Neurobiological overlaps in drug addiction, obesity and violence: focus on the role of dopamine in escalation of rewarding behavior

Essay

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Introduction

Drug abuse, obesity and violence, all behavioral disorders arising from dysregulated neurobiological functioning, are major issues in modern society with very limited success of available treatment strategies. Moreover, given their impact on health care, criminal justice and political legislation, economic burden of these disorders is immense. Drug addiction has been estimated to account for more than 40% of financial costs created by all neuropsychiatric disorders in the US [1]. For obesity, individuals are thought to have approximately 30% greater medical costs than their normal weight peers [2]. Transcending the substantial financial costs to our society, acts of violence account for an estimated annual 1.43 million deaths worldwide [3].

Unsurprisingly, an enormous amount of effort has been made to unravel the underlying mechanisms that characterize these disorders. Although this has led to many valuable insights, successful treatment has proven to be extremely difficult. Fortunately, recent developments in neurobiological research techniques created new opportunities for further characterization of the neurobiological circuitry of normal and dysfunctional brain circuitry. Opto- and chemogenetics allow for highly specific manipulations with a spatial and temporal sensitivity that was previously impossible [4]. These advancements in our understanding are of invaluable importance in the development of new treatment strategies for disorders that have so far been difficult to treat.

Although resulting in distinct phenotypical characteristics, emerging bodies of evidence suggest similarities in the underlying neurobiological mechanisms for the before mentioned conditions [5,6]. All disorders tap into the neuronal mechanisms that modulate motivation, impulsivity and inhibition of behavior that result in a loss of control over normal drug and food intake and offensive aggression. Ideally, successfully targeting the defects in these shared neural mechanisms would contribute to better treatment in any of the disorders. It is therefore of crucial importance to further explore this appealing postulation by taking advantage of the currently available techniques.

Extensive literature is available on the food addiction hypothesis, stating that compulsive overeating and obesity can be regarded as an addiction for highly palatable food [7-10]. This essay will discuss neurobiological evidence for the food addiction hypothesis, extending these ideas into the pathology of offensive aggression, i.e. violence. The focus will be on the dopaminergic system and recent findings derived from opto- and chemogenetic studies, as these provide the most detailed picture of the complex overlapping neurocircuitry of drug addiction, food addiction and violence. First, the neurobiology of acute rewarding effects of the reinforcers will be discussed, followed by a summary of the processes involved in a transition to compulsive reward-seeking behavior. Thereafter, the importance of loss of inhibitory control over behavior will be discussed, finishing with a section on the mechanisms by which negative emotional states can contribute to escalation of drugs and food intake and offensive aggression.

Acute rewarding properties of drugs, food and offensive aggression

The very first step in the development of every addiction to either a recreational drug, food or behavioral act is the initial use and the following rewarding/pleasant experience mediated by, among others, an acute activation of the dopaminergic brain reward system (figure 1). Rewarding stimuli, although different in underlying mechanisms, all act on the reward system by a transient enhancement of dopamine (DA) neurotransmission in the nucleus accumbens (NAc) [8],[11]. In addition, DA-ergic neurons from the ventral tegmental area (VTA) project to the NAc and optogenetic activation of these DAergic VTA neurons is sufficient to induce a conditioned place preference, suggesting a pleasant experience upon stimulation of these neurons itself [12]. Together, these two brain structures form the core of the brain reward system, and have been extensively studied in relation to the acute rewards of drugs of abuse [13]. Blocking the dopaminergic system decreased the acute rewarding properties of cocaine as measured in self-administration and conditioned place preference (CPP) paradigms [14,15]. However, specific

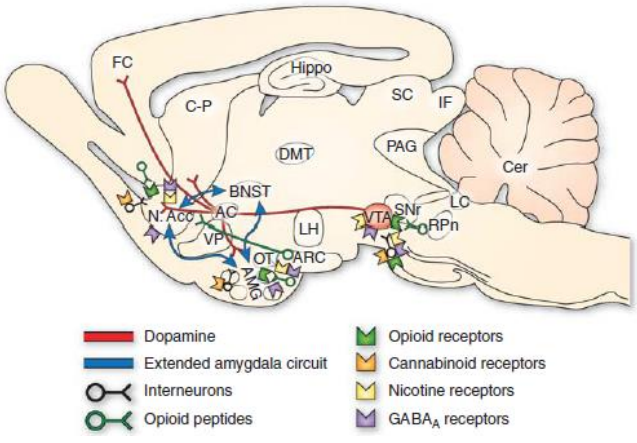

Figure 1 Illustration of the pathways and receptor systems involved in the acute rewarding effects of drugs of abuse in a sagittal section of a rodent brain. Figure derived from [13].

lesions of dopamine in the NAc failed to block heroin and ethanol self-administration [16], suggesting dopamine-independent reinforcement for different drugs of abuse at the level of the NAc. Indeed, other opiate (VTA and NAc) and $GABA_A$ (NAc and amygdala) systems also play an important role in the rewarding effects of different types of drugs of abuse [13].

Interestingly, the rewarding properties of cocaine can be surpassed by allowing a choice for sweetened water (saccharin), suggesting strong rewarding properties of sweet tastings [17]. Moreover, ingestion of nutrients such as fats and sugars can trigger addictive-like behavior in animal models [18,19]. Indeed, upon first exposure to a food reward, DAergic VTA neurons start firing, resulting in an increase of DA in the NAc [20]. However, it is of great importance to note that the rewarding properties of food are much more complex than solely via the dopaminergic system, as it is regulated by a great variety of other neurotransmitters and neuropeptides such as orexin, ghrelin, insulin, PYY and glucagon-like peptide-1 [21]. Interestingly, these neurotransmitters implicated in food reward have also been shown to be affected by drugs of abuse [8]. Supporting this, animal models of obesity have been shown to possess attenuated responses to drug of abuse [22][23]. These results strongly suggest an overlap in reward mechanisms of drugs of abuse and palatable food.

Extending this reward circuitry towards offensive aggression, increasing extracellular DA via METH administration increased offensive aggression in mice [24], whereas DA antagonists decreased aggression [25]. In addition, aggressive encounters were shown to upregulate DA levels in the NAc [26], whereas selectively blocking D1 and D2 receptors in the NAc decreased aggression [27]. Next to the observed effects in the NAc, the VTA is also implicated in the rewarding properties of aggression, as seen by an increase in c-Fos expressing neurons in the VTA in combination with a CPP after social interactions [28]. This study also showed that this effect was correlated to the amount of aggressive/dominance behaviors two months before, suggesting that the reward system is more active in highly aggressive individuals than in low-aggressive conspecifics [28].

It should be noted that social defeat, an extremely aversive and stressful event for rats, also increased phasic dopamine transmission in the mesolimbic pathway [29]. This finding is in line with a more recent view that DA neurons in the VTA differ in functionality through different connection networks. Indeed, it has been postulated that “Some dopamine neurons encode motivational value, supporting brain networks for seeking, evaluation, and value learning. Others encode motivational salience, supporting brain networks for orienting, cognition, and general motivation" [30]. However, the neurochemical role of this difference should be studied in more detail, as DA neurons in the VTA are inhibited by GABA neurons upon a foot shock, a different aversive stimulus. Moreover, optogenetic activation of these GABA neurons is sufficient to drive conditioned place aversion [31]. In addition, optogenetic stimulation of VTA DAergic neurons increased inter-male aggression in mice [32]. It would therefore be of great importance to further elucidate the connecting networks of VTA DAergic neurons in relation to offensive aggression and social defeat.

Nevertheless, experiments showing a positive relation between aggression and cocaine self-administration support a shared reward system of the two behaviors. Highly aggressive mice were shown to self-administer morphine and cocaine at higher doses than nonaggressive animals [33]. In addition, Roman High Avoidance rats, known for increased rates of offensive aggression, also displayed a higher propensity to self-administer cocaine [34]. Moreover, dominant rats displayed increased motivation for food reward, although the authors contribute this finding to increased risk-taking behavior in these individuals [35]. In conclusion, there is compelling evidence for the activation of similar reward circuitry following administration of drugs of abuse, intake of palatable food, or exhibition of aggressive behavior. This is supported on the one hand by separate studies showing activation of similar brain areas (particularly the NAc and VTA). Other evidence is derived from studies directly comparing these behaviors in the same individuals, in which animals display consistencies across the different rewarding behaviors.

The transition to compulsivity

The role of DA extends beyond the acute reinforcement described in the previous paragraph. Due to the strong DA increasing effects of drugs, food and aggression, neutral stimuli that are linked to the availability of these reinforcers acquire the ability to induce a DA increase in the ventral striatum in anticipation of the reward. Once this conditioning has occurred, DA acts as a predictor of reward, resulting in the animal performing behavior that will help to obtain the reward eventually [36].

There is evidence that conditioning of rewarding stimuli co-occurs with a gradual shift of DA increase from the ventral striatum (NAc) to the dorsal striatum [37]. Simultaneously, the role of the VTA decreases and involvement of the substantia nigra (SN) increases [8]. The conditioning is further facilitated by extensive glutamatergic input to the DAergic neurons from regions in the brain involved in sensory input (insula), homeostasis (hypothalamus), reward (ventral pallidum and NAc), emotion (amygdala and hippocampus) and salience attribution (orbitofrontal cortex, OFC) [38].

Indeed, projections from the amygdala and OFC to DAergic neurons and the NAc have been shown to be involved in the conditioned responses to food [39]. In addition, the basolateral amygdala (BLA) and OFC interact in drug context-induced reinstatement of cocaine-seeking behavior [40]. Moreover, optogenetic stimulation of the glutamatergic fibers from the BLA to the NAc in mice resulted in reinforcement when the reward was an additional stimulation of this pathway [41]. Supporting an important role of this pathway in naturally occurring reward, optogenetic inhibition of these neurons reduced cue-evoked sucrose intake [41]. However, the supporting role of the BLA in reinstatement has been studied most extensively in the

context of cocaine [42] and heroin [43] and experiments on reinstatement in food-seeking behavior suggest different subregions of the BLA to be involved in reward-seeking behaviors induced by drug or food related stimuli [44].

Although the underlying mechanisms of compulsive reward-seeking behavior, despite some specific differences, appear to be relatively similar, the strength of the reinforcer is thought to play an important role in the likelihood of reinstatement. Drugs cues are more likely to induce reward-seeking behavior after a period of abstinence than food cues [45]. In addition, stress-induced reinstatement is much more likely to occur for drugs of abuse than for food reinforcers [45]. On the other hand, other studies show that rats readily switched from taking cocaine to saccharin consumption, even after prolonged periods of cocaine use, indicating that cocaine is low on the value ladder of rats [46]. Despite these differences however, the underlying mechanisms appear to be similar and the observed differences are thought to be a matter of degree rather than principle [8].

As with drug and palatable food intake, the execution of offensive aggression is rewarding and can be conditioned. Winning an aggressive encounter increases the probability of winning a future fight in an individual, a phenomenon known as the winner effect [47]. Since aggressive encounters can be rewarding (see previous section), mice can be conditioned to nose poke for aggressive encounters [48,49]. These changes have been associated with increases of DA levels in the NAc [50,51]. Unfortunately, the role of different afferents to the NAc and SN, such as the BLA and OFC, in conditioned aggression has not yet been studied. Future studies should aim at elucidating the role of different brain regions in facilitating reinstatement following exposure to cues that have been linked to the winning of a fight. In addition, it would be interesting to directly compare the rewarding value of a fight with other reinforcers such as drugs of abuse and food.

Although an important component of addiction and addictive-like behavior, the reinforcing properties and following conditioned response towards drugs, food and fighting alone cannot explain the escalation of these behaviors as observed in a subset of individuals. As for drugs, the vast majority of individuals experience drugs as reinforcing, yet a small proportion of the individuals exposed to those drugs develop a fully addicted phenotype. Therefore, other brain areas involved in inhibitory control over behavior and negative emotional states are likely to be involved in the escalation of drug intake, food consumption and offensive aggressive behavior.

Loss of inhibitory control

The prefrontal cortex is an important brain region involved in cognitive and executive processes such as working memory, decision-making, inhibitory response control, attentional set-shifting and the temporal integration of voluntary behavior [52]. Moreover, different subregions of the PFC have been linked to these different processes. In addiction, the previously described effects of increased cravings for reinforcing behavior are accompanied by impairments in inhibitory control over behavior. The main region involved in inhibitory control is the medial prefrontal cortex (mPFC), which has been extensively studied in the context of drug addiction. Prolonged cocaine self-administration in rats has been shown to decrease cellular excitability in prefrontal cortical neurons, suggesting a causal effect of cocaine abuse in diminishing PFC functioning [53]. Moreover, optogenetic stimulation of mPFC neurons inhibited compulsive cocaine seeking as measured by persistence of seeking behavior despite delivery of foot shocks, whereas optogenetic inhibition increased cocaine-seeking behavior [53]. However, in a different behavioral paradigm, cue-induced reinstatement of cocaine-seeking was decreased after inhibition of mPFC neurons [54]. First, this difference highlights the importance of the paradigm that is used to study the loss of control over behavior. Second, it may indicate a highly specific and possibly opposite role of different neurons in the PFC regulating the loss of control over behavior [10]. This possibility is supported by experiments showing that active swimming in a forced swim test was unaffected by optogenetic activation of all PFC neurons projecting to the dorsal raphe nucleus. In contrast, when a specific subset of these neurons was activated, this behavior was promoted [55]. Therefore, future optogenetic experiments using specific stimulation and inhibition of subsets of mPFC neurons are needed to further elucidate the role of the mPFC neurons in inhibition of behavior.

Another well-known effect of long-term exposure to drugs is a downregulation of striatal dopamine D_2 receptor (D2R) availability [8]. In the striatum, D2Rs are involved in the indirect striatal pathway, which is involved in the sensitization of repeated drug exposure [56]. In drug addicted humans, striatal D2R reduction is associated with decreased PFC, OFC, anterior cingulate gyrus (ACC) and dorsolateral PFC (dlPFC) functioning [8]. These regions are involved in salience attribution, inhibition and decision-making, raising the possibility that dysregulation of these brain areas via decreased D2R signaling underlies the loss of control in drug addiction [57]. However, it can also be argued that a predisposition for dysfunctional PFC areas in vulnerable individuals exists that is aggravated by repeated drug use. Human evidence for this is provided by family studies showing increased striatal D2R availability and normal OFC, ACC and dlPFC metabolism in subjects with a positive family history for alcoholism [58]. In addition, twin studies revealed that addicted subjects had decreased OFC volume compared to their non-addicted twins, who showed no difference in OFC size compared to controls [59].

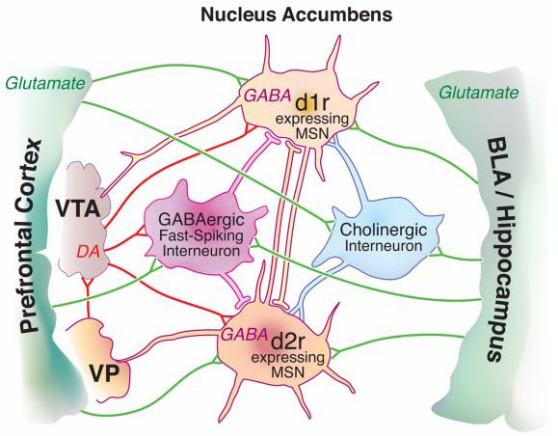

Figure 2. Intrinsic and extrinsic circuitry of the Nucleus Accumbens. MSNs projects to either the VP (D2R expressing) or the VTA/Sn (D1R expressing) and MSN activity is modulated by GABAergic and Cholinergic interneurons. These projections receive input from the mPFC, BLA, hippocampus, thalamus and VTA. Figure derived from [61].

The role of striatal D2R availability in the reinforcing properties of drugs is relatively well-understood. The reinforcing effects of dopamine depend on striatal neurons that receive dopaminergic input from midbrain structures. These striatal neurons are mainly medium spiny neurons. The dopamine D2 receptor is expressed on indirect pathway medium spiny neurons (iMSNs), whereas the direct pathway neurons (dMSNs) express the dopamine D1 receptor [60][61] (see figure 2) . The dopamine D2 receptor is an inhibitory Gi coupled receptor, and dopamine inhibits iMSNs [62]. Direct optogenetic stimulation of these iMSNs indeed promotes aversion [63] and reduces self-administration of cocaine [64]. In addition, chemogenetic inhibition of iMSNs increased the reward of amphetamine and cocaine [56,64]. One hypothesis by which reduced striatal D2R availability may contribute to the escalation of drug use, is through compensation of a blunted dopamine response, i.e. an individual increases its intake to achieve a similar rewarding effect.

These mechanisms may be in play for food addiction as well, as obesity is also associated with impairments in executive function, working memory and attention [65,66] and structural abnormalities in the frontal brain regions of obese individuals [67,68]. In addition, obese individuals also exhibit decreased striatal D2R availability, which is associated with decreased PFC and ACC activity [69]. Moreover, striatal D2R availability is negatively correlated with BMI in both healthy and obese individuals [70,71]. Preclinical evidence supports these findings, showing a reduced preference for palatable food upon D2R agonist administration [72]. These results suggest that the loss of control over food intake may result from similar dysfunctions as seen in drug addiction, although detailed preclinical studies into these mechanisms are needed to elucidate the specific role of different mPFC neurons in inhibitory control over food intake as well.

Providing some insight into this question, optogenetic inhibition of the dorsal mPFC attenuated stress-induced reinstatement of food-seeking behavior in female rats [73]. These results were remarkably similar to the previously described optogenetic inhibition in relation to cue-induced reinstatement of cocaine [54]. However, again, it highlights the importance of elucidating the specificity of certain subsets of prefrontal neurons and their role in food reinstatement. This idea is further supported by evidence showing that, following food and stress reinstatement activated PFC neurons exhibit unique synaptic alterations compared to non-activated neurons [74].

Unsurprisingly, it is well known that the mPFC and OFC are linked to the inhibition of aggression as well. Aggressive encounters in rats have been shown to activate, among several other areas, mostly glutamatinergic pyramidal mPFC neurons [75,76]. In addition, electrical stimulation of the mPFC in cats inhibited aggression [77], whereas bilateral lesions of the mPFC or OFC increased aggression in rats [78,79]. These early findings have been extended using novel techniques like optogenetically stimulating or inhibiting excitatory mPFC neurons in rats, resulting in decreased or increased aggression, respectively [80]. On the other hand, enhancement of glutamatergic AMPA current in the mPFC increased social rank in mice, whereas inhibition decreased social status [81]. These results suggest modulation of several forms of aggression and an important role of the mPFC in regulating a balance between adaptive and maladaptive aggression [6].

Although striatal D2R availability plays an important role in the sensitization of drugs and food, its role in aggression remains a matter of debate. For instance, striatal D2R availability appears to be involved in stress-suppressed aggression and was upregulated upon repeated passive exposure to aggressive encounters in this study [82]. In contrast, a more recent study reported decreased striatal D2R availability upon repeated passive exposure to aggression [83]. The authors contribute this difference to the learned development of aggression, instead of a stress-induced mechanism [83]. Therefore, the mechanisms appear to be similar to the learned effects of food and drugs. However, it is important to note that these studies use passive aggression, rather than direct exposure to aggressive encounters. It would therefore be of great importance to further elucidate the role of striatal D2R availability in inhibition of learned aggression.

Thus, all three disorders are not only characterized by increased reward sensitivity, but also by decreased inhibitory mechanisms via, among others, reduced mPFC functioning and reduced striatal D2R availability. Targeting these networks appears to be a promising line of research for future therapeutics designed to regain control over drug and food intake and aggressive eruptions, although further studies are needed to elucidate the overlaps in specific mPFC neuron functionality.

Negative emotional states

Cravings for the reinforcers and the inability to control them often emerge during periods of stress or emotional stress. Negative emotional states such as anxiety and depression are important factors in the drive to use drugs, eat beyond the homeostatic need or

initiate a fight. This can create a vicious circle, as relapse is most likely to occur during periods of stress and emotional distress, and drugs themselves or withdrawal from them can promote these stressful situations [84]. Similar patterns can be observed in over-eating [85] and aggression [86]. Obese animals exhibit increased levels of anxiety compared to non-obese individuals, suggesting a similar role of highly palatable food and drugs in contributing to these states. A comparable effect on anxiety was observed after repeated winning in low-aggressive mice [87] and rats [88]. In contrast, high-aggressive Wild and Swiss-CD1 mice exhibited lower levels of anxiety in a free-exploratory paradigm [89]. However, highly aggressive dominant Swiss male mice displayed increased levels of anxiety in the elevated-plus maze (EPM), once again indicating the importance of the used paradigm in interpretation of the results [90]. It is important to note that the effects are likely to be caused by the winning itself, as anxiety scores in the EPM before exposure to aggression are unrelated to aggression scores in WTG rats [91]. Altogether, these results indicate that drugs, food and aggression may contribute to a negative emotional state, and that this state can increase expression of the behavior itself.

Several neuromolecular mechanisms may contribute to these effects. As mentioned before, striatal D2R function is reduced in drug addicts, obese individuals and possibly following repeated aggressive encounters. Since the dopamine D2 receptor is a Gi coupled receptor, this may be predicted to elevate activity in iMSNs in these individuals, an effect known to induce aversion in mice [63]. As dopamine inhibits iMSNs, it is possible that individuals consume drugs, food or fight to induce an increase in dopamine in order to escape from the pervasive negative emotional state resulting from reduced striatal D2R availability [10].

A negative emotional state can, next to reduced striatal D2R availability, also emerge from alterations in dopamine producing neurons in the VTA. Highlighting the importance of specific synaptic connectivity in this network, inputs from the laterodorsal tegmentum and lateral habenula contribute to positive and negative states in mice, respectively [92,93]. In addition, selective inhibition of VTA DAergic neurons increased depressive-like behaviors in mice, whereas stimulation of these neurons rescued stress-induced depressive-like behavior in these animals [94]. Instead, experiments testing for susceptibility as oppose to resilience of these behaviors showed that optogenetic induction of phasic, but not tonic, VTA DAergic neurons promoted depression-related behaviors in mice that were previously resilient to repeated social-defeat stress [95]. Again, these results suggest that functional encoding of VTA DAergic for stress and reward (see acute rewarding effects section) is firing-pattern selective and highly context-dependent [95]. Moreover, the effects are dependent on the severity of stress and are projection-pathway specific [96]. Altogether, the VTA networks encoding for negative emotional states and increased reward sensitivity are extremely complex. In order to identify a reliable link between repeated reward-seeking and negative emotional states, future studies directly comparing the two behaviors are needed.

Finally, the amygdala is a brain region that has been linked to a large variety of emotional processes, among which anxiety-disorders [97] and craving for cocaine [98] and alcohol [99], but not for food [100]. In addition, an important role for the amygdala has been suggested in the drive for aggression [3]. Optogenetic studies on this brain structure have helped the understanding of distinct parts of the amygdala regulating anxiety [101], fear [102] and reward-seeking via projections of the BLA to the NAc [103]. However, the exact role of different neurons in the amygdala in determining the emotional significance of environmental stimuli remains elusive, as similar activation patterns in the amygdala were observed for appetitive and aversive stimuli [104]. Therefore, future optogenetic studies that allow for more specific manipulation of distinct synaptic and cellular patterns should help our understanding of the link between amygdala subpopulations and negative emotional states leading to the drive for drugs and violence.

Discussion

The experiments reviewed here highlight the multiple overlaps in neurobiological processes underlying drug addiction, food addiction and escalated offensive aggression, i.e. violence. Shared mechanisms can be observed in the dopaminergic reward circuitry, both for acute rewarding properties of the reinforcers as well as the transition to compulsive reward-seeking behaviors due to conditioning. In addition, the loss of control over behavior that could be aggravated by negative emotional states appears to arise from similar dysfunctionalities in the mPFC and mesolimbic system.

It should be noted that the work summarized here focuses primarily on the dopaminergic system. As mentioned before, a large variety of other neurotransmitters and peptides play a major role in drug addiction and food intake [8]. Among these, the neurotransmitter that is known for a primary role in the regulation of aggression and violence is serotonine (5-HT)[105],[106]. The serotonergic system is involved in virtually every central process that requires a sensory-driven response [107]. Unsurprisingly, serotonin circuitry has also been implicated in psychostimulant addiction [108] and food intake [109]. However, due to a large variety in 5-HT receptor families and subtypes with opposing effects [110],[111], the serotonergic system is extremely complex and exceeds the scope of this essay. Nevertheless, the effects of dopamine and serotonin have been proposed to be consequences of a single root mechanism [112] and it is therefore likely that targeting any of the two neurotransmitters can affect addiction-related behaviors such as decision-making and reinforcement learning. Future studies into the serotonergic circuitry may therefore be effective in situations where dopaminergic manipulation is not.

Next to different neurotransmitter systems in the brain, another brain area that has been associated with drugs, food and aggression is the hypothalamus. As the hypothalamus is the link between the central nervous system and the endocrine system, it is no surprise that it serves a crucial role in food intake [113]. In addition, similar activation patterns of the lateral hypothalamus

were observed in food intake and drug addiction [114]. Novel optogenetic techniques greatly contributed to our understanding of the role of different subregions of the hypothalamus in aggression as well (figure 3). In particular, the ventrolateral subdivision of the ventral medial hypothalamus (VMHvl) seems to be an important node in the neural circuitry that controls aggressive attacks. Optogenetic stimulation of specific neurons within this region robustly triggers offensive attacks towards intruder males, females and inanimate objects [115]. More specifically, manipulation of neurons co-expressing the estrogen-receptor alpha (ER-α) in this region triggered or suppressed fighting upon stimulation or inhibition, respectively [116]. Another hypothalamic nucleus that has been extensively studied in the context of aggressive behavior is the medial preoptic area (MPOA), in which optogenetic stimulation of galanin neurons inhibited inter-male aggression and shifted infanticidal attacks toward offspring to paternal care [117]. These results show the great specificity of different neurons in subregions of the hypothalamus. However, these studies showed acute effects of these neurons in regulating aggression, and their role in animals that have been repeatedly exposed to winning aggressive encounters remains to be investigated. Moreover, their role in drug addiction and food intake is unknown. Future studies using these highly specific manipulations to test for overlapping functionality in different behaviors are essential for our understanding of the role of hypothalamic neuronal subpopulations in drug and food intake.

An often-overlooked or neglected aspect in preclinical research on drug and food addiction and offensive aggression is the large individual variability observed in the human population. Indeed, only 15-20% of the individuals exposed to drugs of abuse develop an addiction [118]. Moreover, every person must eat, yet a small proportion of individuals become obese, although this number is increasing alarmingly [119]. Fortunately, several labs acknowledged this gap between human data and preclinical animal models and developed techniques to study individual vulnerability in these disorders.

For drug addiction, two different approaches have been developed to study individual vulnerability. The first paradigm is based on the DSM-IV criteria for drug addiction and tests rats in a series of cocaine self-administration related behaviors. Animals are exposed to a period of self-administration of cocaine and thereafter tested for (i) persistence of cocaine-seeking despite non-availability, (ii) increased motivation to take the drug measured in a progressive-ratio schedule, and (iii) continued use despite negative consequences (electrical shock). Animals that present the highest scores (top 33%) in all three addiction-like behaviors are considered compulsive-like cocaine users [120,121]. Interestingly, the percentage of rats that show a high score in all three addiction-like criteria is 17%, similar to the human cocaine users diagnosed as addicts [120].

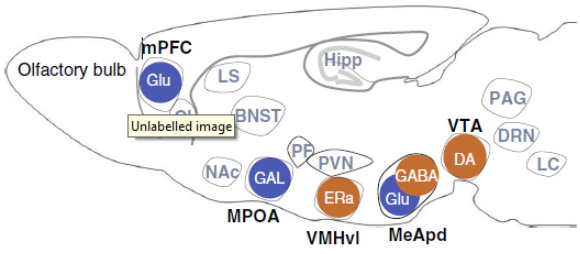

Figure 3. Brain areas that are involved in inter-male aggression in mice. Brain areas that either increased (orange) or decreased (blue) aggression upon optogenetic stimulation. Gray areas have also been reported to be involved in aggressive behavior by c-Fos immunohistochemistry [6].

Another approach takes advantage of the observation that the vast majority of rats that have been trained to self-administer cocaine for prolonged periods rapidly switch to saccharin when this choice is available [17,46],[122,123]. A small proportion of animals continued to choose cocaine over saccharin and was considered vulnerable to addictive-like behavior, as opposed to resilient animals that switched to saccharin intake. An advantage of this approach is that no fixed percentage of animals is considered compulsive cocaine users, although the average proportion again seems to map well with the human population [46,122].

As in drug addiction, there are large individual differences in the susceptibility for metabolic disorders such as obesity and type 2 diabetes. In animals, the previously mentioned Roman High- (RHA) and Low Avoidance (RLA) strains have been related to differences in energy balance and are thought to be helpful in modeling metabolic disorders. These strains, originally selected for high and low responsiveness in a two way active avoidance test, indeed show differences in blood pressure, insulin response, meal patterns and visceral fat [124]. Passive animals (RLA) exhibit hypertension, insulin resistance and visceral adiposity, making it a non-obese animal model for the metabolic syndrome [125]. However, RHA animals display larger amounts of cumulative food intake of normal chow [124], highlighting that increased food intake does not lead to obesity per se. RHA rats are also known for increased levels of cocaine self-administration and offensive aggression [34]. However, when animals were exposed to a high-fat diet, RLA showed increased weight gain compared to RHA animals [126]. These results show that RLA rats are a valuable animal model for studying metabolic disorders, although they contradict increased reward sensitivity to be the underlying cause for weight gain.

Finally, large individual differences in the level of offensive aggression have been observed in an outbred strain of rats, the Wild-type Groningen (WTG) rats. These differences have been linked to a variety of other behaviors, suggesting that this is an indication of an individual's trait-like behavioral response pattern, i.e. coping style [91]. Repeated exposure to an unfamiliar intruder in the home cage results in the development of escalated, persistent, indiscriminating and injurious offensive aggression in a subset (8-12%) of individuals [106]. These animals provide a valuable line of research into the neurobiology of violence. As mentioned before, different coping styles have been linked to differences in cocaine self-administration [33], although this has not been studied in relation to animals that were trained to become violent.

All these models share the finding that some individuals display vulnerability to develop the escalated behavior, whereas others appear to be resilient. It would be of major interest to compare drug intake, food intake and escalated aggression in the same individuals more directly. In doing so, it should become clear whether individuals that are prone to escalate behavior in one aspect are also likely to lose inhibitory control over the other. In addition, the incredible detail of optogenetic studies could be used in studies on these vulnerable and resilient animals in a similar manner as applied in mice previously resilient to development of depressive-like symptoms [95]. Moreover, this technique can also be used in attempting to inhibit escalation of the behaviors specifically in vulnerable individuals. As we gain understanding of the specific neurons, neurotransmitters and receptors involved, it should become clear whether the apparent similarities on the structural level also apply to the deeper molecular mechanisms that underlie escalation of drug- and food intake and violence.

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