on the received care giving or comfort) and continues to rise itself [75,117]. Indeed, microinjections of OT into certain hypothalamic regions decrease the stress-induced rise of plasma ACTH and corticosterone [118,119]. In both animals and humans, OT reduces physiological and behavioral indices of stress [66]. The coupling of these two systems, the HPA-axis and the oxytocinergic system, influences an individual's risk of HPA-axis dysregulation in a similar way that the coupling of the OT system and the dopamine reward system influence an individual's risk of addiction. Hamsters and mice that form social bonds are buffered against stress and heal cutaneous wounds more quickly than socially isolated animals, presumably because the physical contact experienced by the pairs releases OT, which in turn suppresses the HPA axis and facilitates wound healing [120]. There is an abundance of literature on this topic (stress altering development and development altering the stress axis) [24,25,27,29,121]. For an overview of this literature, I refer to Chapter 7 as well.

Serotonin (5-HT) is a neurotransmitter that, like GABA and glutamate, has a very broad influence. It is involved in practically every chemical process in the brain. Essentially, that same conclusion holds for the non-selective molecules acetylcholine, dopamine and norepinephrine [2]. More importantly, 5-HT is a key player in generating a positive mood and thus in creating receptiveness for sociality [66]. This means that, like OT and several other molecules mentioned before, it is a key player for the process of bonding. There are currently 15 serotonin receptors discovered, causing a wide variety of – sometimes converse – consequences due to serotonin increase [2]. Overall, serotonin release is facilitated by OT [121,122]. OT has site-specific, organizational influences on the serotonin system during the neonatal period. For example, OT treatment on post-natal day one affected serotonin axon length density on post-natal day 21 in certain regions of the hypothalamus and amygdala [123]. Serotonin mildly suppresses PANIC-system arousal [2]. Mice knocked-out for pet-1 gene, which is important for adequate serotonin system development, failed in providing maternal care. Their offspring died within five days because of insufficient maternal care [124]. Increased serotonin promotes affiliative behavior in non-human primates

and in humans as well [125]. Significantly increased levels of AVP and OT production were detected in the tissue culture media following 5-HT administration, depending on the 5-HT dose [126]. OT infusion facilitated serotonin release within the median raphe nucleus and reduced anxiety-related behavior. Infusion of a 5-HT2A/2C receptor antagonist blocked the anxiolytic effect of OT, suggesting that OT receptor activation in serotonergic neurons mediates the anxiolytic effects of OT. This is the first demonstration that OT may regulate serotonin release and exert anxiolytic effects via direct activation of OT receptors expressed in serotonergic neurons of the raphe nuclei [122].

This OT and 5-HT coupling probably influences an individual's risk for developing depressive disorders; researchers have convincingly demonstrated the serotonergic systems of depressed patients to be altered [127,128]. Matsushita et al. report that OT levels are significantly lower in patients with depression. Furthermore, a drug for the treatment of sexual dysfunction, sildenafil, enhances the electrically evoked release of OT from the posterior pituitary. Matshushita et al. showed that sildenafil had an antidepressant-like effect through activation of an OT signaling pathway. The antidepressant-like effect was blocked by an OT receptor (OTR) antagonist and was absent in OTR knockout (KO) mice [129]. For a recent review on serotonin and sociality, see Kiser et al. [130].

Norepinephrine (NE) is a biogenic amine, which means that in the first place, it operates as a nonspecific actor (either as a hormone or as a neurotransmitter) for internal state regulation. NE is a precursor to epinephrine (also known as adrenaline), thus the nonspecific controlling of organs and behaviors will be in a sympathetic direction [2]. An article on the role of NE (and other central neuromodulators) in mammalian aggression is published by Yanowitch et al. [131]. Secondly, NE is specifically released in massive amounts at birth [132]. As stated by Hruby et al., NE is involved in the regulation of parental behavior. Female rats that are genetically disabled for synthesis of noradrenaline expressed no care of their youngsters. Despite this condition they developed maternal behavior after application of noradrenaline, when noradrenaline was administered before, but not after birth [133]. This might be because noradrenaline plays an important role in emotional memory processing. It is known that the locus coeruleus (brain noradrenergic center) is markedly interconnected with the amygdala, hippocampus, frontal cortex and other structures associated with storing emotional memory [134]. Therefore, in addition to OT, the presence of NE within the olfactory bulb is important for odor learning [135]. Other substances that are important for odor learning are nitric oxide (a gaseous substance), dopamine, glutamate and GABA [2,22].

A series of complex peptide molecules called neurotrophins probably influence bonding as well, either through odor learning or through directing cell differentiation. For example, "nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) have now been identified to govern maturation and development of specific neural systems. These molecules control very specific growth processes in the brain and they can also protect neurons against various forms of toxicity" [2]. In their review, Marazziti et al. emphasize on the importance of these neurotrophins, stating that recent observations, coming partially from humans, suggest an important role for neurotrophins in the regulation of bonding, while acting as a modulator of different endocrine functions [136].

To conclude, many molecules are involved. Moreover, these molecules are coupled, act together, or are at least influenced by one another to enable optimal adjustment to environmental challenges. Several other signaling molecules that were not described yet are involved as well [137,138]. I aimed to provide an insightful overview by giving a brief description of neuronal factors, hormones, emotional operating systems and their use of signaling molecules, but it appears impossible to provide a comprehensive overview. Important to note therefore is that all signaling molecules are produced because of the transcription of genetic material.

Genetics

Organisms consist of cells containing genetic material in the form of DNA. This material codes for the building up of the entire organism, by providing a manual for protein manufacturing [139]. Hormones and receptors are mostly made of proteins, and enzymes are proteins as well. Enzymes promote three general types of biochemical transactions relevant for neuromodulation and therefore relevant for co-regulation: 1) cleaving mother-proteins to form shorter proteins called neuropeptides, 2) joining molecular fragments to form other brain molecules, such as acetylcholine, 3) modifying amino acids to form many other neurotransmitters (dopamine, NE, serotonin). Receptor manufacturing is also supported by enzymes [2]. Proteins thus are a large class of biomolecules, including many signaling molecules (hormones, neuromodulators etc.), receptors, and cell components. They form blood cells, other components of the immune systems, neurons, glial cells and eventually entire brain regions and their circuitry [61].

Defects in the genetic material, the blueprint for producing proteins, can thus be detrimental [140]. One might wonder whether the genetic material is the conductor of the bonding-orchestra. However, the process of reading and transcribing DNA is highly dynamic. It is majorly influenced by an individual's previous experiences and environmental aspects (both positive and negative), through a phenomenon called epigenetics.

Epigenetic mechanisms

The transition of traits across generations has typically been attributed to the inheritance of genomic information. However, it has been shown that epigenetic mechanisms are capable of mediating this type of transmission [141]. The term epigenetic refers to chromatin modifications that alter gene expression without affecting DNA sequence. In other words, epigenetic mechanisms allow external factors to influence gene expression without changing the DNA material. For instance, a decreased DNA methylation of the CRF gene promotor and increased methylation of the glucocorticoid receptor exon L2 promotor have been demonstrated in the hypothalamus of adult male mice born to gestationally stressed females [46].

The neonatal period is associated with a significant increase of DNA levels in the cortex [48]. During this period the brain rapidly generates nucleic acids and this is directly influenced by experiences, especially social events [142]. According to recent research, the mother-infant bond is an extremely important epigenetic factor. Variations in maternal care influence DNA methylation substantially [143].

Maternal stress is another environmental aspect affecting the offspring. It does not alter DNA sequence, but it alters gene expression. This and more on the exact mechanisms mediating gene expression can be found in many articles on epigenetics [139,141,144,145]. Different proteins (enzymes, hormones, receptors, etc.) will thus be synthesized in offspring in a stressful environment, compared to offspring experiencing a non-stressful environment. This means that receptors can be down- or upregulated due to different experiences [146]. For instance OT receptors can, under influence of persistently high or persistently low OT levels (due to different experiences) be down- or upregulated [147]. Receptors are thus also a factor influencing (co-) regulation, in addition to environmental experiences.

Environmental experiences: individual, cultural, and societal factors

For an extensive report about environmental factors, their psychological and physiological influences and words of caution about the changing (Western) societies, less and less addressing the needs of young children, I refer to the book "From Neurons to Neighbourhoods" by Shonkoff and Phillips [41].

An additional, striking quote related to this topic is one by Carter and Porges: "The brain of a human 'in love' is flooded with sensations, often transmitted by the vagus nerve, creating much of what we experience as emotion. The modern cortex struggles to interpret the primal messages of love, and

weaves a narrative around incoming visceral experiences, potentially reacting to that narrative rather than reality" [49].

This illustrates that the body's regulatory systems are complex [50]. Since bonding is co-regulation, every regulatory system can be involved in bonding if only it is subjected to the influence of another organism. This explains why health and well-being in general can be drastically influenced by bonding [148]. Suboptimal bonding impairs hormonal, epigenetic and neuronal development. Nonetheless, these impairments can be reversed. The aim of this appendix was therefore not to provide a complete understanding of the physiology of bonding (since it is not completely understood), but to paint the bigger picture, and to visualize that bigger picture in a brainstorm tool (figure 1). When interpreting that brainstorm tool, there are words of Panksepp that should be taken into account: there is always the risk of "imposing too much linear order upon ultra-complex processes that are essentially chaotic". As mentioned before, the mechanism of co-regulation is extremely complex. Nonetheless, I hope the tool can inspire clinicians, designers, engineers and researchers in their attempts to devise interventions to enhance bonding.

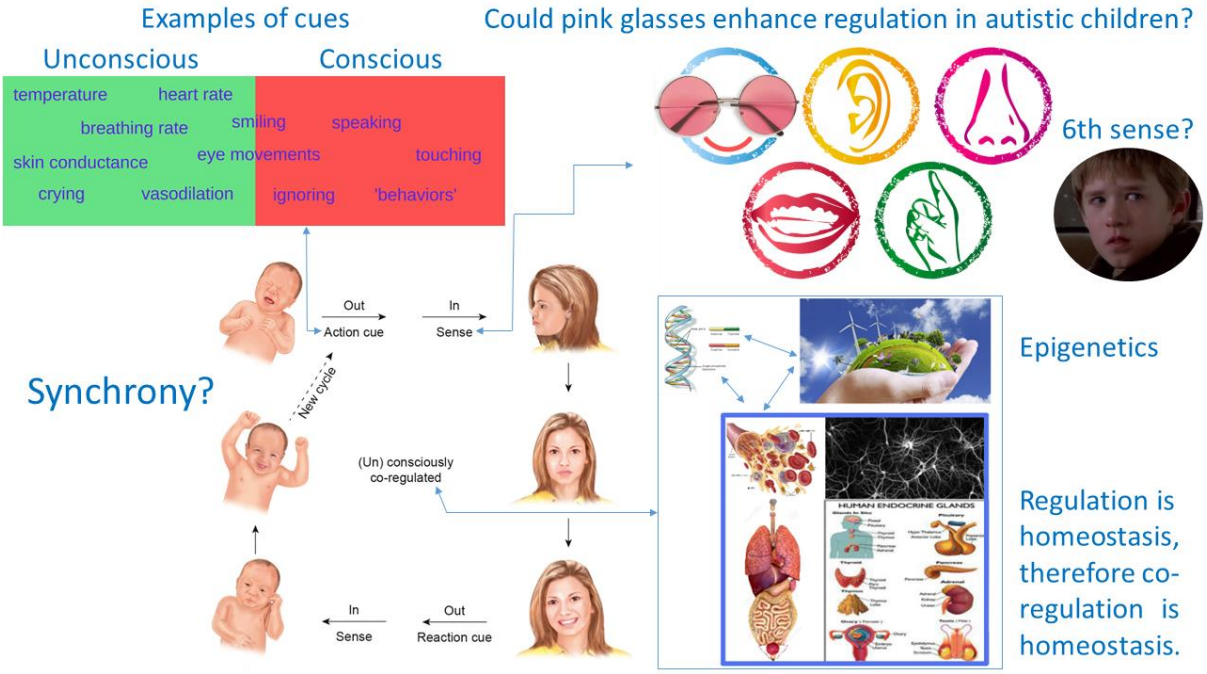

Figure 1. Brainstorm tool for designing interventions aimed at enhancing bonding

CONCLUSION

The physiology of bonding reflects a universal mechanism present in all organisms, built in during evolution. Modern day life makes adequate bonding increasingly difficult. Technological and clinical interventions could help in optimizing bonding. Therefore, I present a simplified overview of important elements for the process of bonding serving as a visual brainstorm tool for engineers, designers or clinicians striving to enhance bonding.

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