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Abstract

Inappropriate interpersonal aggression and disruptive violent outbursts are common problematic symptoms of multiple psychiatric disorders and represent a significant global health issue. Current therapeutic strategies are limited due to a lack of understanding about the neural and molecular mechanisms underlying the "vicious" shift of normal adaptive aggression into violence. However, the advent of new neuroimaging tools for measuring human brain function, structure, chemistry, and connectivity together with the rapidly emerging preclinical tools for mapping, measuring, and manipulating discrete neuronal activity in the animal brain significantly advances our understanding of the precise neural microcircuitry and its dynamic neurochemical functioning underlying the initiation, execution, and termination of aggressive behavior. This chapter presents our current knowledge of the brain regions/circuits and neuromolecular signaling mechanisms underlying the regulation of aggressive behaviors, obtained from both animal research and clinical studies with special attention for the contribution of PET/SPECT neuroimaging tools. The highly detailed picture of the neural and molecular underpinnings of aggression obtained from preclinical animal studies is compared with the more global neuroimaging data from clinical studies, underscoring similarities, reconciling inconsistencies, and addressing putative gaps between the two fields of research.

28.1 General Introduction Aggressive and Violent Behavior

Across the animal kingdom, aggression is the behavioral weapon of choice for individuals to gain and maintain access to desired resources (food, territory, mating partners), defend themselves and their progeny from rivals and predators, and establish and secure social status/hierarchical relationships. Obviously, engaging in aggressive behaviors is risky for an individual, as it must weigh the potential benefits of winning (greater access to mates, territory, resources) against the potential costs of fighting (injury, death, loss of social status). Clearly from a biological point of view, aggressive behavior is considered a highly functional form of social communication leading to active control of resources and the social environment, and thus essential for individual and population survival explaining its evolutionary preservation. It is characterized by a ritualized set of species-specific stereotypical motor patterns performed in close interaction with another individual (Tinbergen 1951). In rodents, offensive aggressive behavior usually progresses from a variable preparatory or appetitive phase that involves approach/investigatory actions and diverse threatening displays signaling aggressive intentions to the more rigid consummatory phase that involves intense physical attack behaviors like kicking, biting, lunging, and chasing.

28.1.1 Different forms of agression in animals and humans

Importantly, two major types of aggression are recognized in both animals (offense and defense) and humans (proactive and reactive) that differ in motor patterns,

eliciting factors, neural pathways, development, and function. While animal *offensive* aggressiveness is a form of agonistic behavior initiated by an aggressor and displayed in the context of competition for resources, *defensive* aggression is elicited in response to threat or attack by an offensive conspecific or predator. For example, an offensive male may compete with other males for food, status, or females. An animal that is attacked by either a dominant male or a predator performs defensive aggression. For offense, the motor patterns are approach, offensive upright/sideways posture, attacks (simple bites or bite and kick), chase, piloerection, and tooth chattering (mainly in rats) or tail rattling (mostly in mice). In the minutes leading up to intense attack bites, the resident animal emits brief pulses of ultrasonic vocalizations in the 50 kHz ranges that may reflect high excitement (affiliative function). The bite targets are primarily the hindquarters of the flanks, back, and base of the tail (less-vulnerable body regions). The function is to obtain and retain resources like space, food, and mates. For defense, the motor patterns are avoidance/freezing, defensive upright and sideways posture (keep away), flight, and attacks (lunge and bite). These defensive motor acts are usually accompanied with urination/defecation and emittance of 22 kHz ultrasonic vocalizations indicative of fearful or adverse experiences (alarming function). The lunge and attack bite targets are primarily the face (snout), neck, and belly (vulnerable body regions). The function is to defend one's self, mates, and progeny from attacks of another animal of the same or different species. Besides offense and defense, additional subforms of aggressive behavior in animal research are distinguished as well, such as infant-directed aggression or infanticide, predatory aggression, play-fighting (in juvenile animals), and maternal aggression. The latter can be observed in females during the late stages of pregnancy and the early phases of nursing. Predatory aggression is known as quiet-biting attack observed as the swift killing of a mouse or a cricket by a rat.

The most basic acts of physical aggression in humans are hitting, kicking, biting, pushing, grabbing, pulling, shoving, beating, twisting, and choking. Threatening (verbal or otherwise) and using objects (weapons) to aggress are also included into this definition (Tremblay and Szyf 2010). However, two main forms of aggression are also recognized in humans (Vitiello and Stoff 1997; Wrangham 2018; Elbert et al. 2018), and the offensive pattern of aggression in animals generally relates to the "hot-tempered" *impulsive-reactive-hostile-affective* aggression subtype in humans. This form of aggression has its strong emotional engagement and autonomic/neuroendocrine arousal in common with offensive aggression in animals. Moreover, both in animals and humans, this form of aggressive behavior is usually initiated in response to a perceived threat such as the intrusion of an unfamiliar conspecific into the territory or in response to fear and frustration (omission of expected rewards). The second type of human aggression is described as the "cold-blooded" *premeditated-proactive-instrumental* aggression. This latter form of human callous-unemotional aggression seems to resemble more the quiet-biting attack or predatory and infanticide forms of aggressive behavior in rodents. Whereas the *reactive* form of aggression is predominantly seen in patients suffering from depression, drug addiction, schizophrenia, PTSD, Alzheimer, or intermittent

explosive disorder (IED), the *proactive* type of aggression is commonly expressed in habitually violent offenders with personality disorders (conduct, antisocial, or borderline) or psychopathic traits. A lack of differentiation of these two main types of aggression often leads to conflicting results in the literature. Recently, a third form of aggression is being distinguished that may derive from the positive reinforcing effects of repeatedly winning social conflicts and/or dominating social targets. This so-called **appetitive** aggression is characterized by a persistent motivation to seek out and compulsively engage in aggressive interactions for reasons of pleasure, i.e., "lust for violence" (Elbert et al. 2018). Finally, it should be noted that aggression in both animals and humans has to be conceptualized into two components, state-like aggressive behavior and trait-like aggressiveness. Whereas the latter refers to an individual's proneness or history to engage in persistently aggressive displays in various different contexts, state-like aggression refers to the actual execution of aggressive behaviors. This temporal distinction appears to be of crucial importance when linking certain physiological or neurobiological parameters to different mechanisms of aggression (Haller 2017). In particular, the preponderance of PET/SPECT brain imaging studies in humans assesses various ligand binding properties within brain regions of normal or personality-disordered individuals that differ in trait-like forms of aggressiveness. Brain imaging studies during the overt execution of some laboratory tasks that provoke at best mild aggressive-like tendencies (e.g., Taylor aggression paradigm, ultimatum game, point subtraction paradigm, etc.) to assess alterations in the executive neural mechanisms that control aggression are scarce.

28.1.2 Violence Is the Pathology of Functional Aggressive Behavior

Although most individuals engage in social conflicts with appropriate and well-controlled (functional) forms of aggressive behavior, a relatively small proportion of individuals escalates their aggression inappropriately and persistently and/or become extremely violent (maladaptive aggression). This small percentage (ranging from 3 to 7% in humans) of aggressive, antisocial, and violent individuals is a major source of death, social stress, and ensuing disability in the victims, thereby constituting one of the most significant problems for the public health, medical institutions, and criminal justice systems worldwide. Actually, interpersonal violence/aggression is among the leading causes of death worldwide for people aged 15–44 and contributes to 21.7 million disability-adjusted life years (WHO, Global Health Observatory Depository). Violent and pathological forms of aggression are not only observed in our general human society but in particular also clinically, co-morbid across a wide spectrum of DSM-V-defined psychiatric and neurological disorders, and are one of the most distressing and disabling sources of impairment (WHO world report on Violence and Health; DSM-V, American Psychiatric Association). Inappropriate aggressive outbursts and/or the inability to control violent impulses are frequently occurring behavioral symptoms that cut trans diagnostically across a spectrum of mental disorders (e.g., schizophrenia, autism, depression, drug

addiction) and aging-associated neurodegenerative diseases (dementia, Alzheimer, Parkinson), perhaps reflecting a shared underlying component at the level of specific neurons, circuits, and/or genes, as conceptually put forth by the NIH's RDoC (Research Domain Criteria; "units of analysis"). Indeed, a large share of homicides (up to 75%) are committed by people with responsibility diminished to a certain extent by mental illness (Vinkers et al. 2011). These clinical observations have motivated much of the scientific interest in aggressive behavior in animals. However, until a decade ago, most ethological animal studies of aggression have focused mainly on the ultimate and proximate mechanisms of normal adaptive aggressive behavior, while clinically the focus is predominantly on violent individuals and excessive or escalated forms of human aggressiveness. Although long considered to be a typical human proclivity, lethal violent-like forms of aggressive behavior are also expressed in 40% of mammalian species and have significant phylogenetic roots (Gómez et al. 2016). Therefore, translational animal models can be developed that capture the essential features of human violence (Miczek et al. 2013). Pathological aggressive and violent-like behaviors in rats and mice are characterized by operational criteria that include elements that are impulsive (absence of any introductory and exploratory social behavior), excessive (high and persistent levels of attacks), and socially atypical (injurious attack topography, disregard for submissive and appeasement signals, and indiscriminate social targeting). Violence can thus be defined as a pathological form of aggressive behavior that is not subjected to inhibitory control mechanisms and that has lost its function in social communication (i.e., aggression out of control and out of context) (Miczek et al. 2007, 2013; De Boer et al. 2017). Several of these signs and symptoms of violent-like aggressive display are reliably engendered in several novel animal models that have achieved, at least to a variable extent, similarity with human violent aggression in terms of symptomatology and phenomenology (face validity), phylogenetic and ontogenetic origins (construct validity), and response to clinically established treatments (predictive validity) (for review of the various animal models, see De Boer et al. 2009, 2017; Haller 2017; Miczek et al. 2013; Covington 3rd et al. 2019). These animal models of more pathological or violent-like aggressive behavior are aimed at identifying the neural processes that motivate an individual to fight excessively under conditions that would not typically produce intense or prolonged attacks.

28.2 Brain Regions and Neural Circuit Mechanisms Underlying the Regulation of Aggressive Behavior

For well over a century, neuroscientists have sought to understand the neural roots of aggression and violence by perturbing and monitoring brain activity through a variety of methods and in a wide variety of experimental animals such as monkeys, dogs, cats, rats, mice, voles, and hamsters. By employing increasingly sophisticated tools of functional neuroanatomy (i.e., from the classic electrical/chemical lesion and stimulation techniques to neurochemical mapping and manipulations), many important strides have been made in understanding the functional brain circuit

organization of different social (aggression, sex, parental care) behaviors, i.e., the structurally and functionally highly interconnected "social behavior neural network" (SBN) (Newman 1999; Chen and Hong 2018). To more comprehensively delineate this SBN, and particularly the specific neural circuitry involved in aggressive behaviors, determining the pattern of immediate early gene (IEG) expression has been employed successfully over the last two decades. Fos is the protein product of an IEG, *c-fos*, which is rapidly expressed in neurons shortly after their depolarization (activation), and consequent elevation of intracellular free calcium. Fos expression can be visualized using histochemical antibody staining or in situ hybridization techniques, and the number of Fos-positive neurons in each brain area is used to quantify the activation of the area, i.e., Fos as a surrogate marker of neuronal activation. Advantages of IEG mapping are that it has single-cell resolution and can be used to systematically map patterns of activity associated with a particular behavior across the entire brain. In addition, the neurochemical identity of the activated cells can be visualized as well by combining it with antibody staining of cytoplasmic or membrane-bound components of neurotransmitters. The disadvantage is obviously the low temporal resolution (30–60 min); the pattern of *c-fos* activation integrates all of the activity that occurred over a behavioral experiment, making it difficult to assign activity to specific actions or elements of aggressive behavior (i.e., social investigation, sniffing, or fighting per se). Nevertheless, application of this technique in aggression paradigms in rats, mice, and hamsters has revealed in great detail the SBN aggression circuitry that encompasses the intimately interconnected forebrain (limbic) structures: medial amygdala (MeA), bed nucleus of the stria terminalis (BNST), lateral septum (LS), mediodorsal and anterior thalamus, several hypothalamic nuclei including the anterior hypothalamic (AHA)/medial preoptic (MPOA) area, ventromedial hypothalamus (VMH), lateral hypothalamus (LH), the ventral portion of the premammillary nucleus (PMv), and anteroventral periventricular nucleus (AVPV). Evidence suggests that these limbic areas collectively encompass a hierarchical role in the sensory processing and generation of the preparatory/appetitive aspects prior to aggression and the final execution of the consummatory aggressive display sequences (Hashikawa et al. 2018; Anderson 2016). In addition, important "top-down" modulatory control is provided by cortical structures like the orbitofrontal (OFC), medial prefrontal (mPFC), and anterior cingulate cortex (ACC), as well as the ascending midbrain monoaminergic nuclei like the dorsal/medial raphe nucleus (DRN/MRN; serotonin), locus coeruleus (LC; noradrenaline), and ventral tegmental area (VTA; dopamine). The production of the autonomic and somatic motor output aspects of the various aggressive behavioral elements are to a large extent coordinated by the periaqueductal gray area (PAG) (see Fig. 28.1 and de Boer et al. (2015) for a more detailed review of the neuroanatomy of offensive aggression). Application of functional magnetic resonance imaging (fMRI) in awake rats that were provoked to be aggressively aroused in the bore of the MRI magnet, the global brain BOLD activation patterns generally overlapped with this neuroanatomically mapped social aggressive behavioral network (Ferris et al. 2008). Extensive comparative research demonstrated that this highly interconnected neural network for aggressive behavior is remarkably similar

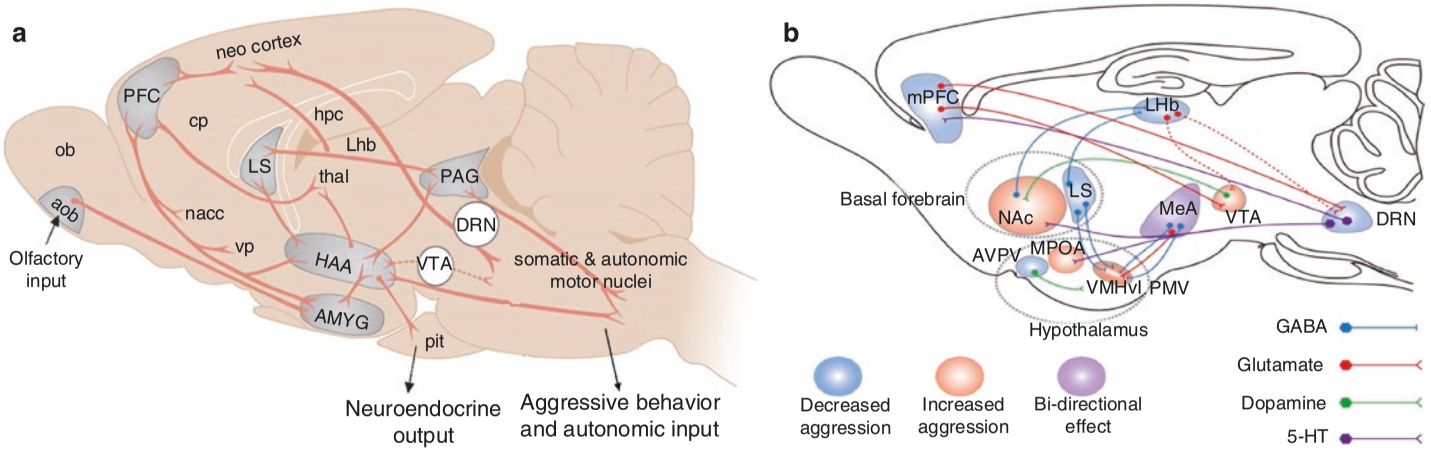

Fig. 28.1 (**a**) Schematic map of the brain areas involved in aggressive behavior. (**b**) Specific neurotransmitter connections that are involved in controlling aggressive behavior (effects on aggression are color coded) in rodents as reviewed in this paper. (Adapted from Aleyasin et al. 2018). *Abbreviations*: *aob* accessory olfactory bulb, *AMYG* amygdala, *cp* caudate putamen, *DRN* dorsal raphe nucleus, *HAA* hypothalamic attack area, which encompasses the *AVPV* anteroventral periventricular nucleus, *SPZ* subparaventricular zone, *MPOA* medial preoptic nucleus, *VMHvl* ventrolateral portion of the ventromedial hypothalamus, *PMV* ventral premammillary nucleus, *hpc* hippocampus, *Lhb* lateral habenula, *LS* lateral septum, *nacc* nucleus accumbens, *ob* main olfactory bulb, *PAG* periaqueductal gray, *PFC* prefrontal cortex, *pit* pituitary, *thal* thalamus, *vp* ventral pallidum, *VTA* ventral tegmental area

in many vertebrate species including human beings, indicating that it is evolutionary ancient and phylogenetically conserved (Goodson 2005; O'Connell and Hofmann 2012). Indeed, this basic brain aggression circuitry (at region level) is generally confirmed in humans by modern brain imaging techniques that allow the in vivo functional/structural (fMRI) analysis of the neuronal nodes/networks and of its associated neurochemistry (PET/SPECT) that are involved in certain types of aggressive behaviors. The brain areas and neural networks that are commonly activated during emotional processing, as well as the structural and functional alterations characterizing subjects with aggressive and antisocial behaviors, can be identified by using a variety of noninvasive imaging techniques (Raine and Yang 2006). For example, molecular imaging techniques used in nuclear medicine, namely, the positron emission tomography (PET) and single-photon emission computed tomography (SPECT), reveal the presence of specific radioactive tracers (injected in the bloodstream) in different brain regions depending on their specific uptake, thus showing the rate of metabolic/functional processes in specific brain regions. In addition, functional magnetic resonance imaging (fMRI) is a generally used tool to investigate the brain function, depending on the cellular oxygen consumption in different brain areas during resting or task-activated states. Below, based on both these preclinical and clinical studies, we further outline the various circuit nodes as well as the numerous neurotransmitter components therein that collectively make up the aggressive brain.

28.3 The Main Nodes/Network Components of the Aggressive Brain

28.3.1 Hypothalamus

Ever since the pioneering knife-cut lesion work of Philip Bard (1928) and the intracranial electrical stimulation experiments of Walter Hess and Bruegger (1943) showing suppression and provoking, respectively, of raging aggressive acts in cats, an extensive series of increasingly sophisticated lesion and electrical stimulation studies delineated the attack area in the medio-basal hypothalamus, hence called the "hypothalamic attack area" (HAA). This HAA consists of a region extending between the caudomedial LH and the ventrolateral VMH rostrally into the anterior hypothalamic/preoptic area (see Kruk (2014) for detailed recent review). While electrical stimulation of the HAA has been reported to induce fierce rivalry attack, stimulating the LH area (lateral to the fornix) promotes more the predatory-like "quiet-biting" attack forms of aggression (Chi and Flynn 1971; Haller 2018). However, despite its anatomical precision, wire electrodes still affect a rather ill-defined population of neurons and fibers of passage that do not allow definite conclusions on the precise causal neuronal and circuit-level mechanisms underlying offensive attack. The brain packs roughly 100,000 neurons and a billion synaptic connections in every cubic millimeter of gray matter tissue, and electrically stimulating or lesioning even a tiny location in the brain will excite/silence a very large

number of intermeshed cells of different kinds. Recently, newly emerging techniques for mapping, measuring, and manipulating neural activity based on genetic targeting of specific neuronal subtypes have solved many of these problems. In particular optogenetic and pharmacogenetic tools have made it possible to rapidly and reversibly activate or inhibit small molecularly distinct populations of neurons (anatomical and genetic precision) at any moment in time (temporal precision). In these methods, a gene that encodes an engineered microbial light-sensitive ion channel (optogenetic effector), or an engineered drug receptor (pharmacogenetic effector), is expressed in a desired subclass of neurons using viral vectors or a heritable transgene. Depending on the type of effector used, the neurons can be activated or inhibited at will in freely behaving animals. Optogenetic effectors are actuated using light of a particular wavelength, delivered into the brain region of interest via an implanted optic fiber (Anderson 2012; Deisseroth 2014). Pharmacogenetic effectors, called DREADDS, are actuated by administration of a designer drug that binds to the engineered receptor; this designer drug does not activate any endogenous receptors, nor do any endogenous ligands activate the synthetic receptor (Rogan and Roth 2011). These revolutionary techniques offer the ability to selectively manipulate distinct neural circuit elements that underlie aggression-relevant behaviors. The first experiments dissecting the microcircuitry of the hypothalamus involved in the regulation of aggression using these new neuronal manipulation tools focused on the ventrolateral subdivision of the VMH, a microscopic area comprised of roughly 10,000 cells. Optogenetic stimulation of these cells in male mice initiated immediate robust offensive attacks directed toward males, castrated males, females, and even inanimate objects (Lin et al. 2011). Accordingly, pharmacogenetic inhibition of these neurons suppressed normal attacks. Subsequent studies have capitalized on the fact that the neurons of the VMHvl are primarily glutaminergic (Choi et al. 2005) and are enriched with estrogen receptors of the alpha subtype (Esr1) and progesterone receptors (PR). Both Esr1/PR-knockout mice and RNAi knockdown of Esr1 in the VMHvl resulted in a dramatic decrease of natural intermale aggression (Sano et al. 2013). Furthermore, optogenetic stimulation of Esr1-expressing VMHvl neurons triggered attack behavior, while optogenetic inhibition suppressed natural fighting, demonstrating that Esr1/PR neurons in this small hypothalamic area are both necessary and sufficient to initiate and terminate bouts of aggression in both male (Lee et al. 2014; Yang et al. 2017) and female mice (Hashikawa et al. 2017). The involvement of Esr1/PR neurons is likely specific, as stimulation of non-Esr1 neurons within the VMHvl is not sufficient to drive aggression (Lee et al. 2014). The essential role of the VMHvl in aggression was further highlighted by in vivo electrophysiological single-unit recording techniques that revealed a prompt and robust increase in VMHvl neuronal activity during natural aggressive behavior (Lin et al. 2011; Falkner et al. 2014, 2016; Hashikawa et al. 2017). To further check whether the VMHvl neurons are also involved in the motivational/preparatory aspects of aggression (appetitive phase) in addition to the established role in initiation/execution of attacks (consummatory phase of aggression), Lin and coworkers adopted an operant responding task to temporally separate the seeking and action phases of aggression (Falkner et al.

2016). Employing in vivo calcium imaging, Lin and colleagues showed that the activity of VMHvl neurons is also increased during aggression-seeking behavior. Furthermore, optogenetic activation/inactivation of these neurons promoted/decreased, respectively, operant responding for access to an intruder that can be attacked (Falkner et al. 2016). These results clearly demonstrated that the role of the VMHvl in aggression extends beyond purely encoding the acute motor commands of fighting and is also involved in the motivational, aggression-seeking aspects. Obviously, the VMHvl is embedded within a larger (extra)-hypothalamic neuronal circuit whose nodes have distinct roles in modulating aggression. The multiple neuronal afferents and efferents of the HAA/VMHvl have been extensively mapped in rats using conventional anterograde and retrograde tracer techniques, thereby already demonstrating its crucial crossroad function to process and organize a wide variety of input and output information (see de Boer et al. (2015) for review). Very recently, the connectional architecture of specifically the Ers1-expressing VMHvl neurons was systematically mapped using six different viral-genetic tracing methods, confirming and extending the early classic track-tracing studies. The data revealed a high level of input convergence and output divergence from and to over 30 distinct brain regions with a high degree of bidirectionality (Lo et al. 2019). Prominent interconnected regions are several other hypothalamic (MPOA, AHA, AVPV, and PMV) and limbic (BNST, MEA, LS, mPFC, SUBv) areas that are well-known to be involved in controlling aggressive behavior, as well as some brain stem "aggression hotspots" (PAGvl, VTA, MRN). Below, we shortly summarize the roles of these other nodes within this extended neural circuit that project to the VMHvl. The MPOA, AHA, and PMV are three other important hypothalamic subareas of the global HAA that, already based on classic lesion/stimulation studies, have been implicated in regulating aggressive behaviors (Adams 2006; Ferris et al. 1997; Kruk 2014 for review; Motta et al. 2013). Recent optogenetic interrogations confirmed and extended their involvement and more precisely dissected the specific neuronal populations that modulate aggressive behavior, i.e., estrogen receptor beta (ER2)-expressing (Nakata et al. 2016) and galanin-containing neurons in the MPOA (Wu et al. 2014), tyrosine hydroxylase (TH)-expressing neurons in the AVPV (Scott et al. 2015), dopamine transporter (DAT)-expressing excitatory neurons in the PMV (Soden et al. 2016; Stagkourakis et al. 2018), and GABAergic neurons in the subparaventricular (SPZ) zone (Todd et al. 2018). This latter projection to the VMHvl seems essential for controlling the daily rhythm of aggression.

Although considerable understudied, there is clear evidence from several lesion and electrical stimulation studies in humans that the hypothalamus is also involved in mediating aggressive behavior similar to that seen in laboratory animals. For example, lesioning the posteromedial hypothalamic area successfully reduced or abolished excessive aggressiveness in violent patients (Sano and Mayanagi 1988; Dieckmann et al. 1988; Ramamurthi 1988; Pedrosa-Sanchez and Sola 2003; Weissenberger et al. 2001; De Almeida et al. 2008; Franzini et al. 2010), while a case study reported that electrical stimulation of this same hypothalamic area induces aggressive outbursts (Bejjani et al. 2002). Only two neuroimaging studies are available that present opposite results: One study shows that the hypothalamus

is more activated in individuals with aggressive features, while the second demonstrates that domestic violence offenders present lower metabolism in this region (George et al. 2004; Van den Stock et al. 2015). Unfortunately, the preponderance of human neuroimaging studies does not include the hypothalamic area and/or subareas as their region of interest, but rather are mainly focusing on temporal (amygdala) and cortical (prefrontal/cingulate) regions.

28.3.2 Amygdala/BNST

The amygdala is an important medial temporal lobe structure that consists of a range of interconnected nuclei having a common output through the central nucleus and the bed nucleus of the stria terminalis (BNST). Generally, it plays an essential role in the processing of a wide range of salient sensory stimuli and mediating autonomic, neuroendocrine, and behavioral responses that enable an organism to adapt to social and environmental challenges (LeDoux 2007). The amygdala, together with the frontal lobe (see below), is one of the brain regions that is consistently identified as showing altered activity in brain imaging studies of pathological aggressive and antisocial individuals. Human amygdala stimulation increases aggression (Vaernet and Madsen 1970), while numerous older studies have reported reductions in the severity and frequency of aggressive behavior after amygdalotomy (see Gouveia et al. (2019) for recent review). More recent MRI imaging studies revealed that adults and youths with psychopathic traits (i.e., premeditated aggressiveness) have reduced amygdala volume (Yang et al. 2009; Pardini et al. 2014) and functioning (Birbaumer et al. 2005; Glenn and Raine 2009), whereas individuals with more impulsive, reactive forms of aggression demonstrate exaggerated amygdala reactivity (Coccaro et al. 2007; Raine 2018; Da Cunha-Bang et al. 2017b). In a study conducted by Schiffer et al. (2011), non-offenders and violent offenders were examined in the forensic setting through MRI imaging. Interestingly, violent offenders presented a larger gray matter volume in the amygdala bilaterally, left nucleus accumbens, and right caudate head and decreased gray matter volume in the left insula. Additionally, regression analysis demonstrated that alterations in gray matter volume that discriminated violent offenders from non-offenders were correlated with psychopathy scores and lifelong aggressive behavior scores Schiffer et al. (2011).

Animal experiments, already at the end of the nineteenth century, showed that large electrolytic lesions of the amygdala had a strong taming effect in feral animals; even the most aggressive animal became docile and submissive by a bilateral amygdala lesion (Goltz 1884; Kluver and Bucy 1937; Rosvold et al. 1954). Particularly the medial amygdala (MeA) and the BNST have been implicated in regulating conspecific rivalry aggression, while the central amygdala (CeA) is more specifically involved in hunting and predatory aggressive attacks (Han et al. 2017). MeA neurons are active during fighting and in response to male/female conspecific chemosensory cues, as evidenced by the induction of c-fos and electrophysiological recordings (Veening et al. 2005; Hong et al. 2014). In addition, early lesion studies

have clearly implicated the MeA and BNST in mating, aggression, and rage-like behavior (Rosvold et al. 1954; Miczek et al. 1974; Kemble et al. 1984; Vochteloo and Koolhaas 1987; Wang et al. 2013). Electrical stimulation studies support the notion that the medial amygdalar area generally promotes aggression (Potegal et al. 1996; Siegel et al. 1999). While the MeA has stimulatory effects, the BNST has inhibitory effects on aggression as electrical stimulation of the BNST suppressed aggression in cats (Shaikh et al. 1986). Both the medial amygdala and BNST receive direct input from the accessory olfactory bulb, which in turn is the main relay station of olfactory information originating from the vomeronasal organ (Luiten et al. 1985). This part of the olfactory system is specialized in the detection of species-specific chemosensory signals. Hence, olfactory information that is crucial for proper social behavior in rodents has a dedicated entrance into the brain, reaching the medial amygdala and BNST almost directly, which in turn project intensively to the PMV and VMHvl, respectively. Unsurprisingly, the medial amygdala has an important function in the modulation of social behaviors on the basis of social experience and social recognition. Recently, it was demonstrated that the majority of c-fos-positive MeA neurons induced by attack are GABAergic. Optogenetic activation of these GABAergic neurons elicits male aggression, whereas stimulation of neighboring MeA glutaminergic neurons suppresses aggressive behavior (Hong et al. 2014). Optogenetic inactivation of MeA GABAergic neurons or permanent ablation of a subpopulation of GABAergic neurons expressing aromatase reduces normal intermale aggression (Hong et al. 2014; Unger et al. 2015). Although the MeA is characterized by a high density of both ER1 and androgen receptors (AR), it is not known whether these are located on these GABAergic cells. Likewise, whether and how these distinct sets of MeA neurons are precisely interconnected with the "attack" neurons in the VMHvl is not known yet, but it seems highly feasible that this is accomplished via its main downstream projection targets, the posterior portion of the BNST; stimulation of MeA-BNST projections results in increased aggression (Padilla et al. 2016). Interestingly, ER1 and AR receptors are also located on MeA neurons that produce the neuropeptide vasopressin (AVP). Interestingly, the synthesis of AVP in these neurons is potently enhanced by testosterone, the male gonadal steroid hormone that is intimately linked to aggressiveness (see below). This testosterone-dependent vasopressinergic system is sexually dimorphic and projects to the lateral septal area.

28.3.3 Septum/Hippocampus

Electrolytic lesioning or chemical inactivation of the lateral septum (LS) in birds and rodents dramatically increases the number of attacks towards conspecifics (Zeman and King 1958; Goodson et al. 1999; Potegal et al. 1981; Wong et al. 2016). Conversely, electrical or optogenetic stimulation of the LS suppresses natural and artificially evoked aggression (Potegal et al. 1981; Wong et al. 2016). Thus, the LS appears to be an essential gatekeeper for the expression of aggressive behavior. The

lateral septum is reciprocally and monosynaptically connected to both the aggression hotspots in the medial hypothalamus and medial amygdala. A recent study by Wong et al. (2016) indeed demonstrated that optogenetically activating GABAergic cells of the LS, which specifically project to the glutaminergic VHMvl "attack" neurons, can effectively suppress natural intermale attack and septal rage but had little effect on male-female mounting or nonsocial anxiety-like behavior. Given that the LS receives dense inputs from the hippocampus, and that some LS neurons show place fields, this pathway may modulate aggression by conveying spatial/contextual information. Furthermore, a recent study showed that the dorsal CA2 region of the hippocampus, which is characterized by expressing vasopressin AVP1B receptors, provides excitatory tone over the dorsal LS (Leroy et al. 2018). The LS is also characterized by a sexual dimorphic density of vasopressinergic fibers originating from the medial amygdala. Males have a higher AVP fiber density than females, and within the male gender, the density is negatively correlated with offensive aggressiveness. Both in rats and mice, highly aggressive males have a less dense vasopressinergic innervation of the lateral septum than low aggressive males.

Human patients with septal forebrain tumors exhibit elevated levels of anger, irritability, and aggressiveness. In addition, two recent structural MRI studies by Raine and colleagues demonstrated that adults with a large cavum septum pellucidum (CSP) showed higher levels of psychopathy and antisocial personality disorder (Raine et al. 2010; White et al. 2013). The septum pellucidum is one component of the septum that forms part of the septo-hippocampal system, and a large CSP is an early marker of abnormal fetal brain development during gestation until approximately 6 months post-birth (Sarwar 1989).

28.3.4 Prefrontal Cortex (PFC), Orbitofrontal Cortex (OFC), and Anterior Cingulate Cortex (ACC)

Frontal lobe impairments are one of the best-replicated factors for enhancing the intentions to behave aggressively in both animals and man (Kolb and Nonneman 1974; Siegel et al. 1999; De Bruin et al. 1983). Patients with damage to the frontal cortex exhibit more aggressive behavior (Anderson et al. 1999). The volume of the PFC gray matter in monkeys and humans correlates with social success and status (Sallet et al. 2011; Lewis et al. 2011). The frontal lobe consists of a number of subregions defined on the basis of their connections with thalamic nuclei and neuronal cytoarchitecture. Although the degree of complexity increases in higher vertebrates, there is a clear homology of frontal structures across a wide variety of vertebrate species. In particular the medial infralimbic (PFCvm), orbitofrontal (OFC), and anterior cingulate cortical areas have been associated with the inhibitory control of offensive aggression in a number of species. A meta-analysis of 43 structural and functional imaging studies found that the largest reductions in structure and function within the frontal lobe of aggressive and antisocial disordered individuals were observed in the orbitofrontal cortex, anterior cingulate cortex, and prefrontal cortex

(Yang and Raine 2009). This brain area is more generally involved in behavioral inhibition or impulsivity and the executive planning of motor output. Indeed, measures of impulsivity in male hamsters and rats are positively correlated with offensive aggression and prefrontal cortex activity measured by c-fos expression (Cervantes and Delville 2007; Coppens et al. 2014). Moreover, reduced prefrontal cortex serotonergic input and functioning has been associated with impulsive and violent forms of aggression in animals and humans (see below). Recently, Takahashi et al. (2014) demonstrated by employing optogenetic techniques that photostimulation of the principal pyramidal excitatory neurons in the mPFC, but not in the OFC, potently suppressed the initiation and execution of intermale aggression in mice, while optogenetic silencing of mPFC neurons caused an intensification of aggressive behavior. Hence, it is very plausible that the mPFC inhibits activity of a neural circuit that is tightly controlling the execution of aggressive attacks (i.e., VMHvl or MeA). In contrast, however, recent studies from Haller and colleagues have shown that postweaning socially isolated rats that demonstrate abnormal aggression exhibit structural deficits (reduced thickness), but higher activity in mPFC cells compared to control rats (Biro et al. 2017). Furthermore, they demonstrated that optogenetic stimulation of mPFC terminals in the mediobasal hypothalamus increased attack bite frequency, whereas the stimulation of similar terminals in the LH specifically resulted in violent-like (predatory) bites (Biro et al. 2018). These results indicate a direct prefrontal control over qualitatively different forms (rivalry vs. predatory) of aggression mediated by distinct hypothalamic circuitries. A recent human study, employing noninvasive transcranial direct current stimulation techniques to activate the dorsolateral prefrontal cortex, provided evidence that increasing prefrontal cortical activity can reduce intent to commit aggressive acts (Choy et al. 2018).

The anterior cingulate cortex (ACC) is another cortical limbic structure that has bidirectional connections with the prefrontal cortex, hypothalamus, amygdala, and hippocampus. In particular the rostral section of the ACC seems to be involved in emotional information processing and regulation of emotional responses (Bush et al. 2000). The cingulate cortex is activated by a variety of situations such as pain, motor function, conflict monitoring, error detection, reward, and during emotion and working memory tasks (Beckmann et al. 2009). The connections between ACC and amygdala through modulation by prefrontal cortex are fundamental for emotional behavior and in particular during anger control (Blair 2010; Davidson et al. 2000). Faulty regulation of emotion could result in impulsive aggression (Davidson et al. 2000). Indeed, several studies have demonstrated that patients with damage to the ACC show lack of empathy, response inhibition, and aggression control (Swick and Jovanovic 2002; Devinsky et al. 1995), while antisocial and violently aggressive individuals show structural ACC abnormalities (Boes et al. 2008; Meyer-Lindenberg et al. 2006; Rogers and De Brito 2016) or impairments in ACC functioning (Kiehl et al. 2001; New et al. 2002; Blair 2013). In contrast however, hyperactivation of anterior cingulate cortex was found in aggressive patients with schizophrenia and antisocial personality disorders if compared with nonaggressive

ones (Joyal et al. 2007). Another study has shown that reduced ACC functioning during a go-no-go task in prisoners doubled the likelihood of rearrest 3 years later, thereby indicating the potential for neuroimaging to provide predictive power for re-offending (Aharoni et al. 2014).

Although considerably less well studied in animals, a recent MRI study demonstrated increased ACC volumes in aggressive BALB/cJ mice, and this was associated with a 40% reduction of 1H-MRS GABA levels and a 20-fold increase of the GABA-degrading enzyme Abat in the ventral ACC (Van Heukelum et al. 2019; Jager and Amiri 2015).

28.3.5 Periaqueductal Gray (PAG)

The periaqueductal gray (PAG) represents one of the most important relays between the prefrontal, amygdala, and hypothalamic aggression nodes and the autonomic and somatic motor neurons in the medulla and spinal cord. The VMHvl, including the subpopulation expressing Esr1/PR, projects heavily to the dorsolateral and ventromedial parts of the PAG (Hashikawa et al. 2017; Lo et al. 2019), supporting older tracing studies that have indeed identified descending glutaminergic PAG projections to the pontine nucleus, raphe magnus and pallidus, medullary reticular formation, and directly to the spinal cord (Shaikh et al. 1986; Cameron et al. 1995). C-fos studies in several species consistently show that the (dorsolateral) periaqueductal gray is activated during offensive aggression (Kollack-Walker and Newman 1995; Haller et al. 2006; Veening et al. 2005). In vivo electrophysiological recording in cats showed that neurons in the dorsal and lateral parts of the PAG responded during agonistic encounters (Adams 1968). Electrical stimulation of the PAG induced aggression in male rats (Mos et al. 1982; Siegel et al. 1999), while PAG lesions may suppress aggressiveness in some (Mos et al. 1983) but not all studies (Lonstein et al. 1998). Collectively, the PAG is therefore generally considered to be the emotional motor output system for offensive aggression, orchestrating the involuntary autonomic physiological and somatic motor patterns of different forms of aggressive behaviors. To date, functional and structural imaging results of the PAG in violent aggressive or antisocial human individuals are not available.

28.3.6 Lateral Habenula (LHb)

A recently uncovered brain area involved in the motivational aspects of aggression is the lateral habenula. The habenula comprise a small group of nuclei that are located just above the thalamus and is divided into two asymmetric halves: the medial habenula (MHb) and the lateral habenula (LHb). The lateral habenula receives afferents from the hypothalamus, lateral septum, amygdala, BNST, nucleus accumbens, ventral pallidum, diagonal band of Broca, and anterior cingulate and prefrontal cortex and in turn sends dense glutaminergic projections

throughout the midbrain aminergic nuclei (Lammel et al. 2012) involved in reward and motivation such as the dopaminergic VTA and serotonergic DRN (see next section). The LHb is pivotal in processing aversive and rewarding information. Aversive stimuli, cues that predict its onset, or even the omission of an expected reward, lead to a strong increase in the activity of LHb neurons. Overactivity in the LHb is seen in both stress-induced learned helplessness (Li et al. 2011) and in depressive patients (Roisier et al. 2009). Conversely, unexpected delivery of rewards and cues predicting a reward decreases LHb neuron firing. The LHb is inhibited more strongly as expected reward probability or magnitude increases (Matsumoto and Hikosaka 2009). Hence, the LHB is generally considered the brain's "anti-reward" control center. A recent study utilizing optogenetics found that stimulation of GABAergic terminals that suppresses LHb firing increases the intensity of aggressive behavior in mice. The reverse was observed after optogenetic inhibition of these GABAergic terminals in the LHb (Golden et al. 2016). Hence, an emerging role for this brain region in controlling aggressive behavior based on emotional valence was recently suggested (Flanigan et al. 2017). To date, functional and structural imaging results of the LHb in violent aggressive or antisocial human individuals are not yet available.

28.4 Neurochemical and Hormonal Modulation of the Aggressive Neural Network

Obviously, the functional activity of this social behavior neural network, and thereby the selection of the appropriate behavioral response to social challenges and opportunities, is determined by a wide variety of molecular substrates (i.e., neurotransmitters, hormones, cytokines, and their respective metabolic enzymes, receptors, and intraneuronal signaling molecules). Undisputedly, among the neurochemical systems that are considered key signaling molecules in this neurocircuitry controlling aggression are the main inhibitory/excitatory amino acids (GABA/glutamate), canonical monoamines serotonin (5-HT) and dopamine (DA), the "social" nonapeptides oxytocin (OXT) and vasopressin (AVP), the "stress" neuropeptide corticotropin-releasing factor (CRF), the "stress" HPA and "sex" HPG axis's steroid hormones (corticosterone, testosterone, estrogen), and their cognate receptors. Indeed, the "aggression" neurons in the hypothalamus and other regions as outlined above receive these neurotransmitter projections and express a variety of their membrane-bound receptors, including serotoninergic 1A/1B and 2A/2C, dopaminergic DRD1/DRD2, and vasopressin/oxytocin AVP1A/AVP1B/OTR receptors, as well as the intracellular steroid hormone AR and EsR1/EsR2, PR, mineralocorticoid (MR), and glucocorticoid (GR) receptors. Since many of these neuromodulators change their levels rapidly and dynamically before, during, and after the execution of aggressive behaviors (see below), they may influence the various nodal neuron excitabilities and hence the initiation, maintenance, termination, and consequent social experiences of aggressive intercourse.

28.5 Serotonin

All major nodes of the neuronal network controlling offensive aggression are substantially innervated by serotonergic (5-HT) fibers originating from neurons in the dorsal and median raphé nuclei in the brain stem. More than any other neurochemical systems, this evolutionary ancient and very well-conserved neurotransmitter system is considered the primary molecular modulator of aggressiveness in a wide variety of animal species, including man (Siever 2008; Nelson and Trainor 2007; De Boer et al. 2015). However, the direction and exact causal linkage of this association is very complex, and it has proven notoriously difficult to unravel the precise role of this amine (and every facet of its synthesis and metabolic pathways, uptake and storage processes, and dynamic receptor signaling mechanisms) in the predisposition for and execution of aggressive behavior. For decades, high levels of aggressive behavior are believed to be associated with low brain 5-HT neurotransmission activity. This frequently reiterated and seductively simple serotonin deficiency hypothesis seems consistent with the fact that serotonergic receptor agonist drugs used to mimic higher serotonergic activity, generally reducing aggressive behavior (see de Boer and Koolhaas (2005) and Takahashi et al. (2012) for reviews). However, recent studies of the functional status of the 5-HT system before, during, and after the execution of normal adaptive and abnormal pathological forms of aggression have led to a somewhat different view. Display of normal adaptive offensive/defensive aggressive behavior aimed at securing territorial control, social dominance, or other resources is associated with enhanced 5-HT neuronal activity (see de Boer et al. (2015) for relevant references). A negative correlation between aggression and 5-HT as captured in the deficiency hypothesis seems to be a trait-like characteristic of pathological and abnormal forms of aggression (e.g., violence). For example, a clear positive correlation was found between the level of normal adaptive expressions of offensive aggression and basal cerebrospinal fluid (CSF) concentrations of 5-HT and/or its metabolite 5-HIAA. A significant negative correlation between aggression and 5-HT levels was found only upon inclusion of samples from abnormally and excessively aggressive trained fighter animals (de Boer et al. 2009). A critical evaluation of the csf 5-HIAA data in aggressive humans confirms this idea that the serotonergic deficiency appears to hold in particular for specific groups of individuals who persistently engage in more aberrant, impulsive, and violent forms of aggressive behavior rather than in individuals with instrumental (functional) forms of offensive aggression.

Treatment with 5-HT_{1A} or 5-HT_{1B} receptor agonists is one of the most potent pharmacological interventions to selectively suppress aggressive behavior in a variety of animal species and experimental paradigms (see Olivier and van Oorschot (2005) and de Boer and Koolhaas (2005) for reviews). However, apart from acting on receptors at postsynaptic sites, these two distinct receptor agonists also affect the two main serotonergic autoreceptors involved in the negative feedback control of the 5-HT neuron at the level of the synapse (5-HT_{1B}) and at the level of the cell soma (5-HT_{1A}). Activation of these receptors by agonists will potently activate the

negative feedback mechanisms and thereby reduce 5-HT neurotransmission. It appears that the anti-aggressive effects of these compounds are largely expressed via their action on the inhibitory autoreceptors located at the cell soma and the nerve terminal, presumably by attenuating intruder-activated 5-HT neurotransmission (De Boer and Newman-Tancredi 2016). Interestingly, highly aggressive animals are characterized by upregulated somatodendritic 5-HT_{1A} and terminal 5-HT_{1B} autoreceptor functionality (Caramaschi et al. 2008; De Boer et al. 2015). This considerably (approximately 20-fold) enhanced tonic inhibitory control of serotonergic neurons in aggressive males may explain the negative correlation between baseline levels of 5-HT and escalated aggression found in many species. Furthermore, to signify the causality of this correlation, 5-HT_{1A} autoreceptor sensitivity increased or decreased upon enhancing (by repeated victorious experiences) or attenuating (by repeated defeat experiences) aggressiveness, respectively. Notably, animals that escalated their aggressiveness and started to engage in violent-like aggressive behavior demonstrated 5-HT_{1A} autoreceptor supersensitivity (de Boer et al., in prep). More persuasively, recent molecular genetic studies have shown that transgenic mice with conditional (at adult age) overexpression of somatodendritic 5-HT_{1A} autoceptors demonstrate suppressed 5-HT neural firing that was associated with a profound hyperaggressive behavioral phenotype (Audero et al. 2013). These animal data confirm the causal role of tonic 5-HT activity in setting a trait-like threshold for executing overt aggressive behavior.

Similar to the findings in animals, agents with significant 5-$HT_{1A/1B}$ receptor agonism (i.e., buspirone, eltoprazine) have been found to be effective, although to variable degrees, in reducing aggressiveness in humans (Ratey et al. 1991; Mak et al. 1995; Santa-Cruz et al. 2017). Furthermore, a consistent finding has been an inverse relationship between 5-HT_{1A} receptor-provoked increases in plasma cortisol and trait aggressiveness in personality-disordered patients (Coccaro et al. 1995; Cleare and Bond 2000), indicative of impaired 5-HT_{1A} heteroreceptor functionality. Only 2 PET studies using the same 5-HT_{1A} receptor radioligand ([^{11}C]WAY100635) have been published: one reporting a positive relation between frontal 5-HT_{1A} receptor availability and trait aggressiveness (Witte et al. 2009), while the second showed an inverse correlation (Parsey et al. 2002). To date, only one recent PET imaging study has been performed examining 5-HT1B receptor availability in pathological aggression; 5-HT1B binding in the ventral striatum, anterior cingulate cortex, and orbitofrontal cortex was positively correlated with trait anger in the violent offender patient group but not in healthy controls (Da Cunha-Bang et al. 2017a). This clinical study reinforces preclinical data suggesting the involvement of 5-HT1B receptors in pathological aggression.

In addition to 5-HT_{1A} and 5-HT_{1B} receptors, another intrinsic feedback control mechanism of serotonin release is mediated by the serotonin transporter (SERT). SERT is distributed along the axons and synaptic terminals of 5-HT neurons and plays an essential role in the clearance of released extracellular 5-HT. In humans and nonhuman primates, polymorphisms in the promoter region of the gene coding for SERT is associated with aggression. Surprisingly, and generally in contrast to

the 5-HT deficiency hypothesis, the short-allele (loss-of-function) variant has been associated with increased levels of aggression both in males and females, presumably due to a disturbed serotonin reuptake (Hallikainen et al. 1999; Retz et al. 2004; Beitchman et al. 2006). In contrast however, gain-of-function polymorphisms in the SERT gene (either long 5-HTTLPR allele or the STin2VNTR12 variant) also has been shown to confer risk for aggression and violence in children (Beitchman et al. 2006; Davidge et al. 2004) and adults (Aluja et al. 2009; Hemmings et al. 2018). In line with this latter clinical finding, rats and mice that have genetically induced SERT deficiency, which consequently demonstrate high tonic extracellular 5-HT levels, generally exhibit a low-aggressive phenotype (Holmes et al. 2002; Homberg et al. 2007). This seems also in line with the observation that highly aggressive dogs exhibit enhanced SERT functionality (Rosado et al. 2010).

When the SERT binding radiopharmaceutical probes [^{11}C]McN 5652 and [^{11}C]DASB became available, SERT binding distribution patterns were quantified in brains of impulsive aggressive individuals and/or personality-disordered populations. One early study found lower 5-HTT binding in the ACC in impulsive aggressive personality-disordered patients (Frankle et al. 2005), indicative of attenuated 5-HT innervation of fronto-limbic regions and is generally in line with the hypo-serotonergic model of impulsive aggression. Another study of the same research group however was not able to extend this finding in a much larger cohort of IED patients but noticed that a measure of psychopathy, callousness, positively correlated with ACC SERT binding (van de Giessen et al. 2014). This again underscores the importance of stratifying personality-disordered patients into reactive or proactive forms of aggressiveness. In a third study, SERT availability was found to be significantly higher in high-impulsive aggressive subjects as compared to low-IA. Post hoc analysis demonstrated that the difference was mainly driven by increased SERT availability in the brain stem, pons, and midbrain. Interestingly, there was a positive correlation between SERT BP_{ND} (binding potential non-displaceable) in the high-IA and measures of childhood trauma. The authors propose that early-life adversity impaired 5-HT function, mainly through epigenetic alterations, leading to high-IA (Rylands et al. 2012).

Another serotonergic receptor implicated in aggression is the 5-$HT_{2A/C}$ heteroreceptor (5-$HT_{2A/C}$R) postsynaptically located on non-serotonergic neurons. Various clinical studies have shown differences of 5-HT_{2A}R binding in human subpopulations, but literature findings are not consistent. Cerebral 5-HT_{2A}R binding has been investigated most frequently in relation to aggressiveness. Violent aggression in humans was reported to be related to a decreased BP_{ND} of the PET tracer [^{18}F]setoperone in prefrontal cortex, especially at young age (Meyer et al. 2008). Using another PET tracer, [^{11}C]MDL 100907, reduced 5-HT_{2A}R availability was also observed across cortical regions in males with extreme levels of impulsive aggression without callous unemotional traits as compared to males with low levels of impulsivity (Rylands et al. 2012). In contrast to these findings, two other PET studies reported that 5-HT_{2A} receptor binding in the prefrontal cortex is increased in physically aggressive patients with impulsive aggressive personality disorder

(Rosell et al. 2010) and in patients with borderline personality disorder (Soloff et al. 2007) as compared to healthy controls. In addition, a postmortem study indicated that 5-HT_{2A} receptor expression in the prefrontal cortex is positively correlated with lifetime aggression in subjects who committed suicide, but not in subjects who died from non-neurological causes (Oquendo et al. 2006). However, a recent study using a large sample of healthy individuals did not find a consistent relationship between 5-HT_{2A}R binding in frontal cortex and the personality traits aggression or impulsivity (da Cunha-Bang et al. 2013).

The putative relationship between 5-HT_{2A}R binding and aggression has also been studied in experimental animals (Popova et al. 2010; Morrison et al. 2011). No change in the functional sensitivity of 5-HT_{2A}R was found in Norway rats bred for high defensive fear-induced aggression towards man, compared to rats with normal aggression, and 5-HT_{2A}R expression was also similar (Popova et al. 2010). 5-HT_{2A}R expression in the hamster brain did not change after social defeat, either in subordinate or dominant animals, as tested by immunohistochemistry (Morrison et al. 2011). Single-photon emission computed tomography (SPECT) studies observed differences in 5-HT_{2A}R binding of impulsive aggressive dogs compared to normal dogs. These dogs showed increased 5-HT_{2A}R binding in cortical areas, which could be ameliorated by administration of the antidepressant citalopram (Peremans et al. 2003, 2005). Finally, a recent rat study using the radiolabeled 5-HT_{2A} antagonist ([3H]MDL 100907) and agonist ([3H]Cimbi-36), no differences in 5-HT_{2A}R binding were observed between high- and low-aggressive WTG rats (Visser et al. 2015). Overall these findings suggest that 5-HT_{2A}R binding is not an important molecular marker of trait aggressiveness.

Ever since Brunner's landmark finding of a single, rare, missense mutation in the MAO-A gene being associated with antisocial and excessive aggressive behavior in a large Dutch family (Brunner et al. 1993), this main catabolic enzyme of monoamines has been the focus of interest in the neurogenetic architecture of human and animal aggression. Carriers of another low-expressing MAOA-VNTR allele similarly exhibit enhanced aggressiveness (Sabol et al. 1998; Manuck et al. 2000) or occur more commonly in violent compared to nonviolent incarcerated males (Stetler et al. 2014). Accordingly, hyper-methylation in the promoter of the MAOA gene is associated with antisocial personality disorder, and this epigenetic modification likely contributes to downregulation of MAO expression and dysregulation of 5-HT system, leading to impulsive aggressiveness and antisocial criminality (Checknita et al. 2015). Additionally, numerous studies have demonstrated gene-environment interaction effects such that greater early-life adversity increases the risk for impulsive aggressiveness in males with the low-expressing MAOA allele (Caspi et al. 2002; see for review Buckholtz and Meyer-Lindenberg (2008)). Similar gene-environment interactions as risk factor for violent traits have been reported for several other serotonin gene polymorphisms such that individuals with a certain allele are particularly prone to engage in violent behavior when they have a history of early-life maltreatment, but the effect disappeared when they are reared in an environment with low stress. Using PET imaging employing the radioligands [^{11}C]

clorgyline or [^{11}C]Harmine to measure MAOA availability, trait aggression in either a healthy population (Alia-Klein et al. 2008) or population of ASPD offenders (Kolla et al. 2015) was negatively associated with MAOA availability in several cortical and subcortical brain regions.

These clinical results linking MAOA dysfunction with enhanced aggressiveness are generally supported by mouse genetic and pharmacological studies. Increased aggression have been observed in both MAOA knockout mice (Cases et al. 1995) and mice with a naturally occurring mutation (Scott et al. 2008). Nonselective inhibitors of MAOA (e.g., phenelzine, tranylcypromine) produce acute anti-aggressive effects only at doses that also induce sedation and alter other nonaggressive behaviors (Valzelli et al. 1967). Intriguingly, and at variance with the serotonin deficiency hypothesis, these findings suggest that chronically increased 5-HT levels that result from reduced MAO function may promote or intensify escalated aggressive displays. However, the findings are consistent with a large body of work across species that links dysregulation (too much or too little) during ontogeny to impulsive aggressive behavior (Buckholtz and Meyer-Lindenberg 2008).

28.6 Dopamine

Dopamine has several important functions in the general control of behavior. The nigrostriatal dopaminergic system originating in the substantia nigra (SNR) has a central function in the control of motor output, which is obviously important for the execution of aggressive behaviors. The mesolimbic dopaminergic system, originating in the ventral tegmental area (VTA) and projecting to the ventral striatum/nucleus accumbens (NAc), is believed to be important for the motivational and rewarding aspects of behavior. Several imaging studies indeed show activation of the NAc during aggression-provoking tasks in human subjects (Buckholtz et al. 2010; Moran et al. 2014; Chester et al. 2016; Gan et al. 2016, 2017). Yet, clinical PET imaging studies assessing the link between dopaminergic synthesis function and aggression are still scarce. One study evaluated aggressive behavior and dopaminergic synthesis capacity employing [^{18}F]F-FDOPA PET imaging in 21 healthy males. A negative correlation between aggressive actions and dopaminergic synthesis capacity was found in the midbrain, caudate nucleus, and putamen (Schluter et al. 2013). Other studies focusing on dopamine receptors imaging (mainly D1-R) have been contradictory. In 2014, Plavén-Sigray and colleagues (Plavén-Sigray 2014) reported a negative correlation between D1-R levels in the limbic striatum and aggressive personality traits, using the PET tracer [^{11}C]SCH23390. In a replication study conducted by the same group, no significant correlations between D1-R in the limbic striatum and aggression were found. The authors argued that these discrepancies might be due to high sample homogeneity or that the previous findings were false positive (Plavén-Sigray 2018).

Studies in animals using c-fos mapping studies and/or in vivo microdialysis have demonstrated increased dopaminergic neuronal activity in VTA and release of

dopamine in the NAc following aggressive social interactions in mice, hamsters, and rats (Veening et al. 2005; Nehrenberg et al. 2013; Beiderbeck et al. 2012; van Erp and Miczek 2000; Ferrari et al. 2003). Furthermore, direct optogenetic activation of VTA dopamine neurons increases aggressive bout severity in mice (Yu et al. 2014). Pharmacological studies have shown that dopamine agonists increase aggressive behavior in rodents (Miczek and Haney 1994; Yu et al. 2014), while systemic injections of DRD1 or DRD2 family antagonists decrease it (Kudryavtseva et al. 1999; Fragoso et al. 2016). However, there is a general lack of behavioral specificity of this effect when the compounds are applied systemically. This is one of the main clinical problems with all the commonly prescribed neuroleptic dopamine antagonists (i.e., haloperidol, risperidone, clozapine, olanzapine) to curb excessive aggression in patients (Campbell et al. 1984; Ostinelli et al. 2017; Calver et al. 2015). While these studies confirmed a functional role for the dopaminergic VTA-NAc system in mediating aggression, they do not specifically address its role in the rewarding properties of, or the motivation for performing, aggressive behavior. Under laboratory conditions, acts of aggression and winning fights are shown to be rewarding, such that animals will strengthen future fighting (de Boer et al. 2009), demonstrate operant (nose-poking, lever-pressing) learning for the opportunity to attack another conspecific as a positive reinforcement (Fish et al. 2002; May and Kennedy 2009; Golden et al. 2017a, b; Falkner et al. 2016), or will exhibit conditioned place preference for a location associated with previously successful aggressive encounters (Martínez et al. 1995; Golden et al. 2016). Actually, individuals seeking out the opportunity to fight, even in the absence of overt threat-provoking cues, appear to engage in aggressive behavior as a source of pleasure. Actually, a significant proportion of individuals may even become "addicted to aggression" (Golden et al. 2017a, b). The term "appetitive aggression" has been used to describe these forms of aggression as a positive reinforcer (Elbert et al. 2018). Earlier microdialysis experiments in aggression-experienced rats have clearly revealed that DA levels in the NAc rise in anticipation of an aggressive social interaction (Ferrari et al. 2003), while another study demonstrated that blocking dopaminergic activity in this brain nucleus using D1 and D2 receptor antagonists reduces operant responding for access to an intruder (Couppis and Kennedy 2008). Similarly, if male California mice are given a DA receptor antagonist after they win a fight, then they fail to develop a strong winner effect (Becker and Marler 2015). In male Syrian hamsters, the accumulation of multiple winning experiences that lead to a strong winner effect is positively associated with substantial increases in TH-positive cells in NAc, BNST, and LS (Schwartzer et al. 2013). Recently, Golden and colleagues (Golden et al. 2017a, b, 2019) provided more direct evidence for the causal involvement of dopaminergic VTA-NAc projections in aggression-seeking behavior and aggression-addiction. They demonstrated that chemogenetically silencing D1-expressing medium spiny GABAergic neurons in the NAc decreased aggression self-administration (Golden et al. 2019). Thus, a growing body of evidence shows that aggression activates dopaminergic reward centers in the brain to promote positive valence and reinforce the motivation to act aggressively.

28.7 Glutamate/GABA

Glutamate and GABA are the main excitatory and inhibitory amino acid neurotransmitters, respectively, in the mammalian brain. Several kinds of mental disorders such as anxiety disorders, depression, autism, and also aggression are attributed to an imbalance between glutaminergic excitation and GABAergic inhibition in limbic areas (Miczek et al. 2007). It is not surprising therefore that many compounds that act as an agonist or antagonist on their cognate receptors can potently alter these disorders as well as aggressive behaviors. Initial preclinical data demonstrated pro-aggressive effects of microinjection of L-glutamate or kainite in the hypothalamic attack area (Brody et al. 1969; Haller et al. 1998). Subsequent pharmacological and genetic studies have shown that almost all subtypes of glutamate (NMDA, AMPA, kainate receptors, and metabotropic glutamate receptors) are involved in aggression, but the nature and extent of the response are highly variable (see Takahashi and Miczek (2014) for review) and behaviorally not specific. For example, antagonists of NMDA receptors may cause enhancement of aggression as well as suppression, together with abnormal locomotor activation or ataxia. Similarly, genetic ablation of subunits of NMDA receptors (Duncan et al. 2014), AMPA receptors(Vekovischeva et al. 2004; Shimshek et al. 2006; Adamczyk et al. 2012), and kainate receptors (Shaltiel et al. 2008) induces a range of abnormal behaviors including diminished aggressiveness in mice.

The inhibitory neurotransmitter GABA stands out as an important modulator of aggressive behaviors. An abundance of preclinical data shows that increasing GABAergic transmission through several pharmacological manipulations often inhibits aggressive behavior in mice (Krsiak et al. 1981; Puglisi-Allegra et al. 1981), rats (Molina et al. 1986) and cats (Cheu and Siegel 1998). Lower levels of GABA and the activity of the glutamic acid decarboxylase (GAD) enzyme are observed in highly aggressive individual rats, mice, and hamsters as well as more aggressive inbred strains of mice (Potegal et al. 1981; Haug et al. 1984; Guillot and Chapoutier 1996). Likewise, in human subjects lower plasma GABA levels (Bjork et al. 2001) and mitochondrial benzodiazepine receptor binding (Soreni et al. 1999) have been found in patients with high ratings of aggression. The aggression suppressing effects of GABA involve both the $GABA_A$ and the $GABA_B$ receptors; muscimol and baclofen, GABA agonists at the $GABA_A$ and the $GABA_B$ receptors, respectively, are effective inhibitors of aggression but in a behaviorally nonselective manner. The most intriguing evidence on the role of GABA in aggressive behavior comes from studies involving positive allosteric modulators such as benzodiazepines, alcohol, and the neurosteroid allopregnanolone. In contrast to the direct GABA agonists, these positive allosteric modulators of the $GABA_A$ receptor were shown to have biphasic effects on aggressive behavior, with low anxiolytic dosages increasing and high sedative dosages decreasing aggressive behaviors (Miczek et al. 2003; Fish et al. 2001; Gourley et al. 2005). The aggression-heightening and aggression-suppressing effects of benzodiazepines can be modified by previous social experiences (Ferrari et al. 1997). Alcohol reliably escalates aggression in approximately 30% of

male mice and rats, whereas the level of aggression in the other 70% either did not change or decreased relative to their basal level after an administration of a moderate dose (Miczek et al. 1998). This individual variation seems to be comparable to the human condition, and differences in the propensity for escalated aggression by alcohol may arise from functional and compositional differences in the $GABA_A$ receptor. Recent evidence in mice has demonstrated that the modulation of 5-HT impulse flow by GABA, acting via distinct receptor subtypes in the dorsal raphe nucleus, is of critical importance in the suppression and escalation of aggressive behavior (Miczek et al. 2015a, b). To date, no clinical PET imaging studies related to GABA/glutamate are available.

28.8 Hormones of the HPA (Cortisol/Corticosterone) and HPG Axis (Testosterone)

The steroid hormones cortisol/corticosterone and testosterone have been the most intensively studied hormones in relation to aggressive behavior. Disruptions of the hypothalamus-pituitary-adrenal (HPA) axis, the body's stress response system that regulates the release of corticosterone/cortisol, are frequently observed in aggressive and antisocial people. Similar to humans, animal studies have shown that low to moderate acute changes are associated with increased aggression in rats, whereas higher or longer-lasting changes are associated with decreased aggressiveness in mice. Recently, Kruk (2014) proposed an interesting concept that the anticipation of an impending conflict rapidly activates the HPA axis, producing an adrenocortical response that promotes an increased sensitivity for aggression, releasing and directing stimuli by a rapid feedforward to appraisal mechanisms in the brain. This stress-aggressive conflict feedforward mechanism seems to depend on the mineralocorticoid receptor (MR) as pretreatment with the MR antagonist spironolactone robustly inhibits resident's offensive aggression towards an intruder (Kruk et al. 2013). On the other hand, sustained glucocorticoid deficiency observed in a number of psychiatric disorders such as antisocial personality disorder and posttraumatic stress disorder is associated with abnormal aggressive behavior in these patients (McBurnett et al. 2000). The causal involvement of glucocorticoid deficiency in aggression and violence has been demonstrated in male rats (Haller and Kruk 2006). Glucocorticoid deficiency created by surgical removal of the adrenal gland and low corticosterone replacement induced violent-like forms of aggressiveness in male rats. These animals direct their attacks to vulnerable parts of the body, an effect that is normalized by corticosterone injections. Further analysis of the abnormal aggressive behavior suggests that the effects of chronic glucocorticoid deficiency on aggression and violence are somehow related to anxiety and/or physiological hypo-arousal.

Testosterone is the main gonadal steroid hormone that has traditionally been tightly associated with male offensive aggressiveness. This link between testosterone and aggression originated from the classic ablation-replacement studies using domestic fowl (Allee et al. 1939), mice (Beeman 1947; Barkley and Goldman 1977), and rats (DeBold and Miczek 1981; Koolhaas et al. 1980), showing a direct

causal relationship. Furthermore, baseline testosterone concentrations are positively correlated with aggressiveness and social dominance status (Schuurman 1980; Gesquiere et al. 2011). While testosterone levels rise rapidly in species ranging from rodents to humans after social competition, this response is generally higher and longer lasting in winners than in losers (Schuurman 1980; Oyegbile and Marler 2005; Fry et al. 2011).

Yet, the relationship between aggression and baseline levels of testosterone in humans is, even if statistically significant, rather small in magnitude. A meta-analysis of over 40 studies in humans found an overall correlation of $r = 0.08$ between testosterone and a variety of measures of aggression (Archer 2006). However, a growing body of evidence suggests that acute changes in testosterone within the context of competition and/or social provocation may be more relevant for the putative testosterone-aggression link. In both humans and animals, winning an aggressive interaction leads to a transient testosterone spike that enhances the chance of winning subsequent interactions (Carré et al. 2013; Trainor et al. 2004; Schuurman 1980). Losing a fight will reduce plasma testosterone levels for a long period of time and renders the defeated individual less motivated or able to aggress (Schuurman 1980). The behavioral effects of testosterone are partly due to its action on peripheral secondary sex characteristics, thereby changing the stimulus characteristics of the animal. More important however is its action on the brain. Exogenous testosterone administrations increased amygdala and hypothalamic reactivity (Hermans et al. 2008; Goetz et al. 2014), reduced orbitofrontal activity (Mehta and Beer 2010), and reduced amygdala-orbitofrontal connectivity (van Wingen et al. 2011) in response to angry facial expressions, which is what is observed in individuals with recurrent problematic impulsive aggressive behavior (Coccaro et al. 2007). During development, testosterone plays an important role organizing brain and behavior into a more masculine direction. Characteristic of the neuronal network for offensive behavior is that several of the subcortical brain structures are very sensitive to gonadal steroids. Social behavior-select neurons in the hypothalamus, medial amygdala, bed nucleus of the stria terminalis, and preoptic area are characterized by a high density of estrogen and androgen receptors (Wood and Newman 1999; Roselli and Resko 2001). Moreover, these neuronal nodes contain high amounts of aromatase and 5α-reductase, enzymes that convert testosterone into estradiol and the androgen dihydrotestosterone, respectively. Both metabolites of testosterone play a distinct role in the modulation of offensive aggression through their respective action on estrogen and androgen receptors. In particular the ER1 receptor has been implicated in the modulation of offensive aggression. Deleting this receptor through genetic modification completely abolishes aggression in male mice (Ogawa et al. 1997). Circulating levels of testosterone can be controlled experimentally through gonadectomy; however, even castrated males generate estrogen from testosterone produced in the adrenals. Therefore, only genetic deletion of aromatase in male mice eliminates estrogen action, resulting in a complete loss of aggressive behavior. Hence, individual variation in offensive aggressiveness may depend on the density of ER1 and/or the amount of aromatase present in various brain areas. Indeed, aggressive males show higher numbers of ER1-expressing cells in the

lateral septal area, the BNST, and the preoptic area. Moreover, the number of ER1 receptors increases with aggression in seasonally reproducing animals. However, also the androgen receptor is involved. Evidence in mice suggests that the androgen receptor increases in various limbic brain areas after winning experience (Fuxjager et al. 2010). One can conclude that the effects of testosterone on aggressive behavior depend on the complex interaction between the balance between the two converting enzymes, the density of ERα and androgen receptors, as well as experiential and contextual factors. The prominent link between gonadal steroids and enhanced aggression is further clearly demonstrated in animals and humans that are exposed to anabolic/androgenic steroids (AAS) during adolescence (Morrison et al. 2015). Several studies have shown that AAS exposure during this developmental period consistently increased aggressive behavior via alterations in several neurotransmitter systems (i.e., 5-HT, DA, and AVP) implicated in the control of aggression within the hypothalamic attack area.

28.9 Vasopressin and Oxytocin

Besides their important peripheral physiological functions as neurohypophysial-released hormones, the neuropeptides arginine vasopressin (AVP) and oxytocin (OXT) are also implicated in interneuronal communication within various nodes of the social brain network to modulate emotional and social behavioral and physiological responding (Lee et al. 2009a). These nonapeptides are arguably the most commonly studied neuropeptides in the modulation of social behavioral functions. AVP is generally known to increase anxiety-like behaviors, stress responsivity, and aggressiveness, whereas OXT has the opposite effects and facilitates social attachment, care, and affiliation (Heinrichs et al. 2009). Existing data from early pioneering work on these neuropeptides convincingly demonstrated opposite roles for AVP and OXT in fear learning processes (Bohus and de Wied 1998). More recent studies in feral wild-type rats and/or artificially selected aggressive and nonaggressive mice have demonstrated that high-aggressive animals exhibit higher levels of AVP release when compared to their nonaggressive counterparts (Koolhaas et al. 2010). In addition, there is abundant experimental evidence to support a causal function of vasopressin in proactive aggressive behavior and OXT in passive affiliative behavior. Direct micro-infusion of AVP or OXT into the cerebral ventricles or in selected brain regions facilitates or suppresses, respectively, offensive aggression (Calcagnoli et al. 2015). In addition, a positive correlation between levels of CSF vasopressin and life history of general aggression as well as aggression towards individuals (Lee et al. 2009a, b) has been reported, whereas impaired brain OXT-ergic signaling has been implicated in several human neuropsychiatric disorders associated with social deficits, impulsivity, and excessive aggression (Lee et al. 2009a, b). Furthermore, mutant mice with the vasopressin receptor V1A/V1B gene deleted showed virtually no offensive aggressive behavior anymore, whereas elevated aggressiveness was found in mice with deletions of the OXT receptor gene. Consistent with the aggression-promoting role of brain AVP, systemic as well as intra-hypothalamic

administration of AVP V1A/V1B receptor antagonists effectively block offensive aggressive behavior in male hamsters and WTG rats (Blanchard et al. 2005; Koolhaas et al. 2010). Basically, an opposite picture seems to emerge for brain OXT signaling. Recent ethopharmacological studies have clearly demonstrated that enhancement of brain OXT-ergic function, using either intraventricular, intra-amygdalar, or even intranasal administration routes, produced marked anti-aggressive and pro-social affiliative effects that are dose-dependent, behavior- and receptor-selective, and long-lasting (Calcagnoli et al. 2013, 2015). To date, no clinical PET imaging studies related to the nonapeptidergic system are available.

28.10 Concluding Remarks and Future Directions

The human and animal neurobiological research findings convincingly demonstrate that abnormal expressions of aggressive behaviors principally find their origin in a dysregulation of the deeply rooted neuronal circuits and/or neurochemical pathways in the brain that mediate normal social affiliative-aggressive behaviors. This highly conserved neural and gene expression brain network includes the intimately interconnected forebrain (limbic) structures amygdala, bed nucleus of the stria terminalis, lateral septum, mediodorsal and anterior thalamus, and several hypothalamic nuclei. Evidence suggests that these limbic areas collectively encompass a hierarchical role in the sensory processing and generation of the aggression aggressive display sequences. In addition, important "top-down" modulatory control is provided by cortical structures like the orbitofrontal (OFC), medial prefrontal (mPFC), and anterior cingulate cortex (ACC), as well as the ascending midbrain monoaminergic dorsal/medial raphe nucleus (DRN/MRN; serotonin) and ventral tegmental area (VTA; dopamine). The structural and functional properties of this social aggressive behavior brain network are established and constantly shaped by a dynamic interplay of genetic and environmental factors (stress, maltreatment, vicarious experiences, substance abuse) in particular during certain sensitive (i.e., perinatal and adolescent) developmental periods. Comparison of the animal and human data regarding the neuroanatomical and neurochemical organization of aggression, as outlined extensively in the previous sections, shows considerable similarities but also several inconsistencies and important omissions. Brain PET/SPECT/fMRI imaging studies largely substantiate that the neural circuitries that mediate aggressiveness in humans overlap with the network of brain regions controlling aggression in animals. However, it is quite surprising that virtually all of the human neuroimaging studies are predominantly concentrating on the cortical (i.e., prefrontal orbitofrontal and cingulate) and temporal lobe (amygdala) brain structures, while nodes like the hypothalamus and associated limbic midbrain (septum, hippocampus) and hindbrain (periaqueductal gray) structures that are significantly involved in the direct causal control of animal fighting and attack usually do not show up in the region of interest analyses. Furthermore, in human neuroimaging studies, the cortical brain nuclei are typically assessed as a large unitary structure, while animal studies clearly demonstrate the finely grained functional subdivision of these

regions, even to the level of distinct neurons. The reasons for this discrepancy likely have to do with the rather poor spatial resolution of the current neuroimaging techniques (1–1.5 mm^3) with respect to neuroanatomical functional subdivision. Another gap between clinical and preclinical studies is the fact that the majority of conducted PET/SPECT studies have focused mainly on the classic serotonergic and dopaminergic systems, whereas preclinical studies clearly demonstrate that several other neurotransmitters and peptides play an important role in aggression. Hence, developing appropriate radiopharmaceutical probes for these systems should advance our understanding of neurotransmitter dysfunctions in excessive and violent aggressiveness. Additionally, various therapeutic targets that deserve further characterization, such as the 5-$HT1_{A/B}$ (auto)receptors, Dad1/Dad2 receptors, and OXT and $AVPV1_{A/B}$ receptors, have been described. PET/SPECT imaging studies of these receptors may help to clarify their role in the pathophysiology of aggression. Obviously, the current emerging circuit-level knowledge of the neuromolecular underpinnings of aggression in both its normal and excessive forms has great potential to guide the rational development of effective therapeutic interventions for pathological social and aggressive behavior. Finally, the potential predictive utility of neuroimaging techniques (i.e., neuroprediction) for medical diagnosis, treatment, and perhaps even legal punishment of violence and other forms of serious antisocial behavior may provide substantial benefits for society.

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Part VI

Miscellaneous Subjects