Communication • DOI: 10.2478/v10134-010-0020-0 • Translational Neuroscience • 1(2) •2010 •148–159

VERSITA

Translational Neuroscience

RECENT ADVANCES IN THE NEUROBIOLOGY OF ATTACHMENT BEHAVIOR

Đurđica Šešo-Šimić[1],
Goran Sedmak[2],
Patrick R. Hof[3],
Goran Šimić[2]*

[1]*Department of Paediatrics, Zagreb-East Medical Center, Zagreb, Croatia*

[2]*Department of Neuroscience, Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia*

[3]*Department of Neuroscience, Mount Sinai School of Medicine, New York, USA*

Abstract

In a biological sense an individual's life is all about survival and reproduction. Beside the selection of a mate, the mutual commitment of a parent to sustain an infant through a period of dependency is amongst the most important aspects of natural selection. Here we review how the highly conserved circuitry of key midbrain and hypothalamic structures, and limbic and frontal cortical regions support these processes, and at the same time are involved in shaping the offspring's emotional development and behavior. Many recent studies provided new findings on how attachment behavior and parental bonding is promoted and maintained through genetic and epigenetic influences on synaptic plasticity of mirror neurons and various neuropeptide systems, particularly oxytocinergic, and how these systems serve to link social cues to the brain reward system. Most of this evidence suggests that stress, early parental deprivation and lack of care during the postnatal period leads to profound and lasting changes in the attachment pattern and motivational development with consequent increased vulnerability of the mesocortical and mesolimbic dopamine-associated reward reinforcement pathways to psychosocial stressors, abuse of stimulants and psychopathology later in life.

Keywords

Aggressiveness • Attachment behavior • Autism • Dopamine • Emotional development
Motivation • Oxytocin • Mirror neurons • Parental bonding • Psychopathology

Received 19 June 2010
accepted 21 June 2010

Introduction

The studies of attachment behavior lie at the crossroad of various disciplines, from sociobiology (particularly ethology) and anthropology to evolutionary and social psychology. Biological approaches traditionally emphasize "nature", while psychological approaches stress "nurture" as a major determinant of behavior [1]. Cognitive neuroscience should reconcile both approaches as the emergence of the attachment behavior (and social behavior in general) depends on complex interactions between genetic predispositions and the environment [2]. Recent evidence clearly shows that the dynamic regulation of gene expression through epigenetic mechanisms is at the interface between the environmental stimuli and long lasting molecular, synaptic, cellular and complex behavioral phenotypes acquired during the periods of developmental plasticity [3].

Attachment theory

Over the last 50 years the attachment theory of Bowlby has been continuously modified mainly as a result of empirical psychological research, but the main concept that a young child needs to develop a relationship with at least one primary caregiver for social and emotional development to occur normally has been generally accepted [4,5]. It is only in the past 20 years that some of the underlying neurobiological foundations of attachment theory have been discovered. With the development of new imaging techniques to visualize the brain activity (fMRI, PET), the integration of results from available human data, animal models, neurophysiology and other related neuroscience disciplines produced striking new findings about when and how specific brain regions, pathways, and circuits participate in the development of attachment behavior. Consequently, this new knowledge opens new ways of treating attachment disorder and other similar, still vaguely defined, psychopathological states. Attachment disorder is a broad term comprising the absent, distorted or problematic age-appropriate social behaviors, expectations and relationships arising from a failure to form normal attachments to primary care giving figures in early childhood [5]. It is most often used to describe emotional and behavioral problems of young children, but is sometimes applied to school-age children or even to adults.

The attachment theory proposes that children attach to caregivers instinctively to increase the probability of survival in stressful situations [6]. Although the biological mother is the usual principal attachment figure, infants will form attachments to any consistent caregiver who is sensitive and responsive in social interactions with them during the period from about 6 months to 2 years of age. As discovered by Ainsworth by using the so-called "Strange Situation" experimental paradigm, the

* *E-mail: gsimic@hiim.hr*

parental responses (or "care-giving bond") lead to the development of individual, but distinct patterns of attachment (secure, insecure-avoidant, insecure-ambivalent/resistant) [7,8]. The fourth type, disorganized/disoriented attachment was identified somewhat later [9] (Table 1).

Some infants direct proximity seeking towards more than one attachment figure almost as soon as they start to discriminate between caregivers; most come to do so during their second year. The quality of the engagement has been consistently shown to be more influential than the amount of time spent. With the development of locomotion, the infant is "using the parent as a secure base from which to explore the world" [7]. Infant exploration is postulated to be greater when the caregiver is present because the infant's attachment system is "relaxed" and free to explore. Insecure patterns are also considered adaptive, as they are suitable responses to caregiver unresponsiveness. They are, however, non-optimal as they may compromise exploration, self-confidence and mastery of the environment [10]. Separation anxiety, fear and illness will cause a child to increase attachment behaviors, again to increase the probability of survival [11]. By age three or four, physical separation is usually no longer such a threat to the children's bond with the attachment figure if they and their caregiver have already negotiated a shared plan for the separation and reunion [12]. Insecurely attached children are believed to be relatively amenable to change throughout their early years. For instance, it has been shown that if a child is securely attached to his father (or to another secondary caregiver, even only a distant relative the child sees occasionally), it will help him overcoming an insecure attachment to his mother [11]. By middle childhood, the goal of the attachment system changes from proximity to the attachment figure to availability. Threats to security in older children (and adults) arise from prolonged absence, breakdowns in communication, emotional unavailability or signs of rejection or abandonment [13].

The attachment theory has been extended to adult romantic relationship, where four styles have been identified (secure, dismissive/avoidant, anxious/preoccupied and disorganized), roughly corresponding to the infant classification [14,15]. Moreover, attachment patterns are transmitted as the parents' perceptions of their own childhood attachments (autonomous, dismissive, preoccupied and disorganized, respective to Table 1) were found to predict their children's classifications about 76-85% of the times [11,16,17].

The role of the brain reward system in the development of motivation and attachment

There is accumulated evidence that the core of the universal brain reward system is composed of projections from midbrain dopaminergic neurons to limbic regions of the ventral striatum (particularly to the nucleus accumbens, NAc), the amygdaloid complex of nuclei, hippocampus and the frontal reward regions (particularly orbitofrontal cortex, OFC) [18,19] (Figure 1). The firing frequency of these dopaminergic ventral tegmental area (VTA) neurons (mainly from the A10 group) increases during any naturally-occurring pleasant experiences of eating food, during sexual activity or while bonding with a child ("behavioral activation") [20]. When electrodes

Table 1. Attachment patterns before the age of 18 months according to [7-9].

Attachment pattern	Child's behavior	Caregiver's behavior	Percentage of children from middle-class U.S. homes studied
SECURE	Uses caregiver as a "secure base for exploration". Seeks proximity and protests caregiver's departure, and is comforted on return (returning to exploration). May be comforted by the stranger but shows clear preference for the caregiver.	Responds appropriately, promptly and consistently to child's needs.	~65%
INSECURE-AVOIDANT	In contrast to the secure child there is little affective sharing or joint play with the attachment figure. There is usually little, if any, "checking back" to the caregiver, little or no distress on departure, little response to return, ignoring or turning away with no contact if picked up. Child becomes distant, as to say: „Who needs you – I can do it on my own". Treats the stranger in a similar way.	Little or no response to distressed child. Discourages crying and encourages independence. Some parents convince themselves that their child is superior to other children, having an excuse for their lack of nurturing attention: „This kid is special, he barely needs me, and he's been doing his own thing practically since he was born".	~20%
INSECURE-AMBIVALENT/ RESISTANT	Preoccupied (addicted) with caregiver's availability, desperately seeking proximity before separation occurs, but resisting contact angrily when it is achieved (punishing caregiver for being unavailable). Unable to use caregiver as a secure base. Not easily calmed by stranger.	Inconsistent between appropriate and neglectful responses. Will respond sometimes perhaps out of guilt – if the child pleads and makes a big enough fuss.	~10%
INSECURE-DISORGANIZED/ DISORIENTED	Contradictory attachment strategy, chaotic and disoriented behaviors such as approaching with the back turned. Stereotyped behavior on return of the caregiver such as rocking or freezing.	Frightened or frightening behavior, making errors in emotional communication, withdrawal, aggressiveness, maltreatment, abuse.	<5%

were implanted into the animal reward regions (such as septal region near or in the NAc and other parts of the ventral striatum) and the animals were allowed to press a lever to stimulate their brain electrically, most of the animals preferred self-stimulation to obtaining food or water, engaging in sexual behavior, or any other naturally rewarding activity [21,22]. Such experiments of deep brain stimulation in humans, now forbidden for ethical reasons, had similar results. For example, during a three-hour session, a subject, electrically self-stimulated his reward circuitry some 1,500 times, was experiencing an almost overwhelming euphoria and elation, and had to be disconnected, despite vigorous protests [23]. Actually, the stimulating electrode producing the same effect can be placed anywhere along the trajectory of the medial forebrain bundle (MFB) that contains dopaminergic fibers from VTA [21] (Figure 2).

Subsequent more detailed studies showed that electrical stimulation of MFB maintains self-stimulation by activating dopaminergic cells only indirectly. The most effective electrical stimuli activate a group of non-dopaminergic neurons in the MFB that project to the midbrain and there activate the dopaminergic neurons with ascending projections [24]. Homozygotic mice with disrupted gene encoding for the dopamine transporter (through homologous recombination) expectedly showed no behavioral activation after systemic administration of cocaine or amphetamine [25]. Similarly, dopamine receptor antagonists, such as the antipsychotic drugs haloperidol and chlorpromazine, reduce the rewarding effect of food and intracranial stimulation, whereas drugs that facilitate dopamine transmission enhance the processes by which otherwise neutral stimuli aquire reinforcing properties and further drug-seeking behavior [26,27]. Whereas ordinary rewards are effective only if the animal/subject is in a particular drive state (e.g., food serves as a reward only when the animal/subject is hungry), electrical stimulation of these mesencephalic dopaminergic projections both evokes a drive state and recruit neural circuits that are ordinarily activated by reinforcing stimuli. Therefore, the mesolimbic and mesocortical dopamine system is thought to gate signals that regulate both biological drives and motivation.

For decades it was thought that addiction resulted from adaptation to the acute effects of an individual drug such that the underlying cause of addiction was different for different drugs and the drive for addictive behavior was to overcome the effects of withdrawal. This is no longer considered to be the case.

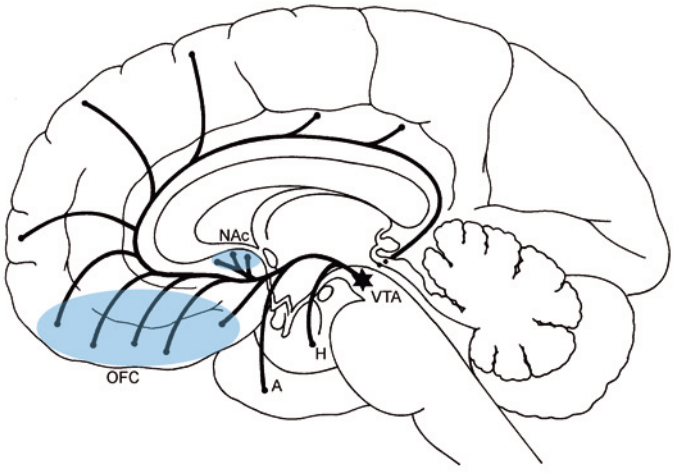

Figure 1. Simplified schematic representation of midbrain dopaminergic projections from ventral tegmental area (VTA, star) to nucleus accumbens (NAc, small blue ellipse), medial orbitofrontal cortex (mOFC, large blue ellipse), hippocampus (H) and amygdala (A). These projections comprise the universal brain reward system. Dopamine release in the NAc has been linked to the efficacy of unconditional rewards. Dopamine release in a broader range of structures, such as hippocampus (H) and amygdala (A) has been implicated in the „stamping-in" of memory that attaches motivational importance to otherwise neutral stimuli. Scheme made according to [26,27,32,34]. See text for details.

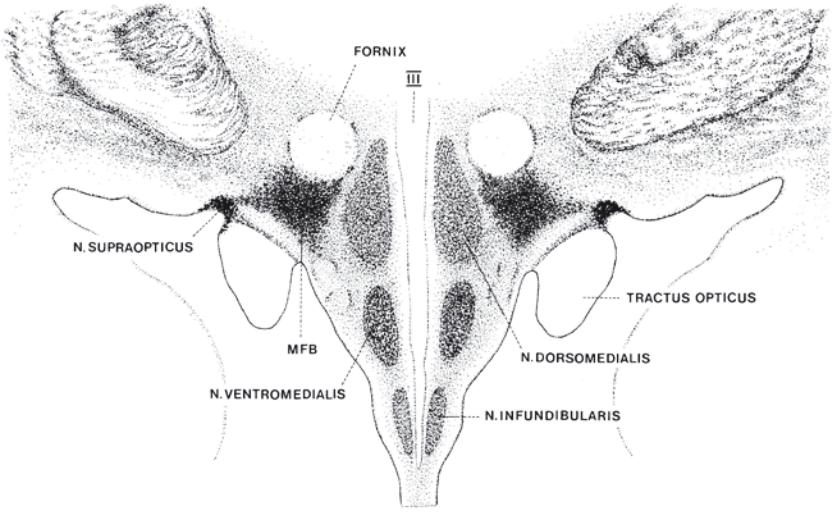

Figure 2. Frontal section through the tuberoinfundibular portion of the hypothalamus (schematized from a Weigert-stained section). Fibers of the medial forebrain bundle (MFB, *fasciculus telencephalicus medialis*) are running through the lateral hypothalamus, giving rise to collaterals for supraoptic, paraventricular and other hypothalamic nuclei. The bundle contains efferent dopaminergic fibers from ventral tegmental area (VTA), mostly from A10 group of dopaminergic neurons, but also from other sources of monoaminergic fibers innervating the cerebral cortex and afferent fibers of non-dopaminergic neurons that project to the midbrain where they activate the dopaminergic neurons with ascending projections (according to [24]). See text for details.

Although withdrawal symptoms are specific to an individual drug, the adaptation that is responsible for addiction is in response to activation of the brain's universal reward circuit and therefore common to most, if not all, drugs of abuse [28]. Indeed, through interactions with a variety of transporters, ionotropic and metabotropic receptors, it has been shown that opioids (e.g., mu opioid agonists through inhibition of GABAergic neurons that normally suppress VTA dopaminergic neurons), cocaine (by blocking the dopamine transporter), amphetamines (by increasing concentrations of dopamine in cytosol of presynaptic neurons and interacting with dopamine transporter to induce reverse transport of dopamine from presynaptic neuron into the synaptic cleft) [29,30], nicotine (by acting on presynaptic cholinergic receptors), alcohol, cannabinoids, and others drugs of abuse all act as positive reinforcers by increasing the firing of dopamine afferents to limbic and frontal cortical regions. The rise in dopamine transmission in these regions is then translated into a motivational activity such that the behavior of an animal/subject is repeated [31,32]. After repeated pairing of visual and auditory cues followed by reward in naïve macaque monkeys, the time of phasic activation of the VTA dopaminergic neurons changes from firing just after the reward is delivered to firing at the exact time the cue is presented [33]. Because this pattern of activity resembles the transfer of an animal's appetitive behavioral reaction from the unconditional to the conditional stimulus, these findings suggest that mesencephalic dopaminergic neurons actually encode expectations about external rewards by coding for an error value in prediction of reward [19,26,34]. In other words, when a reward is greater than expected, the firing of certain VTA dopaminergic neurons increases, consequently increasing the desire or motivation toward the reward in the OFC.

Dopamine release in the NAc has been linked to the efficacy of the unconditional rewards (such as food, water, intercourse), whereas dopamine release in a broader range of structures (Figure 1) has been implicated in the "stamping-in" of memory that attaches motivational importance to otherwise neutral stimuli [26,27]. By contrast, very few dopaminergic neurons respond to stimuli that predict aversive outcomes. It is mostly the posterior cingulate cortex (PCC), which mediates classical conditioning of negative (i.e., painful) stimuli in escape and avoidance learning ("aversive conditioning") [35].

The multifaceted, but critical roles of OFC in attachment behavior

The OFC is involved social reasoning, emotional control, and flexibility of decision making, particularly in moral dilemmas [2]. The meta-analysis of 267 areas of activation in stereotaxic space [36] showed that there is a medial to lateral distinction in the human OFC [37], such that activity in the medial OFC is related to the monitoring, learning and memory of the reward value of reinforcers, whereas lateral OFC activity is related to the evaluation of punishers that can lead to a change in behavior (Figure 3). Similarly, a posterior to anterior distinction was shown, with more complex or abstract reinforcers (such as monetary gain and loss) being represented more anteriorly in OFC than less complex reinforcers such as taste [38]. Compared to other cortical areas, OFC matures very late during development, perhaps in parallel with "social referencing" and psychosocial development [39].

As documented in experimental models using a "water vs. cocaine" paradigm, it is the OFC glutamatergic projections that regulate activation of motor responses to motivation-related events through thalamic motor nuclei and NAc, while blocking dopamine D1 receptors in OFC prevents drug-seeking behavior (direction of behavior or choice) [19]. In the case of a failure to achieve planned goals, particularly in the long-term when the free cortisol levels raise and are responsible for the sense of hunger (chronic stress), the reward mechanism is often activated by the compensatory displaced behavior, such as overeating (representing an easier and quicker way to achieve subjective feeling of satisfaction/reward). While many people also experiment with drugs, relatively few individuals develop a true addiction. Such individual differences might be determined by early emotional experience. In one experimental model maternally separated and non-handled animals were shown to be hyperactive when placed in a novel setting and displayed a dose-dependent higher sensitivity to cocaine and amphetamine-induced locomotor activity [40]. They also responded to a mild stressor (tail-pinch) with significantly greater increases in NAc dopamine levels, and had increased dopamine D3 receptor binding and mRNA levels. Due to changes in regulation of motivation circuits and pathological long-term alterations in synaptic plasticity of OFC neurons that project to the ventral striatum, in the last phase (dependence and drug abuse) such animals are looking for and taking drugs compulsively [40]. These findings provide a

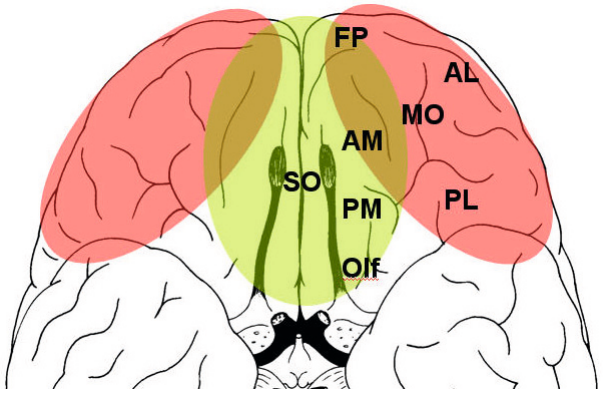

Figure 3. Activity in the medial orbitofrontal cortex (green ellipse) is related to the learning, monitoring and memory of the reward value of positive reinforcers, whereas lateral orbitofrontal cortex activity (red ellipses) is related to the evaluation of negative reinforcers (punishers). The scheme is based on [36,38]. OFC fields designation is made according to [37]. Legend: AL = anterolateral region, AM = anteromedial region, FP = frontopolar region, MO = medial orbitofrontal (central) region, Olf = olfactory tubercle, PL = posterolateral region, PM = posteromedial region, SO = sub-orbital cortex (inferior rostral sulcus).

clue that lack of care during early postnatal period can lead to profound and lasting changes in the emotional development and pattern of attachment (from secure to insecure) with consequent increased responsiveness of mesocortical and mesolimbic dopamine neurons to stress and stimulants.

It has been suggested that distorted attachment patterns grow out of the way the child learns to deal with his negative feelings. A secure child is able to communicate negative feelings, confident of a sensitive response. The insecure children do not have this confidence. As a result, his or her negative feelings are either increased to the point where become overwhelming or are being "walled off" from consciousness. The OFC control of behavior, particularly in opposition to emotional drive, can be so strong that even unwanted memories (such as sexual abuse in childhood) can be suppressed by reduction of hippocampal activation during a conscious recall [41].

The newer imaging studies showed that, besides OFC, the final decision-making (affective go/no-go decisions) relies strongly (in normal people) on interactions between the OFC and anterior cingulate cortex (ACC). When the function of ACC is no longer maintained because of inhibitory influence of amygdala (possibly also via the dopaminergic projections from VTA), the phenomenon of learned helplessness is elicited [42]. Further experiments led some researchers to propose that chronic failure, depression, and similar conditions are all forms of learned helplessness. Indeed, empirical studies confirmed that learned helplessness often occurs in children who are raised in harsh social environments where success is difficult to achieve. These children suffer motivational losses, most probably as a result of pathological synaptic plasticity in the reward circuit and particularly in OFC.

The OFC is also one specifically involved in recognition of mother's own infant distress. Infant cues, such as smiling or crying facial expressions, are powerful motivators of human maternal behavior that activate dopamine-associated reward circuits. It has been recently shown that mothers with secure attachment show greater activation of medial OFC, ventral striatum and the oxytocin-expressing hypothalamic regions, while insecure/dismissing mothers showed greater insular activation in response to their own infant's sad faces (see below).

Medial prefrontal cortex, theory of mind, and the importance of the mirror neuron system for attachment behavior

Primates, especially humans, stand out in their ability to attribute mental state to others. These abilities, globally known as theory of mind, are orchestrated by the medial prefrontal cortex [2], emerge at about four years of age and are probably assembled out of a collection of more basic skills by which we assign actions, goals and intentions to stimuli and imitate other people's behavior [2,43]. Imitating another subject's actions through observation activates the so-called mirror neurons. Mirror neurons were discovered in early 1990s by a group of researchers from Parma, Italy [44]. While conducting single-neuron recordings in the premotor cortex, they noticed that some of these neurons responded not only when the monkey was performing a certain act (e.g., grasping food) but also while the monkey was observing others performing the same motor action (*i.e.*, researcher grasping food in front of a monkey) [45]. However, in the following years a rapidly growing number of studies that were conducted on various experimental animals and humans justified the importance to elucidate location and function of these neurons (for review see [45-48]). Some of the most interesting functional implications for mirror neurons are their presumed roles in language evolution, bonding, and empathy.

The first mirror neurons were described in monkey ventral premotor cortex – area F5 [44], which has its human counterpart – the Broca language area (Brodmann's areas 44 and 45). Monkey's area F5 and Broca's area are found to be especially rich in mirror neurons. On the basis of these and other observations it has been proposed that vocalization and spoken language evolved from an expanded mirror neuron system located in the Broca's region [49]. Further evidence for mirror neuron involvement in language production was obtained from transcranial magnetic stimulation (TMS) studies showing facilitation of tongue [50] and lip [51] muscles, as well as functional MRI (fMRI) studies showing activation of mirror neurons while listening to speech [52]. More recently mirror neurons have been implicated in empathy ([53]; for review see [48]) and early maternal communication with a child [54]. This system comprised of mirror neurons in the frontal cortex, anterior insula and the limbic system has been found highly activated during mothers' observation of their infants. The system is significantly more activated during observation of mother's own child than someone else's [54] and this activity positively correlates with mothers' ability to interpret child's emotions. Dysfunctions in the mirror neuron system have been observed in several severe developmental disorders, for example in autism spectrum disorder ([55]; for review see [45,56,57]). In one of the recent studies that examined mirror neuron abnormalities in autism, high-functioning children with autism and matched controls underwent fMRI while imitating and observing emotional expressions [58]. Although both groups performed the tasks equally well, children with autism showed no mirror neuron activity in the opercular part of the inferior frontal gyrus. Actually, activity in this area was inversely related to symptom severity in the social domain, confirming that a dysfunctional mirror neuron system may be responsible for the deficits in social competencies observed in autism.

The special roles of amygdala in social referencing and attachment behavior

While investigating the evolution of emotional responses and facial expressions, it was Darwin who first proposed that emotions allow an organism to make adaptive responses to stimuli in the environment [59]. However, for many years, emotions remained an elusive scientific topic. In a simplified view, during the period of behaviorism (roughly between the 50s and mid-70s of the 20th century), except for a few visionary scientists [60,61], emotions

were generally not considered relevant and important for behavior. In the next period of "cognitive revolution" (roughly between 70s and 90s) emotions were generally defined in opposition to cognition as that which moves us in some way (as is implied by the Latin root *movere*, to move), but it was still generally believed that it is our "cognitive" minds that primarily affect the behavior. Finally, since early 90s to the present day, an "emotional revolution" in terms of number, scope and depth of scientific investigations devoted to emotions has been steadily expanding our knowledge on the subject, with each new study adding a data to the fact that emotions and emotional development affect enormously our thinking, behavior and psychopathology.

As they are mediated by multiple and overlapping neural networks, emotions represent complex behavioral states comprised of many components: autonomic (hormonal and visceral), cognitive (subjective feelings and thoughts), motor expressions (face, body, voice), conscious perceptive awareness, unconscious perception (for example of pheromones and other molecules that can induce different emotions, fearful faces in the blind part of the visual field – "fear blindsight", infant facial cues that serve to elicit parental instincts and bonding accompanied by increased aggressiveness toward perceived threats, etc.), attention (external and internal), memories, and others [62]. It seems that different emotions have different adaptive functions and underlying neural mechanisms. Key to emotion is readiness to act because emotions actually help making decisions and give priority to action, especially in situations in which an individual faces risk, conflict, or potential partner. Emotions are not discrete; rather they have dimensions (low to high arousal, pleasant vs. unpleasant valence, approach vs. avoidance, etc.). Some emotions last for several seconds, while others (such as moods) can last from a few minutes to several weeks. Finally, personality traits of emotional nature may be life-long. For all of these reasons, emotions are relatively easily recognized, but difficult to quantify [62]. According to Ekman and Friesen, there are 6 basic (primary) emotions (being afraid, angry, disgusted, happy, sad, and surprised) because these emotions are cross-culturally recognized regardless of experience [63]. Primary emotions are innate (inborn) and appear by the middle of the first postnatal year. They remain a part of the basic palette of emotional repertoire during lifetime. However, the circumstances which evoke them change with age (due to maturation) and socialization (due to changing goals: an emotion is experienced when evaluating an event as relevant to some important goal – it is positive if advances goal and negative if impedes goal). Fear normally appears at 6 to 7 months of age [64]. Two particularly important early fears are a fear of strangers (stranger anxiety) and a discomfort at being separated from caregivers (separation anxiety).

By 7 to 10 months of age, infants are capable of "social referencing", which enables them to asses how they ought to be feeling or behaving in a variety of uncertain situations. During the second and third year of age secondary (social) emotions of guilt, shame, embarrassment, jealousy, pride and others develop. These emotions require an extended representation of one-self as situated within the society [2]. Social emotions function to comply with culturally defined emotional display rules and to regulate social behaviors often in the long-term interests of a social group rather than the short-term interests of the individual. Since emotional socialization is being fostered by detailed elaboration of emotions through the dialogue with a primary caregiver, feral children do not develop secondary emotions. Young infants are almost totally dependent on caregivers to calm them and regulate their distress. By the end of the first year, infants develop various strategies for regulate negative emotions, and during the preschool years they develop strategies to moderate or sometimes intensify emotional arousal to achieve their objectives [64]. As previously stated, distorted attachment patterns seem to grow out of the way the child learns to deal with negative feelings. A secure child is able to communicate negative feelings, confident of a sensitive response, whereas the insecure children do not have this confidence.

There is accumulated evidence that the amygdala represents the emotional center within the human brain, which gives emotional (affective) tone to the sensory information input even before its conscious (cortical) processing (the so-called emotional filter). In patients with frontal lobe damage, a tendency to forget how information is acquired can often be seen. However, even when the original information (fact) is not retained, the emotional tone and context (e.g., the tone of voice) remains (source amnesia) [62]. This happens particularly when the source of information is unreliable, such as media. Through direct reciprocal connections with the hypothalamus, the amygdala influences regulation not only of endocrine functions, but also autonomic component of emotional expressions and behaviors aimed at individual and collective survival. In addition, one of the most important of its specializations is recognition of facial expressions.

Facial expressions convey information about identity, mood, and intention. Emotions read from facial expressions are not specified by a single facial cue, but multiple, so that signal value is remarkably robust [65]. Such diverse information is analyzed in an extensive network that, besides amygdala, includes large regions of the inferior frontal, posterior temporal, parietal and occipital cortices, the extended amygdala (bed nucleus of stria terminalis, shell of NAc) and associated paralimbic cortex, and the hypothalamus.

All animals inherently detect and respond to danger, and the related neural activities in the amygdala evolve to produce a feeling – in this case, fear. Our fear system includes both unconscious fear responses (through genetically-programmed networks that mediate "instinctive" behaviors) and conscious awareness of subjective feelings and thoughts of fearful stimuli (through massive reciprocal frontolimbic connections shaped by learning from experience about dangerous stimuli for which evolution could not prepare us). However, not all learning is beneficial. It is clear that disorders of the hippocampal formation interfere with the development of contextual fear associations. Panic disorder, post-traumatic stress disorder, obsessive-compulsive disorder,

anxiety and phobias illustrate the extreme power of fear-related events to affect cognition by classical fear conditioning, suggesting that evolution has crafted a powerful mechanism for forming such associations [62].

Lesions of the right and left hemispheres have different effects on emotional behaviors. Left-hemisphere lesions produce catastrophic reactions characterized by fearfulness and depression, while damage to the right hemisphere appears to produce larger effects, mostly indifference, or flattening of mood. It seems that the left amygdala plays a special role in generating fear. Subjects with bilateral lesions of amygdala (such as in Rössle-Urbach-Wiethe syndrome due to selective bilateral calcification of amygdala) are impaired at recognizing negative expressions (such as fear), but not at recognizing happy faces (besides loss of fear, they are also unable to comprehend social signals and modulate episodic memory emotionally) [62]. Overall, the two sides of the brain play balancing and harmonizing roles in emotional behavior, the right being more engaged in the automatic components of emotion and generation of emotional feelings, whereas the left being engaged in the overall cognitive control of emotion (presumably because "speaking" hemisphere acts like an "interpreter" of these feelings) and affective behavior [62].

Promotion and maintenance of the parental bonding through various neuropeptide systems, mainly oxytocinergic

Ensuring offspring survival, the early attachment relationship between infants and their parents lies at the heart of emotional and social development of all mammals. The relationship between a mother and her infant is particularly important because the processes of pregnancy, parturition and lactation additionally contribute to the establishment of the strong mother-infant bond. Several recent studies are adding to a body of literature which shows that various neuropeptides, mainly oxytocin (OXT), vasopressin, corticotropin-releasing factor (CRF) and endogenous opioids systems play a key role in promoting and maintaining maternal bonding and social affiliation. Feldman and colleagues [66] demonstrated this association for the first time in humans. Plasma OXT levels across pregnancy and postpartum period in 62 pregnant women predicted mother-infant bonding. Women with higher levels of OXT bonded better with their babies. Levels of OXT positively correlated with a clearly defined set of maternal behaviors including gaze, vocalization, positive affect, affectionate touch, attachment-related thoughts and to frequent checking of the infant [66]. OXT is a 9-amino-acid peptide synthesized in the paraventricular and supraoptic nucleus (Figure 2) of the hypothalamus. Its release into the circulation by axon terminals in the posterior pituitary occurs within seconds of stimulation such as infant suckling, touch, or even the sight or sound of a nursing mother, having half-life of about 6-7 minutes.

Intranasal OXT administration improves eye-gaze when viewing faces, enhances recognition and memory of facial expressions and increases manifestations of trust [67,68]. Since oxytocin receptors are particularly abundant in NAc and other regions of the ventral striatum, where OXT binding is linked functionally to maternal behavior [69], besides OXT well-known central (onset of maternal behavior) and peripheral actions (uterine contraction during labor and milk ejection during lactation), it also may likely serve to link social cues (such as infant facial expressions) with dopamine-associated reinforcement pathways. This has been recently further substantiated by the demonstration that mothers with secure attachment show greater activation of medial OFC (as a potential site of parental instinct), ventral striatum and the OXT-associated hypothalamic regions by infant cues (whether positive or negative in affect) thus reinforcing and motivating responsive maternal care, while insecure/dismissing mothers showed relatively greater activation of the anterior insular cortex in the right hemisphere (a cortical region associated with feelings of unfairness, disgust and pain) in response to their own infant's sad faces [70]. Likewise, animal studies demonstrated a developmental relationship between exposure to extra OXT in early life and subsequent maternal and social behaviors [71]. For instance, when prairie voles had received a low dose of OXT in early life, adult females were slow to approach pups; when they received higher doses of the hormone were more likely to care for them (and, interestingly, no longer displayed a partner preference too) [72].

An early study had shown that children with autism have lower levels of circulating OXT [73], while adults diagnosed with autism or Asperger's syndrome who received OXT showed an improved ability to identify emotional content on a speech comprehension task (whereas those on a placebo did not) [74]. Moreover, when urine levels of OXT and vasopressin were compared in two sets of children—one raised from birth with their biological parents and one adopted after living in orphanages in Russia and Romania—following contact with their mothers the levels of OXT rose in the biological children but remained the same in the adopted children [75]. Comparing the normalized glucose metabolic rates to those of normal adults, the Romanian orphans showed significantly decreased metabolism bilaterally in the OFC, the prefrontal cortex, the medial temporal structures (amygdala and head of hippocampus), the lateral temporal cortex, and brainstem [76]. Altogether, these findings suggest that a failure of development of various neuropeptide systems, mainly oxytocinergic, may represent the biological underpinnings for the observation that some adopted children, in particular those from deprived circumstances, have difficulty forming secure relationships, despite living in loving homes. A recent case report of a lower CSF OXT concentration in women with a history of childhood abuse further indicates that childhood trauma might cause long-lasting alterations in central nervous system function [77].

One of the newest studies also showed clear association of OXT and prolactin plasma levels with the father-infant affect synchrony in the social context and father-infant coordinated exploratory play, respectively [78]. Furthermore, it has been shown that interactions with dogs, especially those initiated by the dog's gaze, increase the urinary OXT concentrations of

their owners as a manifestation of attachment behavior [79]. These and other results open new research and therapeutic avenues aimed at better understanding of various neuropeptide systems involvement in the development of human fathering and inter-species social bonding, but also both maternal and romantic love and other adaptive social behaviors [80].

Genetic influences on attachment behavior

Stresses caused by experiences, such as abuse of alcohol and drugs, smoking, poverty, neglect, or sensory deprivation, can switch genes on or off at the wrong times, forcing them to build abnormal neuronal networks. Regardless of their social or economic status, however, some children seem to be genetically more vulnerable to stress. By using gene knockout technology, at least 12 different genes have been identified as necessary for the expression of one or more aspects of parental bonding and attachment behavior (Table 2) [81-84]. Stressful environments may cause these and other, yet undiscovered genes important for survival, to become under- or overexpressed, sometimes making individuals more aggressive, violent, or depressed.

Slight modulations in serotonin levels, turnover, and metabolism, or in receptor type activation, density, and binding activity seem to be particularly important in this respect because it may strongly condition aggressive behavior. For example, children carrying the short form of the mono-amino oxidase A (MAO-A) promoter gene, which confers decreased MAO-A activity, are more likely to develop conduct disorders and increased antisocial behavior when exposed to abusive home environments [85,86]. Unmet needs for social bonding and acceptance early in life might also increase the emotional attractiveness of gangs or sects, with violent and authoritarian values and leadership [87]. The OFC and the amygdala have been both implicated in violent behavior, especially if their activity is compromised early in life [88,89]. Namely, developmental frontal lobe damage often result in impairments similar to those seen in psychopaths, notably an inability to know right from wrong in moral action. Criminal psychopaths show structural abnormalities (reduced grey-to-white matter ratio) in PFC [89] and abnormal activation of OFC and the amygdala in fMRI studies [90,91], together with reduced autonomic emotional responsivity.

Epigenetic influences on attachment behavior

The term 'epigenetic' refers to chromatin modifications that alter gene expression without affecting DNA sequence. Epigenetic control of gene expression is mediated via multiple post-translational modification of histone proteins (methylation, acetylation and ubiquitination, which can alter the accessibility of DNA and the density of chromatin structure), microRNA and DNA methylation [3]. There is an increasing body of evidence for the role of epigenetic factors in sustaining the effects of environmental experience in the context of both the pre- and postnatal mother-infant interactions. For instance, in hypothalamus of adult male mice born to gestationally stressed females a decreased DNA methylation of the CRF gene promotor and increased methylation of the glucocorticoid receptor exon 1_7 promotor (GR exon 1_7) has been recently demonstrated [92]. Some of the postnatal examples are findings of decreased promotor methylation of rat hippocampal GR exon 1_7 and hypothalamic estrogen receptor alpha (ERα) genes associated with low levels of maternal care [93,94], increased promotor methylation of GR 1F in fetal blood samples of depressed mothers [95] and increased methylation of exon IV of the brain-derived neurotrophic factor (BDNF) and consequent decrease in BDNF mRNA in PFC after abusive maternal care in rats [96].

Besides high levels of maternal care, an exposure to juvenile environmental enrichment has also been shown to improve the capacity for learning and memory through LTP enhancement due to activity of NMDAr/p38 signaling pathway [97], increased histone acetylation in the hippocampus [98] and improved contextual fear conditioning [99]. Moreover, DNA methylation through methyl-CpG-binding protein 2 (MeCP2) pathway has been shown to occur in response to synaptic activity [100,101], suggesting another epigenetic mechanism through which neurons can adjust neurotransmitter output, dendritic growth and spine maturation (with consequent changes in network excitability and circuit refinement). Impairments in MeCP2 pathway may lead to developmental brain abnormalities such as Rett syndrome, autism, mental retardation and schizophrenia [102], whereas targeted deletion of MeCP2 in the amygdala impair learning and memory and lead to increased anxiety-like behavior in mice [103].

Conclusions

Neglect and abuse during early life may cause bonding systems to develop abnormally and compromise the capacity for rewarding interpersonal relationships and commitment to social and cultural values later in life. Means of stimulating the reward pathways in the brain, such as drugs, sex, aggression, and intimidating others, can then become more attractive and less constrained about violating trusting relationships. All types of attachment behavior and bonding are accompanied by increased aggression toward perceived threats to the object of attachment as well as diminished fear and anxiety in stressful situations [87].

Because „therapies based on mirror neuron system could provide a non-invasive approach in treatments of emotional disorders" [104], the relationship of the (right) frontoparietal mirror neuron system - a distinct class of neurons that transform specific sensory information to motor activity that appears to be important to all aspects of social cognition and learning - as a neural substrate for understanding emotions in others (empathy) represents an important avenue for future research.

Acknowledgement

We thank the late Edita Schubert for drawing Fig. 2.

Table 2. Summary of knock-out studies on genetics of maternal behavior (from references [81-84]).

Gene	Observed deficit in maternal behavior	Preserved maternal behavioral capacities
FosB Transcription factor	Maternal behavior: Nest building Pup retrieval Crouching Nursing Sensitization: Pup retrieval	Maternal behavior: Exploration and sniffing of pups Sensitization: Exploration and sniffing of pups
Peg3 Paternal expressed gene-3 Transcription factor	Maternal behavior: Nest building Pup retrieval Crouching Nursing Sensitization: Nest building Pup retrieval	Maternal behavior: Exploration and sniffing of pups
Fkh5 Fork head-5 Transcription factor	Maternal behavior: Nest building Pup retrieval Crouching Nursing	
Mest/Peg1 Mesoderm specific transcript/Paternal expressed gene-1 Enzyme	Maternal behavior: Nest building Pup retrieval Crouching Nursing Placentophagia Sensitization: Nest building Pup retrieval	Maternal behavior: Exploration and sniffing of pups Sensitization: Exploration and sniffing of pups
Dbh Dopamine beta hydroxylase Enzyme	Maternal behavior: Nest building Pup retrieval Crouching Nursing Placentophagia Sensitization: Nest building Pup retrieval	
nNOS Neural Nitric oxide synthetase Enzyme	Maternal behavior: Aggression	Maternal behavior: Nest building Exploration and sniffing of pups Pup retrieval
ERα Estrogen α receptor Receptor	Maternal behavior: Unable to evaluate Sensitization: Pup retrieval	Maternal behavior: Unable to evaluate
PRLR Prolactin receptor Receptor	Maternal behavior: Nest building Pup retrieval Crouching Nursing Sensitization: Pup retrieval	Maternal behavior: Exploration and sniffing of pups Sensitization: Exploration and sniffing of pups
Oxytocin Neuropeptide	Maternal behavior: Effective nursing	Maternal behavior: Nest building Exploration and sniffing of pups Pup retrieval Placentophagia Crouching Aggression
CRFR1 Corticotropin-releasing factor receptor I Receptor	Maternal behavior: Nursing, licking and grooming of pups Maternal aggression	Maternal behavior: Pup retrieval Nest building
CRF-BP Corticotropin-releasing factor binding protein	Maternal behavior: Maternal aggression	
TRPC2 Ion channel	Maternal behavior: Nest building Maternal aggression	

References

[1] Sameroff A., A unified theory of development: a dialectic integration of nature and nurture, Child Dev., 2010, 81, 6-22

[2] Adolphs R., Cognitive neuroscience of human social behavior, Nature Neurosci., 2003, 4, 165-178

[3] Fagiolini M., Jensen C.L., Champagne F.A., Epigenetic influences on brain development and plasticity, Curr. Opin. Neurobiol., 2009, 19, 207-212

[4] Rutter M., Clinical implications of attachment concepts: retrospect and prospect, J. Child Psychol. Psychiatr., 1995, 36, 549-571

[5] Cassidy J., The nature of child's ties, In: Handbook of attachment: theory, research and clinical applications (eds. Cassidy J, Shaver PR), New York: Guilford Press, 1999, 3-20

[6] Bowlby J., The nature of the child's tie to his mother, Int. J. Psychoanal., 1958, 39, 350-373

[7] Ainsworth M.D., Blehar M., Waters E., Wall S., Patterns of attachment: a psychological study of the Strange Situation, Hillsdale NJ: Lawrence Erlbaum Associates, 1978

[8] Weinfield N.S., Sroufe L.A., Egeland B., Carlson E., Individual differences in infant-caregiver attachment, In: Handbook of attachment: theory, research and clinical applications (eds. Cassidy J, Shaver PR), New York and London: Guilford Press, 2008, 78-101

[9] Main M., Solomon J., Discovery of an insecure disoriented attachment pattern: procedures, findings and implications for the classification of behavior, In: Affective development in infancy (eds. Brazelton T, Youngman M), Norwood, NJ: Ablex, 1986

[10] Prior V., Glaser D., Understanding attachment and attachment disorders: theory, evidence, and practice, Jessica Kingsley Publishers: London and Philadelphia, 2006

[11] Karen R., Becoming attached: first relationships and how they shape our capacity to love, New York: Oxford University Press, 1994

[12] Marvin R.S., Britner P.A., Normative development: the ontogeny of attachment, In: Handbook of attachment: theory, research and clinical applications (eds. Cassidy J, Shaver PR), New York and London: Guilford Press, 2008, 269-294

[13] Kobak R., Madsen S., Disruption in attachment bonds, In: Handbook of attachment: theory, research and clinical applications (eds. Cassidy J, Shaver PR), New York and London: Guilford Press, 2008, 23-47

[14] Fraley R.C., Shaver P.R., Adult romantic attachment: theoretical developments, emerging controversies, and unanswered questions, Rev. Gen. Psychol., 2000, 4, 132-154

[15] Rholes W.S., Simpson J.A., Attachment theory: basic concepts and contemporary questions, In: Adult attachment: theory, research, and clinical implications (Rholes WS, Simpson JA, eds), New York: Guilford Press, 2004, 3-14

[16] Main M., Kaplan N., Cassidy J., Security in infancy, childhood and adulthood: a move to the level of representation, In: Growing points of attachment theory and research (Bretherton I, Waters E, eds), Chicago: University of Chicago Press, 1985

[17] Steele H., Steele M., Fonagy P., Associations among attachment classifications of mothers, fathers, and their infants, Child Dev., 1996, 67, 541-555

[18] Wise R.A., Bozarth M.A., Brain reward circuitry: four circuit elements „wired" in apparent series, Brain Res. Bull., 1984, 12, 203-208

[19] Arrias-Carrión O., Pöppel E., Dopamine, learning, and reward-seeking behavior, Acta Neurobiol. Exp., 2007, 67, 481-488

[20] Burgdorf J., Panksepp J., The neurobiology of positive emotions, Neurosci. Biobehav. Rev. 2006, 30, 173-187

[21] Olds J., Milner P., Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain, J. Comp. Physiol. Psychol., 1954, 47, 419-427

[22] Olds M.E., Olds J., Emotional and associative mechanisms in the rat brain, J. Comp. Physiol. Psychol., 1961, 54,120-26

[23] Moan C.E., Heath R.G., Septal stimulation for the initiation of heterosexual activity in a homosexual male, J. Behav. Ther. Exp. Psychiatr., 1972, 3, 23-30

[24] Gardner E.L., Lowinson J.H., Drug craving and positive/negative hedonic brain substrates activated by addicting drugs, Sem. Neurosci., 1993, 5, 359-368

[25] Giros B., Jaber M., Jones S.R., Wightman R.M., Caron M.G., Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter, Nature, 379, 606-612

[26] Wise R.A., Dopamine, learning and motivation, Nat. Rev. Neurosci., 2004, 5, 483-494

[27] Lisman J.E., Grace A.A., The hippocampal-VTA loop: controlling the entry of information into long-term memory, Neuron, 2005, 46, 703–713

[28] Pierce R.C., Kumaresan V., The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse?, Neurosci. Biobehav. Rev. 2006, 30, 215-238

[29] Rothman R.B., Baumann M.H., Balance between dopamine and serotonin release modulates behavioral effects of amphetamine-type drugs, Ann. N.Y. Acad. Sci., 2006, 1074, 245-260

[30] Kahlig K.M., Binda F., Khoshbouei H., Amphetamine induces dopamine efflux through a dopamine transporter channel, Proc. Natl. Acad. Sci. USA, 2005, 102, 3495-3500

[31] Gonzales R.A., Job M.O., Doyon W.M., The role of mesolimbic dopamine in the development and maintenance of ethanol reinforcement, Pharmacol. Ther., 2004, 103, 121–146

[32] Gardner E.L., Endocannabinoid signaling system and brain reward: emphasis on dopamine, Pharmacol. Biochem. Behav., 2005, 81, 263-284

[33] Schultz W., Dayan P., Montague P.R., A neural substrate of prediction and reward, Science, 1997, 275, 1593-1599

[34] Schultz W., Behavioral theories and the neurophysiology of reward, Annu. Rev. Psychol. 2006, 57, 87-115

[35] Bromm B., Brain images of pain, News Physiol. Sci., 2001, 16, 244-249

[36] Kringelbach M.L., Rolls E.T., The functional neuroanatomy of the

human orbitofrontal cortex: evidence from neuroimaging and neuropsychology, Prog. Neurobiol., 2004, 72, 341-372

[37] Hof P.R., Mufson E.J., Morrison J.H., Human orbitofrontal cortex: cytoarchitecture and quantitative immunohistochemical parcellation, J. Comp. Neurol., 1995, 359, 48-68

[38] Kringelbach M.L., The human orbitofrontal cortex: linking reward to hedonic experience, Nat. Rev. Neurosci., 2005, 6, 691-702

[39] Gogtay N., Giedd J.N., Lusk L., Hayashi K.M., Greenstein D., Vaituzis A.C., et al., Dynamic mapping of human cortical development during childhood through early adulthood. Proc. Natl. Acad. Sci. USA, 2004, 101, 8174-8179

[40] Brake W.G., Zhang T.Y., Diorio J., Meaney M.J., Gratton A., Influence of early postnatal rearing conditions on mesocorticolimbic dopamine and behavioral responses to psychostimulants and stressors in adult rats, Eur. J. Neurosci., 2004, 19, 1863-1874

[41] Anderson M.C., Ochsner K.N., Kuhl B., Cooper J., Robertson E., Gabrieli S.W. et al.,Neural systems undelying the suppression of unwanted memories, Science, 2004, 303, 232-235

[42] Bauer H., Pripfl J., Lamm C., Prainsack C., Taylor N., Functional neuroanatomy of learned helplessness, Neuroimage, 2003, 20, 927-939

[43] Siegal M., Varley R., Neural systems involved in 'theory of mind', Nat. Rev. Neurosci. 2002, 3, 463-471

[44] Di Pellegrino G., Fadiga L., Fogassi L., Gallese V., Rizzolatti G., Understanding motor events: a neurophysiological study, Exp. Brain Res., 1992, 91, 176-180

[45] Rizzolatti G., Fabbri-Destro M., Mirror neurons: from discovery to autism, Exp. Brain Res., 2010, 200, 223-237

[46] Rizzolatti G., Craighero L., The mirror-neuron system, Annu. Rev. Neurosci., 2004, 27, 169-9

[47] Fabbri-Destro M., Rizzolatti G., The mirror system in monkeys and humans, Physiology, 2008, 23, 171-179

[48] Iacoboni M., Imitation, empathy, and mirror neurons, Annu. Rev. Psychol., 2009, 60, 653-670

[49] Rizzolatti G., Arbib M.A., Language within our grasp, Trends Neurosci., 1998, 21, 188-194

[50] Fadiga L., Craighero L., Buccino G., Rizzolatti G., Speech listening specifically modulates the excitability of tongue muscles: s TMS study, Eur. J. Neurosci., 2002, 15, 399-402

[51] Watkins K.E., Strafella A.P., Paus T., Seeing and hearing speech excites the motor system involved in speech production, Neuropsychologia, 2003, 41, 989-994

[52] Wilson S.M., Saygin A.P., Sereno M.I., Iacoboni M., Listening to speech activates motor areas involved in speech production, Nat. Neurosci., 2004, 7, 701-702

[53] Carr L., Iacoboni M., Dubeau M.C., Mazziotta J.C., Lenzi G.L., Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas, Proc. Natl. Acad. Sci. USA, 2003, 100, 5497-5502

[54] Lenzi D., Trentini C., Pantano P., Macaluso E., Iacoboni M., Lenzi G.I., et al., Neural basis of maternal communication and emotional expression processing during infant preverbal stage, Cereb. Cortex, 2009, 19, 1124-1133

[55] Williams J.H.G., Whiten A., Suddendorf T., Perrett D.I., Imitation, mirror neurons, and autism, Neurosci. Biobehav. Rev., 2001, 25, 287-295

[56] Iacoboni M., Dapretto M., The mirror neurons system and the consequences of its dysfunction, Nat. Rev. Neurosci., 2006, 7, 942-951

[57] Rizzolatti G., Fabbri-Destro M., Cattaneo L., Mirror neurons and their clinical relevance, Nat. Clin. Pract. Neurol., 2009, 5, 24-34

[58] Dapretto M., Davies M.S., Pfeifer J.H., Scott A.A., Sigman M., Bookheimer S.Y. et al., Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorder, Nat. Neurosci., 2006, 9, 28-30

[59] Darwin C.R., The expression of emotions in man and animals, London: John Murray, 1872

[60] Plutchik R., Outlines of a new theory of emotion, Trans. NY Acad. Sci., 1958, 20, 394-403

[61] Russell P.A., A circumplex model of affect, J. Pers. Soc. Psychol., 1971, 39, 1161-1178

[62] Kolb B., Whishaw I.Q. (eds.), Fundamentals of human neuropsychology, 6th edition, Worth Publishers, 2008

[63] Ekman P., Friesen W.V., Constants across culture in the face and emotion, J. Pers. Soc. Psychol., 1971, 17, 124-129

[64] Shaffer D.R., Social and personality development, 6th edition, Belmont, CA: Wadsworth, 2009

[65] Oster H., Emotion in the infant's face: insights from the study of infants with facial anomalies, Ann. NY Acad. Sci., 2003, 1000, 197-204

[66] Feldman R., Weller A., Zagoory-Sharon O., Levine A., Evidence for a neuroendocrinological foundation of human affiliation: plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding, Psychol. Sci., 2007, 18, 965-970

[67] Baumgartner T., Heinrichs M., Vonlanthen A., Fischbacher U., Fehr E, Oxytocin shapes the neural circuitry of trust and trust adaptation in humans, Neuron, 2008, 58, 639-650

[68] Guastella A.J., Mitchell P.B., Dadds M.R., Oxytocin increases gaze to the eye region of human faces, Biol. Psychiatry, 2008, 63, 3-5

[69] Olazábal D.E., Young L.J., Oxytocin receptors in the nucleus accumbens facilitate „spontaneous" maternal behavior in adult female prarie voles, Neuroscience, 2006, 141, 559-568

[70] Strathearn L., Fonagy P., Amico J., Montague P.R., Adult attachment predicts maternal brain and oxytocin response to infant cues, Neuropsychopharmacology, 2009, 34, 2655-2666

[71] Bales K.L., van Westerhuyzen J.A., Lewis-Reese A.D., Grotte N.D., Lanter J.A., Carter C.S., Oxytocin has dose-dependent developmental effects on pair-bonding and alloparental care in female prairie voles, Horm. Behav., 2007, 52, 274-279

[72] Ahern T.H., Young L.J., The impact of early life family structure on adult social attachment, alloparental behavior, and the neuropeptide systems regulating affiliative behaviors in the monogamous prairie vole (Microtus ochrogaster), Front. Behav. Neurosci., 2009, 3, 1-19

[73] Modahl C., Green L., Fein D., Morris M., Waterhouse L., Feinstein C., et al., Plasma oxytocin levels in autistic children, Biol. Psychiatry, 1998, 43, 270-277

[74] Hollander E., Bartz J., Chaplin W., Phillips A., Sumner J., Soorya L., et al., Oxytocin increases retention of social cognition in autism, Biol. Psychiatry, 2007, 61, 498-503

[75] Fries A.B., Ziegler T.E., Kurian J.R., Jacoris S., Pollak S.D., Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior, Proc. Natl. Acad. Sci. USA, 2005, 102, 17237-17240

[76] Chugani H.T., Behen M.E., Muzik O., Juhász C., Nagy F., Chugani D.C., Local brain functional activity following early deprivations: a study of post-institutionalized Romanian orphans, Neuroimage, 2001, 14, 1290-1301

[77] Heim C., Young L.J., Newport D.J., Mletzko T., Miller A.H., Nemeroff C.B., Lower CSF oxytocin concentrations in women with a history of childhood abuse, Mol. Psychiatry, 2009, 14, 954-958

[78] Gordon I., Zagoory-Sharon O., Leckman J.F., Feldman R., Prolactin, oxytocin, and the development of paternal behavior across the first six months of fatherhood, Horm. Behav., 2010, Epub ahead of print

[79] Nagasawa M, Kikusui T, Onaka T, Ohta M, Dog's gaze at its owner increases owner's urinary oxytocin during social interaction, Horm. Behav., 2009, 55, 434-441

[80] Neumann I.D., The advantage of social living: brain neuropeptides mediate the beneficial consequences of sex and motherhood, Front. Bioendocrinol., 2009, 30, 483-496

[81] Leckman J.F., Herman A.E., Maternal behavior and developmental psychopathology, Biol. Psychiatry, 2002, 51, 27-43

[82] Gammie S.C., Bethea E.D., Stevenson S.A., Altered maternal profiles in corticotropin-releasing factor receptor 1 deficient mice, BMC Neurosci, 2007, 8, 17 doi:10.1186/1471-2202-8-17

[83] Gammie S.C., Seasholtz A.F., Stevenson S.A., Deletion of corticotropin-releasing factor binding protein selectively impairs maternal, but not intermale aggression, Neuroscience, 2008, 157, 502-512

[84] Hansen N.S., Gammie S.C., Trpc2 gene impacts on maternal aggression, accessory olfactory bulb anatomy and brain activity, Gene Brain Behav, 2009, 8, 639-649

[85] Caspi A., McClay J., Moffitt T.E., Mill J., Martin J., Craig I.W., et al., Role of genotype in the cycle of violence in maltreated children, Science, 2002, 297, 851-854

[86] Nelson R.J., Trainor B.C., Neural mechanisms of aggression, Nat. Rev. Neurosci., 2007, 8, 536-546

[87] Pedersen C.A., Biological aspects of social bonding and the roots of human violence, Ann NY Acad SCI, 2004, 1036, 106-127

[88] Anderson S.W., Bechara A., Damasio H., Tranel D., Damasio A.R., Impairment of social and moral behavior related to early damage in human prefrontal cortex, Nat. Neurosci., 1999, 2, 1032-1037

[89] Raine A., Lencz T., Bihrle S., LaCasse L., Coilletti P., Reduced prefrontal grey matter volume and reduced autonomic activity in antisocial personality disorder. Arch. Gen. Psychiatry 2000, 57, 119-127

[90] Kiehl K.A., Smith A.M., Hare R.D., Mendrek A, Forster B.B., Brink J., et al., Limbic abnormalities in affective processing by criminal psychopats as revealed by functional magnetic resonance imaging, Biol Psychiatry 2001, 50, 677-684

[91] Le Doux J.E., Emotion circuits in the brain, Annu. Rev. Neurosci., 2000, 24, 155-184

[92]Mueller B.R., Bale T.L., Sex-specific programming of offspring emotionality after stress early in pregnancy, J. Neurosci., 2008, 28, 9055-9065

[93] Champagne FA, Weaver IC, Diorio J, Dymov S, Szyf M, Meaney MJ, Maternal care associated with methylation of the estrogen receptor-alpha1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring, Endocrinology, 2006, 147, 2909-2915

[94] Weaver I.C., Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl J.R., et al., Epigenetic programming by maternal behavior, Nat. Neurosci., 2004, 7, 847-854

[95] Oberlander T.F., Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin A.M., Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol stress responses, Epigenetics, 2008, 3, 97-106

[96] Roth TL, Lubin FD, Funk AJ, Sweatt JD, Lasting epigenetic influence of early-life adversity on the BDNF gene, Biol. Psychiatry, 2009, 65, 760-769

[97] Champagne DL, Bagot RC, van Hasselt F, Ramakers G, Meaney MJ, de Kloet ER, et al., Maternal care and hippocampal plasticity: evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress, J. Neurosci., 2008, 28, 6037-6045

[98] Fischer A, Sananbenesi F, Wang X, Dobbin M, Tsai LH, Recovery of learning and memory is associated with chromatin remodelling, Nature, 2007, 447, 178-182

[99] Arai JA, Li S, Hartley DM, Feig LA, Transgenerational rescue of a genetic defect in long-term potentiation and memory formation by juvenile enrichment, J. Neurosci., 2009, 29, 1496-1502

[100] Zhou Z., Hong E.J., Cohen S., Zhao W.N., Ho H.Y., Schmidt L., et al., Brain-specific phosphorylation of MeCP2 regulates activity-dependent BDNF transcription, dendritic growth, and spine maturation, Neuron, 2006, 52, 255-269

[101] Nelson E.D., Kavalali E.T., Monteggia L.M., Activity-dependent suppression of miniature neurotransmission through the regulation of DNA methylation, J. Neurosci., 2008, 28, 395-406

[102] Moretti P, Zoghbi H.Y., MeCP2 dysfunction in Rett syndrome and related disorders, Curr. Opin. Genet. Dev., 2006, 16, 276-281

[103] Adachi M, Autry A.E., Covington H.E., Monteggia L.M., MeCP2-mediated transcription repression in the basolateral amygdala may underlie heightened anxiety in a mouse model of Rett syndrome, J. Neurosci., 2009, 29, 4218-4227

[104] Leslie K.R., Johnson-Frey S.H., Grafton S.T., Functional imaging of face and hand imitation: towards a motor theory of empathy, Neuroimage, 2004, 21, 601-607