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Physiological pathways to rapid prosocial evolution

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Dogs (*Canis lupus familiaris*) descend from wolves (*Canis lupus*) sharing the same ecological niche of cooperative hunters, as humans. Initially, humans and wolves were competitors starting interspecific communication in order to avoid risk of injury. The evolutionary continuity of mammalian brains enabled interspecific prosocial contacts between both of them, which reduced stress, and enabled behavioral cultures leading to genetic isolation of those wolves. Dogs are the first domesticated animal living together with humans for about 25,000 years. Domestication means decreased aggression and flight distance toward humans, thus changes in the stress axis are crucial. The hypothesis of Active Social Domestication considers genetic selection as a necessary prediction but not a sufficient explanation of dog domestication. In addition, dog domestication is suggested to be an epigenetic disclosure. Due to changed stress activity, epigenetic mechanisms affect cerebral receptor activity and regulate transposon expressions, thus shaping brain function and behavior. Interspecific prosocial contacts initiated via serotonin release an enzymatic cascade enhancing, epigenetically, the glucocorticoid negative feedback loop. Reduced chronic stress improved social learning capability and inhibitory control. Over time, those wolves could integrate themselves into human social structures, thus becoming dogs. In analogy, human mental skills, such as creating art and culture, might have also improved during the Upper Paleolithic.

HYPOTHESES OF DOG DOMESTICATION

Today, it is commonly accepted that dogs were domesticated as the first animal about 25,000 years ago (Thalmann et al., 2013). Researchers are still figuring out, why and how this domestication process started, wondering how a wolf as a predator and competitor to humans could become a dog known as "man's best friend."

The first hypothesis of dog domestication supported by Lorenz (1967) and Zimen (1977) considered human hand-reared wolf pups as dog's ancestors. But even a hand-reared pup is, as an adult wolf, a potential risk for humans (Kubinyi et al., 2007). Coppingers and Coppinger (2001) argued that waste dumps as a new ecological niche were the place where dogs evolved. Those scavenging wolves were considered to have shown higher reproductive success compared to strictly hunting wolves; thus, they had been selected over time for more tolerance toward humans in a process of self-domestication. However, archeologists proclaim that waste dumps are a characteristic of modern times (Havlicek, 2015; Pichtel, 2005). In addition, it is commonly agreed that dog domestication began in the Upper Paleolithic period, but human settlement started only in the Neolithic period (Shipman, 2015; Thalmann et al., 2013). Therefore, the hypothesis of dog domestication at the waste dump also appears rather unlikely, although the idea of a self-domestication is still plausible because intentional breeding of wild wolves could not have been accomplished by hunter–gatherers without chains or stables (Jung & Pörtl, 2018). Therefore, genetic selection caused by intentional breeding cannot be the initiating first step of domestication from wolf to dog, although it surely played an important role in further dog breeding. Hare et al. (2012) evolved a hypothesis of self-domestication concerning primates and dogs in which social and friendly behavior is suggested to be the selective criterion of the self-domestication process. Our recent efforts suggest the hypothesis of Active Social Domestication (ASD; Pörtl & Jung, 2017) as a possible model of dogs' self-domestication. About 45,000 years before our time, ancient wolves lived in cohabitation but also in competition with humans; hence, meeting each other during a hunt or while scavenging

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a carcass was common. Ancient wolves with genetically predisposed friendly behavior and modern humans are supposed to have started interspecific prosocial communication, first in all likelihood, in order to avoid risk of injury. As social mammals, both species were skilled with pretty similar social communication gestures using refined social communication consisting of complex mimicry, joint attention, and howling (Marshall-Pescini et al., 2017; Mech, 2009; Range & Virány, 2011) based on evolutionary-conserved similar brain structures (Berns et al., 2012). Thus, both of them were enabled to communicate with each other (Heberlein et al., 2016); hence, stress was reduced. Stress activity is known to be crucial for shaping behavior and brain function, often with long-lasting effects (Hunter et al., 2015). Meaney and Szyf (2005) describe that the intensity of prosocial behavior can modulate brain function via epigenetic modulations, thus affecting stress activity, social learning capability, and inhibitory control. The results of the famous Siberian farm fox experiment (Trut et al., 2009) as an experimental model of dog domestication describe changes in stress activity, epigenetic modulations, and increased mental skills like using basic human communicative gestures and better social problem-solving skills in experimental fox kits (Hare et al., 2005) during the domestication process. ASD focuses on mutual interspecific prosocial communication and stress reduction considering genetic selection as a necessary prediction but not a sufficient explanation of dog domestication, because domestication syndrome occurs very rapidly and frequently and therefore cannot be explained solely by selection for mutations. In addition, dog domestication is suggested to be an epigenetic disclosure affecting social brain function due to altered stress conditions, shaping the domestication syndrome. In this contribution, we investigate more closely the physiological evidence for the hypothesis of ASD as a model of dogs' self-domestication. Reduced chronic stress and increased mutual interspecific prosocial interactions between wolves and humans are considered to play an important role by shaping genomic and brain plasticity altering the phenotype and the social behavior due to epigenetic modulations, which affect glucocorticoid receptor activity and transposon expressions.

EVOLUTIONARY CONTINUITY OF MAMMALIAN BRAINS

Ancient gray wolves are the ancestor of all dogs, although dog domestication might have started at various places and different times (Thalmann et al., 2013). Wolves and humans are highly social and cooperative mammals (Marshall-Pescini et al., 2017; Mech, 2009; Range & Virány, 2011) and thus they are able to form close individualized emotional bonds, which are suspected to be crucial for the evolution of dogs.

The evolutionary continuity of mammalian brains suggests that the limbic brain including the dopaminergic reward system, the stress axis, and mirror neuron mechanisms are evolutionary conserved in all mammals (Ferrari, 2016; Ledoux, 2012; Reep et al., 2007). Recent functional magnetic resonance imaging (fMRI) studies in humans and dogs confirm similar activation patterns in the brain (Andics et al., 2014). Human mothers have similar brain activation in limbic brain regions when viewing their own child and their dog (Stoeckel et al., 2014). Berns et al. (2012) describe, in their fMRI studies of awake unrestrained dogs, that dogs sniffing their owner show increased caudate activation indicating positive reward feelings due to their positive emotional attachment bonds with their owners. Furthermore, caudate activation was found in dog brains as a response to hand signals denoting reward versus no-reward similar to fMRI studies of human brains (Berns et al., 2012). Dogs and humans also show a similar physiological response to human infant crying (Yong & Ruffman, 2014). The mirror neuron mechanism is involved in empathy and prosocial behavior (Gallese, 2001). It is confirmed for human (Lamm et al., 2007) and non-human primates (de Waal et al., 2005) and behaviorally implied in social mammals like rodents, wolves, and dogs (Bartal et al., 2011; Joly-Mascheroni et al., 2008; Romero et al., 2014). Areals of mirror neurons are experimentally verified invasively in macaques (Rizzolatti & Craighero, 2004) and even songbirds (Welberg, 2008) and with non-invasive electroencephalogram and fMRI studies in non-human and human primates (de Waal et al. 2005; Oberman et al., 2007). Imitation suggests that other social mammals like wolves and dogs also have mirror neurons although they are not directly confirmed (Ferrari, 2016; Range & Virány, 2014; Whiten, 2013). Mirror neuron cells fire when both individuals are equipped with the same neuronal representation of an emotion or an action (Kilner & Lemon, 2013). Similar learning experiences of ancient humans and wolves should have created equal neuronal representations, coding the observed actions and emotions. In addition, the neuropeptide oxytocin (OT), which is produced in the hypothalamus and released into the bloodstreams by the posterior pituitary gland, plays an important role in mammalian bonding, empathy, social memory, trust, and in-group behavior (Kosfeld et al., 2005; Lim & Young, 2006). Yawn contagion in humans and bonobos is shown to be due to emotional affinity (Palagi et al., 2014). Domestic dogs show contiguous yawns, while watching human yawns, which correlate with the intensity of dog's social attachment to the yawning person (Joly-Mascheroni et al., 2008) thus implying empathy. Even wolves are vulnerable to contiguous yawns correlating with the level of social attachment within the pack (Romero et al., 2014). Nagasawa et al. (2015) show that gazing into each other's eye mediated by OT also exists between human owners and their dogs implying interspecific empathy. During the Palaeolithic period, the similar social behavior due to evolutionary-conserved brain structures (Reep et al., 2007) enabled prosocial contacts between humans and wolves reducing stress and improved interspecific empathy (Beetz et al., 2012) eventually culminating in the dog domestication process.

GENETIC SELECTION AND THE DOMESTICATION PROCESSES

In domestication syndrome (Hare et al., 2012), the characteristics, such as less aggressive, less fearful, and hypersocial

behavior, are accompanied by morphological changes like reduced cranial capacity, partial depigmentation, and increased fertility (Trut et al., 2009). The most well-known experiment modeling canine domestication is the Siberian farm fox experiment (Trut et al., 2009). Only foxes with low aggression having minimum but daily contact with humans were chosen for further breeding within the experimental group. The control line was reared randomly under identical conditions avoiding contact with humans. Within 20–40 generations in the experimental group, numerous features of domestication syndrome were observed. First, physiological changes, including changes in the adrenal cortex, serotonergic, and limbic systems, related to a downregulation of the hypothalamic–pituitary–adrenal (HPA) axis, were identified. The brains of experimentally domesticated foxes exhibit elevated levels of serotonin and tryptophan hydroxylase relative to unselected control line (Hammer et al., 1992; Kulikova et al., 1989; Popova et al., 1980; Trut et al., 2009). Cortisol levels in domesticated foxes were also lower. They had less corticosteroid reactivity and changes in gene expression in the HPA axis (Gulevich et al., 2004; Plyusnina et al., 1991; Trut et al., 2009) compared to control group foxes. Subsequently, experimental group foxes showed behavioral and morphological changes (Trut et al., 2009). Finally, cognitive changes in social problem-solving skills improved (Hare et al., 2005; Miklósi et al., 2003); eventually, domesticated fox puppies were as skilled as dog puppies in using human communicative gestures (Hare et al., 2005) (Fig. 1).

As a form of a natural genetic selection in dogs' self-domestication process, we assume that genetically predisposed less aggressive and less fearful ancient wolves should have been the ones becoming more confident to humans (Hare et al., 2012). Genetic polymorphism can modulate the function of evolutionary-conserved complex mammalian brain systems such as the OT and the serotonin system. The OT is well known for its role in mammalian bonding. Single nucleotide polymorphism (SNP) in the cerebral OT receptor (OTR) gene as well as in the cerebral serotonin transporter gene is known in humans, wolves, and dogs (Kis et al., 2014; Kumsta et al., 2013; Oliva et al., 2016) modulating social behavior and general sociality (Li et al., 2015) like higher or lower proximity seeking and friendliness (Kis et al., 2014). In addition, mutations in the OTR gene have been found in samples of dogs and wolves providing evidence that SNPs in this OTR gene might have played a role in dog domestication (Oliva et al., 2016). However, there might be many less-known genetic variations influencing social behavior. Gene expression changes in the brains of domestic dogs compared to wild wolves are confirmed due to brain function and nutrition (Axelsson et al., 2013; Saetre et al., 2004). Hypersociability, a core symptom of domestication, is associated with structural gene changes in dogs that are linked in humans to the Williams–Beuren Syndrome (WBS; vonHoldt et al., 2017). However, no genetic evidence indicates that the changes seen in domesticated animals are the result of a single mutation. It is suggested that the domestication syndrome results from a mild neural crest cell migration deficit during embryonic development during which migration defects are particularly important (Wilkins et al., 2014). To what extent maternal cortisol levels might influence embryonic neural crest cell migration deficits is still an open question. In the farm fox experiment (Trut et al., 2009), first changes concerned a lowered corticosteroid reactivity and gene expression changes in the HPA axis (Gulevich et al., 2004; Plyusnina et al., 1991; Trut et al., 2009) within a few generations suggest evidence that domestication is essentially an epigenetic process regulating the activity of the HPA axis (Herbeck et al., 2017).

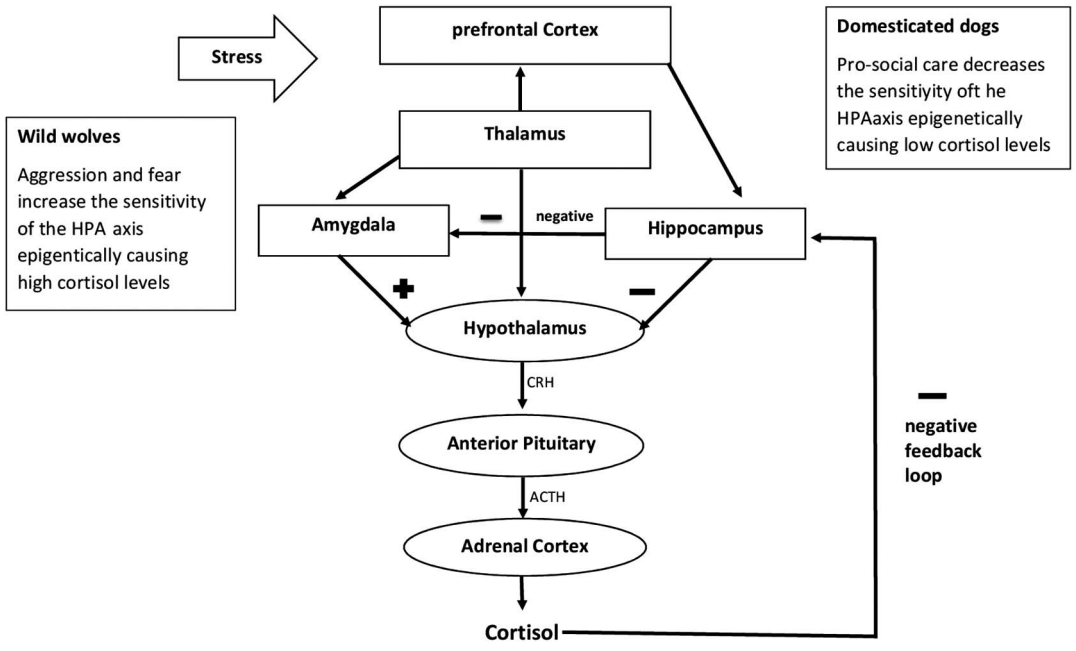

Fig. 1. HPA stress axis and glucocorticoid negative feedback loop

EPIGENETIC MODULATION OF THE HPA AXIS

Belyaev (1979), father of the farm fox experiment, suspected "sleeping genes" and epigenetic inheritance as mechanisms of fox domestication. Waddington (1952) deduced that genes can also be defined by their functional role of variations in phenotype and behavior and recent studies support this. Steroids and their receptors are known to control transposons and chromatin structure epigenetically (Hunter et al., 2015; Jensen, 2015). Transposable elements (including DNA transposons and retrotransposons) are parasitic genetic elements that can "jump" to different locations within a genome. Retrotransposons function by a "copy and paste" mechanism generating some new copies inserting elsewhere in the genome affecting gene expression. They are mostly silenced by epigenetic mechanisms like CpG methylation but can be expressed again due to stress. Rutherford and Linquist (1998) investigated the Chaperone H90 to play an important role in ontogentic development as a canalizing agent. Under high stress condition, H90 shift to repair thus giving space for expression of other so far inactivated genes. Platts et al. (2009) suggested that phenotypic variations in populations without genetic variability are caused by epigenetic modulations. Epigenetic input like DNA methylation is known to impact the regulation of the HPA axis (Buschdorf & Meaney, 2015; Herbeck et al., 2017; Meaney & Szyf, 2005). With this in mind, due to the results of the farm fox experiment (Herbeck et al., 2017; Trut et al., 2009), we consider that domestication is essentially an epigenetic programming changing the sensitivity of the HPA axis mediating stress behavior and its interaction with the 5-hydroxytryptamine (5-HT) system mediating calming effects.

Limbic brain regions such as the hippocampus, the amygdala, and the prefrontal cortex are important for mood control (Kosfeld et al., 2005; LeDoux, 2012) and they are the central organs of stress and stress adaptation because they perceive threats and initiate behavioral and physiological responses. The HPA axis is influenced through an enhancement of the amygdala and an inhibition through the hippocampus (LeDoux, 2012) and the limbic brain structures are sensitive to glucocorticoids and innervated by serotonergic projections. Under basal resting conditions, cortisol levels in the plasma are low and preferentially occupy mineralocorticoid receptors (MR) in the hippocampus, which exhibit roughly a 10-fold greater affinity for cortisol than hippocampal glucocorticoid receptors (hGCRs). At a stress peak, cortisol is first elevated physiologically via HPA axis activation to levels that occupy subsequently both, hippocampal MR and GCR (Reul & de Kloet, 1985), thus initiating negative cortisol feedback loop due to occupied hGCRs. The sensitivity of the HPA axis is pogrammed via hGCR density due to early life stress and has been well-studied in animal models (Buschdorf & Meaney, 2015; Meaney & Szyf, 2005). The HPA axis and the 5-HT system are natural antagonists closely cross-regulated under physiological conditions (Lanfumey et al., 2008). If stress disappears and therefore cortisol levels decrease, serotonin levels increase, thereby enhancing prosocial behavior, juvenilized social behavior, and learning ability (McEwen & Morrison, 2013; Murrin et al., 2007; Niehoff, 1999). Thus, changes in the interactions of the HPAaxis and the 5-HTsystem are of particular relevance regarding the domestication process.

ACTIVE SOCIAL DOMESTICATION – THE ROLE OF EPIGENETICS IN DOMESTICATION SYNDROME

First contacts between wild animals and humans are stressful events and stress is an important factor in shaping behavior and brain function. Subsequently, genetically predisposed friendly wolves are supposed to have come into prosocial contacts with humans like shown for foxes in the Siberian farm fox experiment. Experimental group foxes show changes in their adrenal cortex, serotonergic, and limbic systems related to a downregulation of the HPA axis within only a few generations compared to the control group foxes (Gulevich et al., 2004; Hammer et al., 1992; Kulikova et al., 1989; Plyusnina et al., 1991; Popova et al., 1980; Trut et al., 2009). These results are corresponding to epigenetic modulation of the HPA axis due to increased social affection (Buschdorf & Meaney, 2015; Herbeck et al., 2017; Meaney & Szyf, 2005). We hypothesize that epigenetic modulation of the HPA axis might be an important mechanism contributing to the domestication syndrome (Herbeck et al., 2017; Jensen, 2015). There is evidence in humans and rodents that parental care and prosocial affection can affect endocrine and autonomic response to stress via epigenetically altered receptor density that endure into adulthood (Champagne et al., 2003; Meaney & Szyf, 2005). Thus, the same stressor can cause different stress behaviors in different individuals. The sensitivity of the HPA axis and the serotonin and the OT system are defined genetically and epigenetically by the number and the sensitivity of their receptors, which, in turn, influence neurotransmitter and (neuro)hormone levels via feedback mechanisms. A central neuroanatomical circuity in the female rat brain mediates maternal responsive behaviors. The DNA methylation process regulates gene expression. Typically, a decrease in DNA methylation at gene promoter regions is associated with an increase in expression of that gene. In infancy, the female offspring of high pup licking and grooming (LG+) rat mothers show increased estrogen receptor (ER)-alpha function in (meso)limbic brain structures due to DNA demethylation of the ER-alpha promoter region, which is maintained into adulthood (Champagne et al., 2003; Weaver, 2011), hence shaping maternal licking behaviors. ER-alpha, although not necessary for basal OTR synthesis, is absolutely necessary for the induction of OTR binding in the brain by estrogen, which is critical for reproductive success (Young et al., 1998). The adult offspring of LG+ rat mothers is less fearful. Social factors like licking and grooming enhance hGCR expression via increased serotonin and subsequently increased nerve growth factor binding on hGCR promoter region causing its DNA demethylation (Buschdorf & Meaney, 2015; Meaney & Szyf, 2005). This offspring has a significant increase in the number of hGCR enhancing glucocorticoid negative feedback sensitivity and decreasing corticotropin-releasing factor (CRF) levels.

Whereas the offspring of stressed low licking rat mothers (LG-) is more fearful, showing decreased hGCR expression with high CRF levels. Cross-fostering the biological offspring of LG+ and LG- mothers reverses the phenotype, suggesting a direct relationship between variations in the maternal care and response of HPA axis to stress. The stress response in the adult rat is programmed early in life by maternal care and associated with epigenomic marking [DNA (de)methylation] of the hGCR promoter region (Meaney & Szyf, 2005; Weaver 2011). Even in human brains, a significant relationship between childhood abuse and epigenomic marking of the hGCR promoter region has been established (McGowan et al., 2009). Due to the evolutionary continuity of mammalian brains, the HPA axis is likely established since millions of years (LeDoux, 2012) according to the same functional principles; therefore, it is plausible to predict similar epigenetic modulation in the HPA axis of rodents (Meaney & Szyf, 2005) and humans (McGowan et al., 2009) as well as in wolves, dogs, and foxes (Herbeck et al., 2017; Jensen, 2015) (Fig. 2).

Achieving an evolutionary benefit, reduced environmental stress of wolves and humans created less stressed individuals able to show increased prosocial behavior causing epigenetically reduced sensitivity of the HPA axis in their offspring due to increased maternal care. Thus, over generations, cortisol sensitivity decreased more and more while the cross-regulated sensitivity for prosocial neurotransmitters and neuropeptides like serotonin and OT increased. Subsequently reduced cortisol levels might also be involved in mild neural crest cell migration deficiency during embryonic development. Cortisol can cross the placenta, thus altered maternal cortisol levels can alter cross regulated embryonic serotonin levels which might influence epigenetically embryonic brain development as well as receptor density in specific brain areas (Ahmed et al., 2014; Trut et al., 2009; Weaver, 2011). Furthermore, even a single acute stress is known to regulate the expressions of retroposons in the rat hippocampus via epigenetic mechanisms (Hunter et al., 2015). Activation of (retro)transposons by stress was first discovered by McClintock (1984). She described epigenetic mechanisms as controlling elements, which permitted the genome to respond more flexibly to

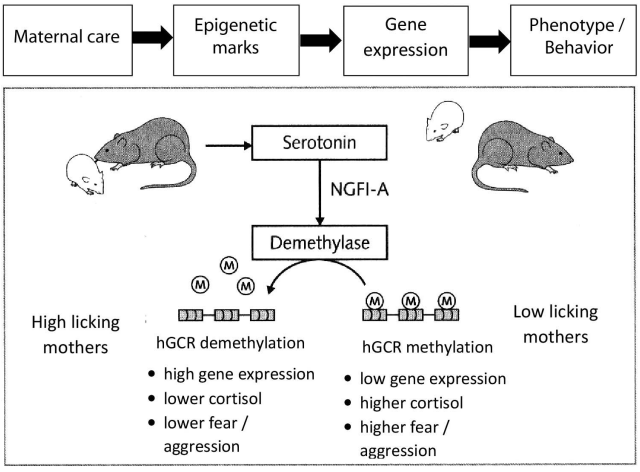

Fig. 2. Epigenetic programming due to prosocial behavior

stress. Increased stress is suggested to induce the expression of so far-silenced (retro)transposons epigenetically (Hunter et al., 2015). Especially, steroids and their receptors are linked in a variety of ways to the regulation of chromatin structure and retroposons. For example, hypersociability as a core symptom of domestication is associated with dogs undergoing structural gene changes like retroposons with high rates of insertions (vonHoldt et al., 2017) linked to human WBS. However, further research is required to better understand how (prenatal) cortisol levels, epigenetic modulations, and retroposons interact with each other.

Stress affects brain plasticity especially in the amygdala, the hippocampus, and the prefrontal cortex (Huang et al., 2015; McEwen & Morrison, 2013; Radley et al., 2018), which are important for fear, social control, and learning (Arai et al., 2009). Brusini et al. (2018) have shown, using high-resolution brain magnetic resonance imaging in wild and domestic rabbits, that amygdala volume is reduced, and medial prefrontal cortex volume is enlarged in domestic animals, supporting that areas linked to fear have lost volume while areas controlling fear and aggression have gained volume. Furthermore, the activity of the prefrontal cortex can enhance glucocorticoid feedback inhibition of the HPA axis via serotonergic innervation. Chronic stress reduces structural plasticity parallel with increased vigilance, aggressiveness, and anxiety (Hunter et al., 2015; Roozendaal et al., 2009; Vyas et al., 2002). On the other hand, reduced cortisol levels promote the function of the prefrontal cortex contributing to better executive functioning capability including increased cognitive inhibition and improved social learning capability (McEwen & Morrison, 2013). Thus, human-like social skills of first wolf dogs are suspected to have emerged, such as following human referential gestures (Range & Virányi, 2013), joint attention (Nagasawa et al., 2015), and attachment to human owners (Prato-Previde et al., 2003). Tame wolves were able to grow into domesticated social dogs capable of working together with humans in an active form of partnership developing complex human-analog social behavior (Marshall-Pescini et al., 2012, 2014; Topál et al., 2009). Compared to wolves, dogs are suggested to possess a higher level of inhibitory control concerning humans that means dogs show less aggressive behavior even toward foreign people compared to wolves (Marshall-Pescini et al., 2015). Hunting together during the Upper Palaeolithic was the first big evolutionary benefit of human–dog partnership (Shipman, 2015). Later on, dogs helped humans in transporting materials, even tending their sheep and goats. Eventually, wolf dogs integrated themselves in human social structures. Accepting humans as their preferred social binding partner (Range et al., 2014), tame wolfs became domestic dogs.

Our hypothesis of ASD is, at present, a comprehensive concept explaining domestication as a self-domestication process due to changes of stress, interspecific prosocial behavior, epigenetics, and genetics. Genetic polymorphisms and epigenetic mechanisms modulate the functions of complex brain systems in both species (Meaney & Szyf, 2005; Oliva et al., 2016). Genetic variants of genes important for brain function (Axelsson et al., 2013; Saetre et al., 2004) are known to be crucial during natural selection from wolf to dog (Hare et al, 2012; Oliva et al., 2016). Epigenetic

modulations of the HPA axis and the epigenetic machinery controlling transposons can induce genomic plasticity (Hunter et al., 2015) filling the gap between the rapid and frequent onset of domestication and selection for mutations. Hypersociability toward humans is associated in dogs with structural gene changes like insertions (von Holdt et al., 2017) and might be due to epigenetic mechanisms controlling retroposons triggered by changed stress conditions. Stress has a well-established influence on brain structure. Epigenetic studies indicate that a less stressful environment and higher social affection decrease cortisol levels epigenetically via increased hGCR expression. Simultaneously, serotonin and OT levels increase. Thereby, executive functions like cognitive inhibition and improved social learning capability (McEwen & Morrison, 2013) increase. Thus, ancient wolves could associate closer with humans and understand human social gestures better. Stray dogs, not used to human presence in their critical period (3–10 weeks of age), often show fear of humans, which may override dog's cognitive capacity to use humans' social cues (Range & Virányi, 2013; Udell et al., 2010). This may support the importance of epigenetic mechanisms in the domestication processes. We proclaim epigenetic modulation of HPA axis due to increased interspecific prosocial interactions to be crucial in self-domestication processes, not only in dogs, but even in domestication of other mammals and in human cultural evolution as well (Hare et al., 2012). Other mammals are known to live in larger groups due to inhabiting ecological niches with low stress factors like Florida Key deer (*Odocoileus virginianus clavium*) in urban areas showing higher fitness (Harveson et al., 2007). Darimont et al. (2014) describe low aggressive behavior of island wolves consistent with a dietary niche. Diet is also known to effect epigenetic gene regulation of HPA axis (Waterland & Jirtle, 2003) additionally influencing domestication. During the Neolithic period, humans and dogs began adapting to starch-rich diet (Axelsson et al., 2013). Most dogs probably digest starch more efficiently than wolves do. The increase of high amylase activity in dogs is associated with a drastic increase in copy numbers of the gene for pancreatic amylase, AMY2B, allowing dogs to digest starch-rich meals more efficiently (Arendt et al., 2014). The AMY2B shows high copy numbers in a majority of dogs but no or few duplications in only a small group of dogs originated mostly in Australia and the Arctic (Arendt, 2016). This pattern correlates geographically to the spread of prehistoric agriculture. Thus, increased numbers of AMY2B may not have been associated with initial domestication but rather the development and spread of agriculture. Carbohydrate meals lack tryptophan compared to high-protein meals, but they cause insulin secretion. Insulin, in turn, decreases plasma levels of large neutral amino acids that normally compete with tryptophan for transport across the blood–brain barrier. Therefore, tryptophan can pass the blood-brain barrier preferentially. Thus, in the brain, tryptophan as a precursor of serotonin increases, hence improving the serotonin synthesis (Spring, 1984) leading to reduced aggression and improved prosocial behavior (Chamberlain et al., 1987; Waterland & Jirtle, 2003).

Epigenetic modulation of the HPA axis due to social affection has had an effect probably not only in wolves and dogs but also in humans (Hare et al., 2012). Today, social interactions between humans and dogs still reduce stress activity in both species and thus improve prosocial behavior via cross-regulated increased OT release (Beetz et al., 2012) as previously described. Reducing stress as well as invigorating social learning abilities is known to be the reason of the benefit of dog-facilitated therapy in medical and social treatment (Beetz et al. 2012; Julius et al. 2014). Studies (Siewertsen et al., 2015) have shown positive effects of dog-facilitated therapy also for people with autism, who have impaired ability to engage in social interactions and communications including a reduced ability to read the mental and emotional states of others. Gotts (2012) has shown in fMRI studies that connection patterns of the social brain (Brothers, 1990) are disrupted in the brains of autistic patients. In addition, autism is characterized by abnormally decreased levels of OT (Modahl et al., 1998) and as well reduced OTR density corresponding to abnormally increased DNA methylation of OTR promoter region (OXTR) (Haas & Smith, 2015). Studies reveal that nasal OT can increase the attention to social stimuli and their understanding in patients with autism (Gordon et al., 2016). In addition, people with autism are often more interested in contacts with dogs than with humans (Siewertsen et al., 2015). Thus, it seems plausible that increased OT levels due to dog interactions (Beetz et al., 2012) are responsible for improving patient's social, emotional, and cognitive functioning (Siewertsen et al., 2015) due to the described mechanisms in ASD. Many genetic aberrations are likely to contribute to autism disorder. Those affected genes are located as an extra copy (duplication) or a de novo mutation on chromosome seven (Sanders et al., 2015). They are suspected to be involved in synaptic pruning (Tang et al., 2014), which is reduced in autism. When that same region of chromosome seven is lost (deletion with a minimum of 15 genes), the result is WBS, virtually the reverse of autism. People with this genetic disorder are extremely social, friendly, trusty even to strangers, have no difficulty reading the emotions of others, and they have good language skills; they often tend to be musical. The WBS patients suffer additionally on vascular anomalies and some other symptoms. However, they show mostly mental retardation in standardized IQ test. Genes deleted in WBS or copied in autism may influence the development of the human social and emotional brain. However, there is currently no evidence suggesting that genes coding for OT synthesis or OTR are located within the WBS deletion region/autism insertion region, although OTR overexpression and increased OT are evaluated in WBS patients and decreased OT and OTR density are known for autism (Haas & Smith, 2015). But recent evidence indicates that autism is associated with abnormally increased DNA methylation of OXTR, whereas WBS is associated with abnormally decreased DNA methylation of OXTR suggesting altered function of epigenetic mechanisms most likely due to changed functioning of methyltransferase genes located in WBS locus (Haas & Smith, 2015). This might be an interface between WBS, autism, and epigenetic modulation of HPA axis influencing the serotonin and OT system. In dogs, structural variants (insertions) of gene GTF2I and GTF2IRD1 on chromosome six are linked to human WBS with deletion on chromosome seven contributing even to extreme sociability in dogs (von Holdt et al., 2017).

But neither mental retardation nor vascular anomalies are known for dogs. Thus, we suspect that mental retardation in humans suffering on WBS is due to other lost genes of chromosome seven, which are likely not affected in dogs. However, it might be worth to think about an analogy between musicality and enhanced linguistic usage of WBS patients and improved barking of dogs compared to wolves during domestication. Humans' social and learning abilities are supposed to have already improved during the Paleolithic period. Within a narrow time frame of dogs' domestication, archeologists described a sudden further stage of human cultural development (Mellars, 2005) in the Upper Palaeolithic (approximately 45,000–11,700 years ago). First flutes, sculptures, cave paintings, and javelin spins appeared and simultaneously modern humans started living in larger social groups, held together by their increased cultural practice.

CONCLUSION FOR FUTURE BIOLOGY

The hypothesis of ASD proclaims that dog domestication is not primarily due to mutations and genetic selection but essentially an epigenetic-based process focusing on "environmental programming." Epigenetic inheritance and the functional role of genes shaping genomic plasticity (Hunter et al., 2015) are suspected to be crucial in domestication processes. During dog domestication, reduced chronic stress and increased interspecific mutual and prosocial behavior altered gene expressions via epigenetic modulations modifying the phenotype and behavior leading to domestication syndrome (Meaney & Szyf, 2005; Trut et al., 2009). Epigenetic marks can alter social brain functions inducing structural changes of social brain systems. During the domestication process, the amygdala reduced volume and the medial prefrontal cortex increased volume (Brusini et al., 2018) reducing fear and aggression and facilitating emotional inhibitory control, executive function, and social learning capability. Changes of environmental stress conditions and social behavior can shape epigenetically brain plasticity and subsequently brain structure as well as genomic variation on a functional and structural level, thus also highlighting the value for evolution of social brains and domestication processes, in general. Thus, ASD provides new ideas of mutual connections between environmental factors, social behavior, and genetics linked by the epigenetic machinery shaping behavior as well as the brain and genomic plasticity.

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