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Stress-induced plasticity and functioning of ventral tegmental dopamine neurons

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ABSTRACT

The ventral tegmental area dopamine (VTA-DA) mesolimbic circuit processes emotional, motivational, and social reward associations together with their more demanding cognitive aspects that involve the mesocortical circuitry. Coping with stress increases VTA-DA excitability, but when the stressor becomes chronic the VTA-DA circuit is less active, which may lead to degeneration and local microglial activation. This switch between activation and inhibition of VTA-DA neurons is modulated by *e.g.* corticotropin-releasing hormone (CRH), opioids, brain-derived neurotrophic factor (BDNF), and the adrenal glucocorticoids. These actions are coordinated with energy-demanding stress-coping styles to promote behavioral adaptation. The VTA circuits show sexual dimorphism that is programmed by sex hormones during perinatal life in a manner that can be affected by glucocorticoid exposure. We conclude that insight in the role of stress in VTA-DA plasticity and connectivity, during reward processing and stress-coping, will be helpful to better understand the mechanism of resilience to breakdown of adaptation.

1. Introduction

Although the stress response is essential for adaptation and survival, the term 'stress' is today generally associated with a negative experience (McEwen, 2013a,b). Work-related stress is common and chronic exposure to stress is linked to various neuropsychiatric disorders, such as major depressive disorder (Calabrese et al., 2009; Kessler, 1997). However, the underlying causative mechanism of these stress-related disorders remains poorly understood and the etiologic knowledge is limited to risk factors and vulnerability (Chrousos, 2009; Nestler et al., 2002). Therefore, the understanding of the neurobiology of stress may help the prevention and treatment of mental disorders.

One of the neurotransmitters that is profoundly affected by stress is dopamine (DA), which is classically associated with sensorimotor functions, incentive motivation, reward processing, and reinforcement learning (Arias-Carrión et al., 2010; Cabib and Puglisi-Allegra, 2012; Ljungberg et al., 1992; Romo and Schultz, 1990; Schultz et al., 1993, 1997). Of crucial importance in this respect is the mesocorticolimbic DA circuitry, which originates from the ventral tegmental area (VTA) neurons (Holly and Miczek, 2016; Trainor, 2011; Tye et al., 2013;

Abbreviations: ACTH, adrenocorticotropic hormone; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; MPAR, AMPA receptor; BDNF, brain-derived neurotrophic factor; BLA, basolateral amygdala; BNST, bed nucleus striae terminalis; CMS, chronic mild stress; CRH, corticotropin-releasing hormone; CRS, chronic restraint stress; CSDS, chronic social defeat stress; CUS, chronic unpredictable stress; DA, dopamine; DOR, δ-opioid receptor; GABA, γ-aminobutyric acid; GABAR, GABA receptor; GR, glucocorticoid receptor; GSK3, glycogen synthase 3; HPA-axis, hypothalamus-pituitary-adrenal axis; IP3, inositol 1,4,5-triphoshpate; IP3R, IP3 receptor; ISDS, intermittent social defeat stress; KOR, κ-opioid receptor; LTD, long-term depression; LTP, long-term potentiation; mEPSC, miniature excitatory postsynaptic currents; mGluR, metabotropic glutamate receptor; MOR, μ-opioid receptor; mPFC, medial prefrontal cortex; MR, mineralocorticoid receptor; mTOR, mammalian target of rapamycin; N/OFQ, nociceptin/orphanin FQ; NAc, nucleus accumbens; NE, norepinephrine; NMDA, *N*-methyl-D-aspartate; NMDAR, NMDA receptor; NO, nitric oxide; NOPR, nociceptin/orphanin FQ receptor; PAG, periaquaductal grey; PI3K, phosphatidylinositol 3 kinase; PKA, protein kinase A; PKC, protein kinase C; PLCγ, phospholipase C-γ; POMC, pro-opiomelanocortin; PPTg, pedunculupontine tegmentum; PVN, paraventricular nucleus; TH, tyrosine hydroxylase; vHipp, ventral hippocampus; VP, ventral pallidum; VTA, ventral tegmental area

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Valenti et al., 2012) and has a high grade of neuronal connectivity with limbic structures and the medial prefrontal cortex (mPFC) (Beier et al., 2015; Watabe-Uchida et al., 2012). This VTA network is important for processing the linkage of internal states with appraisal of environmental stimuli, thereby forming emotional-motivational valuations (Burke et al., 2014; Lloyd and Dayan, 2016; Papageorgiou et al., 2016; Salamone and Correa, 2012). The valuations allow an organism to prioritize its goals and to adjust its choice of behavioral response to cope with a challenge (Burke et al., 2014; Moore and Depue, 2016; Papageorgiou et al., 2016). For instance, if a stimulus is considered rewarding, the individual will approach the reward rather than avoid it (Burke et al., 2014; Dayan and Berridge, 2014). Such valuations may change rapidly, however, when the rewarding stimulus turns into an adverse one, and results in a switch from approach into avoidance behavior (Berridge et al., 1984; Burke et al., 2014; Dayan and Berridge, 2014; Rangel et al., 2008; Robinson and Berridge, 2013; Tindell et al., 2009). This conflict between approach and avoidance also may occur if (anticipation of) reward presentation is compromised by a potential threat or stressor (Stanton et al., 2019). Mesocorticolimbic DA neurotransmission may be involved, therefore, in the pathophysiology of mood, anxiety, and addiction disorders, of which the deficit in emotional-motivational activation of reward-seeking is a core symptom (Grace, 2016; Nestler and Carlezon, 2006; Polter and Kauer, 2014).

Excellent reviews on the theme of stress and VTA-DA function have appeared (Belujon and Grace, 2015, 2017; Chrousos, 2009; Hollon et al., 2015; Ironside et al., 2018; Kalafatakis et al., 2016; Koob and Volkow, 2016; Kwako and Koob, 2017; Lammel et al., 2014a,b; Le Moal and Simon, 1991; Nestler and Carlezon, 2006; Polter and Kauer, 2014; Russo and Nestler, 2013; Stanton et al., 2019; Weger and Sandi, 2018; Wise, 2004). Here, we will delineate how plasticity and connectivity of VTA-DA neurons may change in response to acute and chronic stressors. In order to understand how such stressors may act, we focus on the hormones of the hypothalamus-pituitary-adrenal (HPA) axis (de Kloet et al., 2005; McEwen, 2007; Ulrich-Lai and Herman, 2009). This includes the action of corticotropin-releasing hormone (CRH), which orchestrates the HPA-axis response to stress in the paraventricular nucleus (PVN) and also acts as neuropeptide produced in *e.g.* the extended amygdala, a region that consists of the amygdala and bed nucleus striae terminalis (BNST). Also opioids are briefly discussed as part of the stress response system and their inherent addictive properties. We will focus in particular on the master regulator of stress-adaptation, the adrenal glucocorticoid hormone, and its downstream targets such as the locally produced brain-derived neurotrophic factor (BDNF). The review is concluded with a conceptual framework of the function of the VTA-DA system in stress-coping and adaptation.

2. Acute stress and VTA-DA circuitry

2.1. The stress response

The brain coordinates the response to stressors, decides on the selection of an appropriate coping strategy, and promotes adaptation (McEwen, 2016). If something novel happens, first the perception of salient sensory information triggers an *alarm* resulting in increased arousal, alertness, vigilance, and focused attention with the goal to instantaneously defend the 'self'. The stressor can be physical such as pain, blood loss, or tissue damage, and these reflexive autonomic reactions are triggered by brain stem nuclei that convey visceral information *via* ascending aminergic pathways to frontal brain regions including the PVN (McCarty and Gold, 1996). If the stressor is psychogenic the *alarm* results in rapid activation of the locus coeruleus noradrenergic network and the sympathetic nervous system including the adrenomedullary release of adrenaline (Reyes et al., 2015). Psychogenic stressors have a strong anticipatory component implying that the stress reaction may start even by imagination without an environmental trigger (Herman et al., 2003; Ulrich-Lai and Herman, 2009; Cabib and Puglisi-Allegra, 2012). All real and anticipated stressors activate the PVN-CRH/vasopressin neurons which orchestrate control of the autonomic and pituitary adrenocorticotrophic hormone (ACTH) reactivity resulting in increased secretion of the glucocorticoids cortisol and corticosterone, the latter steroid only in rodents (Spencer and Deak, 2017).

Besides triggering an immediate *alarm* reaction, stressors are subject to *appraisal.* Alarm reactions and appraisal processes interact and produce the selection of a coping strategy (de Kloet et al., 2019). The circuitry underlying appraisal and choice of coping style is organized by the mPFC, which exerts *top-down* its executive control over limbic, striatal, midbrain, and hypothalamic neurons (Ulrich-Lai and Herman, 2009). These neurons are also a target for the glucocorticoids secreted by the adrenal cortex. Glucocorticoids provide energy substrates by gluconeogenesis and allocate these substrates to cells and tissues in need, exert anti-inflammatory and immunosuppressive actions, and have profound actions on brain and behavior. Within the brain the glucocorticoids control numerous processes involved in processing of stressful information. The hormones exert a negative feedback action on the synthesis and release of CRH in the PVN, and on pituitary pro-opiomelanocortin (POMC) synthesis and ACTH release. At other sites glucocorticoids promote the synthesis of CRH. One of these sites is the central amygdala nucleus and BNST, which is a hub for processing of stress, fear, and anxiety (Makino et al., 1994, 1995; Zalachoras et al., 2016). Finally, glucocorticoids promote the storage of memory and of energy substrates in fat and liver in preparation of future challenges.

The actions exerted by the glucocorticoids are mediated by two closely related receptor types: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) (Reul and de Kloet, 1985). MR binds the naturally occurring glucocorticoids with high affinity and are expressed abundantly in neurons of the hippocampus, lateral septum, and amygdala as well as striatal and cortical regions (Reul and De Kloet, 1986; Ahima et al., 1991; Diorio et al., 1993; Brinks et al., 2007); MRs also occur as aldosterone-selective receptors in the nucleus tractus solitarii (NTS) (Gasparini et al., 2018). GRs are widely expressed in the brain and display a lower affinity to cortisol and corticosterone, implying that these receptors become only substantially occupied at high hormone levels after stress and at the circadian peak (Reul and de Kloet, 1985). MR and GR are nuclear receptors engaged in regulation of gene expression, but recently also rapid non-genomic actions were identified in brain (Di et al., 2003; Karst et al., 2005). MRand GR mediate in complementary fashion the action of glucocorticoids: MR activation may modulate the activity of neuronal circuits underlying appraisal processes and decision-making. *Via* GR the glucocorticoids regulate energy allocation, and act on brain circuits to promote motivation, emotional expressions, cognitive performance, behavioral adaptation and memory performance. These actions exerted by the glucocorticoids are context-dependent and procede in concert with neurotransmitters, neuropeptides, and growth factors over different time domains (de Kloet et al., 2005; McEwen, 2007; Joëls et al., 2007).

Thus, the stress response is the body's signaling system to coordinate defense, coping, and adaptation. Appraisal processes direct the decision how to cope with stress. For this purpose the mPFC, limbic structures, the VTA-DA circuitry, and the stress system are of crucial importance. Repeated failure to cope properly may cause a condition of chronic stress, which is characterized by lack of control, uncertainty, and fear, while motivation and reward processing regulated by the VTA-DA circuitry become compromised. In the next sections, the function, plasticity, and connectivity of the VTA-DA circuit is discussed in response to acute and chronic stressors. Validated animal models, used for these studies, are presented in Box 1.

2.2. The VTA-DA circuit supports adaptive behavior

Over the past decade, the concept of the VTA changed from a simple homogeneous group of neurons – sharing analogous biomolecular,

Box 1
Animal models of chronic stress exposure.

There are a number of validated animal models of 'chronic stress'. In these models, the animals are repeatedly exposed to a combination of stressors (Christoffel et al., 2011; Krishnan et al., 2008a; Krishnan and Nestler, 2011). Chronic restraint stress (CRS), chronic mild (CMS) or chronic unpredictable stress (CUS), and chronic social defeat stress (CSDS), are widely and commonly applied chronic stress paradigms.

Chronic restraint stress (CRS). An animal is repeatedly restrained in a restraint device (a bag or cage) for usually a minimal period of three weeks, 1–6 h a day. The CRS model is an inescapable and relatively mild type of chronic stress. A disadvantage of this model is that animals predict the beginning and the end of the daily exposure and thus habituate to the stress, which is illustrated by attenuated HPA-axis activation over time and accompanied by a more recuperative behavioral phenotype (Radley et al., 2006; Stetler and Miller, 2011; Watanabe et al., 1992).

Chronic unpredictable stress (CUS) or chronic mild stress (CMS). To overcome the habituation effect of CRS, the CUS or CMS model can be used. This paradigm applies for several days or weeks, in a semi-random or unpredictable order, a variation of physical and psychological "micro-stressors". Application of this stressor paradigm produces numerous changes in brain and behavior, and reveals a decreased reward responsivity. The relatively mild nature of the stressors combined with the cumulative nature underpins great construct validity. See for a comprehensive overview (Willner, 2017).

Chronic social defeat stress (CSDS). In the CSDS model, animals are exposed to a single bout of social defeat by a larger and aggressive conspecific. Then, the animals are separated by a physical barrier but still can see and smell each other. Social defeat stress can be applied in an intermittent variant (ISDS), where the animal is exposed four times to SDS in 10 days, or for ten consecutive days (CSDS); phenotypes like anhedonia, anxiety, and social-avoidance behaviors are a result of exposure to SDS. An experimental advantage of the SDS paradigm is that animals can be distinguished already after the first session of social defeat, while the outcome of the next encounter is predictable. A major caveat is the exclusivity of SDS to males, given that female rodents rather socialize and 'tend-and-befriend' than fight (Taylor et al., 2000; Christoffel et al., 2011; Golden et al., 2011; Krishnan and Nestler, 2011; Nestler and Hyman, 2010).

electrophysiological, and functional characteristics – to a complex heterogeneous structure containing neuronal subtypes, which are often associated with distinct molecular and synaptic characteristics (See Box 2 Beier et al., 2015; Holly and Miczek, 2016; Ikemoto, 2007; Lammel et al., 2008, 2011, 2012, Margolis et al., 2006, 2008; Morales and Margolis, 2017; Watabe-Uchida et al., 2012; Parker et al., 2019). Specifically, its main neuronal population, the DA neurons, respond to a broad array of environmental stimuli, these responses are context-dependent, and can ultimately lead to the modulation of distinct behavioral patterns (Bromberg-Martin et al., 2010; Kessler et al., 2003; Lammel et al., 2012; Matsumoto and Takada, 2013; Zweifel et al., 2011; Belujon and Grace, 2015; Grace, 2016; Lammel et al., 2014a,b; Moore and Depue, 2016). Given their unique characteristics – and especially their high degree of neuronal connectivity (see Fig. 1; Beier et al., 2015; Juarez and Han, 2016; Morales and Margolis, 2017; van den Heuvel and Sporns, 2013; Watabe-Uchida et al., 2012) – VTA-DA neurons in the mesocorticolimbic circuitry can be considered as a hub linking circuits involved in emotional-motivational appraisal of salient information with networks underlying executive functioning (Juarez and Han, 2016; Melis and Pistis, 2012; Polter and Kauer, 2014).

Besides rewarding stimuli, the appraisal processes concern aversive stimuli as well. The VTA-DA circuitry, thus, plays a significant role in learning and memory processes that contribute to an animal's ability to differentiate between "good and bad". Accordingly, many behavioral and cognitive changes that are influenced by VTA-DA modulation are at least partially beneficial and promote adaptive responses on the basis of these learned associations (Bromberg-Martin et al., 2010; Cabib and Puglisi-Allegra, 2012; Cools, 2016; Hauser et al., 2017; Lloyd and Dayan, 2016; Pignatelli and Bonci, 2015). The VTA-DA circuitry is thus of crucial importance in effort- and value-based decision-making and provides a mechanism to determine the value of different options in order to fulfill goal-directed behavior, which in the case of stressors is directly related to the animal's well-being (Lloyd and Dayan, 2016). Therefore, key functions where VTA-DA stress responses are involved include updating the assignment of expected value of behaviorally relevant stimuli and behavioral outcomes and, additionally, the modulation of coping strategies in order to efficiently deal with the specific stressful situation (Burke et al., 2014; Lloyd and Dayan, 2016; Salamone and Correa, 2012).

Survival of most animal species depends on behavioral patterns that maximize contact with beneficial stimuli while contact with harmful stimuli is preferably avoided (Burke et al., 2014). The ability to make such differentiations evolves over lifetime and are thought to largely depend on processes of VTA-DA neuron-dependent reinforcement learning (Lloyd and Dayan, 2016; Salamone and Correa, 2012). During reinforcement learning processes, formerly neutral stimuli can reinforce or strengthen behaviors through the formation of associations with certain cues (Koob and Volkow, 2016; Lloyd and Dayan, 2016). Consequently, in the face of adversity, this stimulus-dependent learning mechanism combines past experiences with information about the current state of the environment, leading to learning of both danger- and safety-predicting conditioned stimuli (Grupe and Nitschke, 2013; Lloyd and Dayan, 2016). This VTA-DA-dependent learning increases the predictability of future events, and enables an organism to choose and execute behavioral actions more precisely and with the appropriate behavioral vigor (Lloyd and Dayan, 2016; Salamone and Correa, 2012).

Such behavioral decisions are, however, not rigid but state-dependent, (Burke et al., 2014; Papageorgiou et al., 2016). This is illustrated, for instance, by salt-appetite (Berridge et al., 1984; Robinson and Berridge, 2013; Tindell et al., 2009). In normal situations, rats usually do not ingest extremely salty solutions and avoid cues that predict them. In salt-deficient situations, however, rats do ingest salt. This example also describes that a previously disgusting taste can become rewarding to approach, demonstrating that internal states can have profound effects on motivational processes for behavioral activation (Dayan and Berridge, 2014; Papageorgiou et al., 2016). These often subjective state-dependent value representations allow an animal to prioritize its goals, and lead to the generation of both proximal (direct approach or avoidance) and distal (allocating resources for effortful approach or avoidance of a goal stimulus) motivated behaviors (Abraham et al., 2014; Salamone and Correa, 2012). Thus, by combining past experiences with information about the current internal and external states, relevant behavioral decisions can be made.

A mismatch between such predicting stimuli and reality generates a prediction error signal of any kind and it is well known that in this context dopamine signals the prediction of a reward (den Ouden et al., 2012; Schultz, 2016). As was recently proposed, stress can be conceptualized as a cumulative state of prediction errors (Trapp et al., 2018). Or, similarly, Peters et al. (2017) defined stress as *"the individual state of uncertainty about what needs to be done to safeguard physical, mental or social well-being"* (Peters et al., 2017). These views align with the notion that loss of control and lack of information are amongst the most potent stressors that evoke a profound sympathetic and HPA-axis response (Mason, 1971; Levine, 2005; Koolhaas et al., 2011; McEwen

Box 2
Characterization and identification of VTA-DA neurons: from homogeneity to heterogeneity.

VTA-DA neurons are generally characterized as tyrosine hydroxylase (TH) and transmembrane DA transporter (DAT) expressing neurons which release DA and exhibit characteristic *in vivo* firing patterns (Fig. 2A). However, considering therapeutic relevance, it is of crucial importance to increasingly recognize, identify, and understand why specific subsets of midbrain dopamine neurons are vulnerable to pathogenesis, while others show resilience. It is evident that VTA-DA neurons show connectivity, electrophysiological, and biomolecular variation.

Connectivity. VTA-DA neurons are heterogeneous in their afferent connectivity (Fig. 1). Specific synaptic connectivity profiles of specific VTA-DA neurons – determined both by afferents and efferents – may reflect functional relevance (Bariselli et al., 2016; Beier et al., 2015; Juarez and Han, 2016; Morales and Margolis, 2017; Watabe-Uchida et al., 2012). This is especially relevant for phasic dopamine activity as, despite this high degree of innervation, the population activity of VTA-DA neurons appears to be mainly regulated by direct high-frequency GABA-ergic input from the ventral pallidum (VP). The hyperpolarizing input from the VP is potently controlling the gain of phasic VTA-DA responses by regulating the number of tonic firing DA neurons. VP activity is, in turn, powerfully modulated by the hippocampus subiculum and the basolateral amygdala (BLA) which have activating and inhibitory inputs, respectively, and are circuits that belong to a network driven by neuronal ensembles of the infralimbic prefrontal cortex. Remarkably, these are all brain regions which are highly involved in the appraisal of environmental information (see reviews Belujon and Grace, 2015; Grace, 2016; Belujon and Grace, 2017). In addition, DA can target D1-like and D2-like receptors, which may have opposing effects on intracellular signaling cascades. Moreover, distinct VTA-DA neuron projection sites may express these receptors differentially, adding another level of complexity to the possible behavioral consequences of stress-induced changes in VTA-DA neuron excitability.

Electrophysiology. To identify VTA-DA neurons electrophysiologically, a number of conventional electrophysiological criteria have been used in *in vivo* experimental settings. The presence of a hyperpolarization-activated cation current (I_h), a distinguishable small conductance calcium-activated potassium (SK) channel-mediated after-hyperpolarization in action potential waveforms, and autoinhibition by high-affinity somatodendritic D2 receptors linked to G protein-coupled inwardly rectifying potassium channels (GIRKs) were used as reliable criteria for the classification of VTA-DA neurons (Cao et al., 2010; Juarez and Han, 2016; Margolis et al., 2006; Morikawa and Morrisett, 2010). These electrophysiological criteria are based on features of substantia nigra pars compacta (SNc) DA neurons, since VTA-DA neurons lose their characteristic phasic activity in *ex vivo* slice preparations. Recent studies, however, demonstrated variation in these stereotypical electrophysiological features in VTA-DA neuron subpopulations (see Juarez and Han, 2016). While D2 receptor-mediated autoinhibition (Chiodo et al., 1984) and apamin-sensitive (SK) channel-mediated after hyperpolarizations (Ji et al., 2009; Ji and Shepard, 2006) are inconsistently found across the VTA, diversity in I_h can be designated to a posterior-medial subpopulation of TH-expressing VTA neurons (Ford, 2006; Lammel et al., 2008; Margolis et al., 2006). Thus, the validity of these electrophysiological markers used for general identification of VTA-DA neurons is unreliable, since the use of these classically used SNc DA neuron-based criteria raised doubts (Margolis et al., 2006). Thus, VTA-DA neurons show heterogeneous electrophysiological properties as well.

Molecular Composition. Key enzymes of DA synthesis and signaling are used to identify DA neurons in the VTA (Subramaniam and Roeper, 2017). DA is synthesized from the amino acids phenylalanine and tyrosine by, successively, tyrosine hydroxylase (TH) and L-DOPA decarboxylase (DDC). Subsequently, DA is actively stored into vesicles by vesicular monoamine transporter 2 (VMAT2) and transported towards the synaptic cleft, ready for exocytosis. Moreover, upon release DA can be cleared from the extracellular space by the transmembrane DA transporter (DAT). There are, however, subsets of TH-expressing neurons that lack expression of DAT or VMAT2 (Morales and Margolis, 2017), and, furthermore, the VTA is not restricted to solely DA neurons. Recent studies showed that the VTA additionally contains GABA-ergic (20–40 %) and glutamatergic (2–3 %) neurons (Nair-Roberts et al., 2008), which form local and transregional projections (Fields et al., 2007; Omelchenko and Sesack, 2009). Interestingly, some VTA neurons release multiple neurotransmitters from different vesicles (Berrios et al., 2016; Root et al., 2014; Zhang et al., 2015).

Single cell RNA sequencing. The emergence of genomics, transcriptomics, proteomics, and metabolomics, will yield a more exhaustive understanding of midbrain dopamine neurons. These techniques, or a combination thereof, will reveal specific, imperative biomarkers that support systematic molecular classification. These, in turn, can be targeted or used in various experimental setups, while the complexity that surrounds both the heterogeneity of midbrain dopamine neurons and the etiology of pathological cascades can be taken into account, including sex differences.

Tiklová et al. (2019) used single-cell RNA sequencing to reveal mouse midbrain dopamine neuron diversity during development (Tiklová et al., 2019). Seven different groups of midbrain neurons expressing *Pitx3*, a gene encoding a transcription factor specific for midbrain dopamine neurons (Smidt et al., 1997) were identified. These neuron subgroups reside in anatomically defined positions within the adult midbrain, and of these subgroups five express dopaminergic markers. Molecular characterization of midbrain dopamine neurons, as provided by Tiklová and colleagues, will provide valuable information for elucidating the function of subgroups of dopamine neurons.

et al., 2015; Reyes et al., 2015). Since perception of sensory information is based on expectations, the cumulative prediction errors may cause a stress response aimed to promote adaptation to these repeated expectations. Therefore, it was proposed recently that repeated failures to precisely predict upcoming events can modify the way one will perceive the world through reinforcement learning processes (Trapp et al., 2018).

Furthermore, when an initially selected coping strategy defies expectancies about response-outcome relationships, the "*ability to switch behaviors when contexts change, or to switch from an ongoing behavior to a new one*", commonly referred to as *behavioral flexibility* (Baker and Mizumori, 2017), is an essential adaptive mechanism in the attempt to successfully deal with the situation. Specifically, in the case of novel unescapable or uncontrollable stressful situations, the behavior that is initially selected is generally aimed to remove, avoid, or control the source of the stressor. This is indicated as an *active* coping strategy, which is characterized by behavioral responses that act upon the source of the stressor and are directed to defend the "self" (Carroll, 2013a; Wood and Bhatnagar, 2015). If, however, an animal's experience of stress cannot be terminated by using its own resources, which will depend on the interaction between genetic predisposition and life-experience (Daskalakis et al., 2013), animals tend to switch to *conservation withdrawal* (Henry and Stephens, 1977), which is a more *passive* coping strategy (Cabib and Puglisi-Allegra, 2012). *Passive* behaviors support more altruistic solutions and thereby rely more on others to solve or terminate the emotional aspects of the stressful experience (Carroll, 2013b; Wood and Bhatnagar, 2015). Therefore, whether the stressful situation is appraised as "controllable" is of crucial importance to the increased expression of a particular behavioral coping strategy. Accordingly, behavioral flexibility may support coping when the situation goes beyond the animal's initial own abilities (Cabib and Puglisi-Allegra, 2012; de Kloet and Molendijk, 2016; Tye et al., 2013).

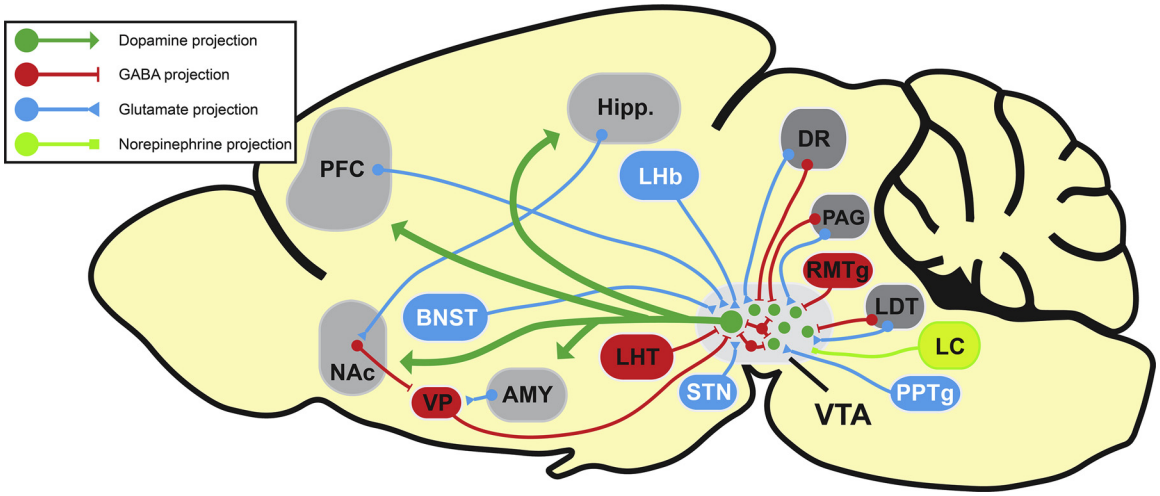

Fig. 1. Simplified schematic representation of the mesocorticolimbic dopamine circuitry.
VTA dopamine neurons project (in green) to various limbic and cortical brain regions. GABA-ergic intra- and innervating projections (in red) and glutamatergic input (in blue) onto VTA dopamine neurons are integral to this circuitry (Watabe-Uchida et al., 2012; Barrot, 2014; de Kloet et al., 2015; Beier et al., 2015; Belujon and Grace, 2015; Juarez and Han, 2016; Bariselli et al., 2016; Morales and Margolis, 2017; Ghosal et al., 2019). Note that the mesocortical circuit contains a positive feedback loop from the prefrontal cortex to the VTA to sustain more demanding cognitive and motivational aspects of reward processing and social interactions. The hippocampal input disinhibits VTA-DA activity in support of contextual aspects serving reinforcement learning. The amygdala input may inhibit VTA activity as reflection of emotional aspects in reward processing.
Abbreviations: AMY, amygdala; BNST, bed nucleus of the stria terminalis; DR, dorsal raphe nucleus; GABA, γ-aminobutyric acid; Hipp, hippocampus; LC, locus coeruleus; LDT, laterodorsal tegmentum; LHb, lateral habenula; LHT, lateral hypothalamus; NAc, nucleus accumbens; PAG, periaqueductal grey; PFC, prefrontal cortex; PPTg, pedunculupontine tegmentum; RMTg, rostromedial tegmental nucleus; STN, subthalamic nucleus; VP, ventral Pallidum; VTA, ventral tegmetal area.

In conclusion, the VTA-DA circuitry supports adaptive behavior by assigning prediction and valence to a salient stimulus. Positive valence is linked to a reward, but fear and uncertainty are examples of negative valence. Coping with a stressor – either passive or active – can be considered a rewarding experience as opposed to failure to cope that may result ultimately in chronic or 'toxic' stress (McEwen et al., 2015). Behavioral flexibility or the ability to rapidly adjust coping with a changing context and valence is essential for adaptation to stress and involves the VTA-DA circuit.

2.3. Tonic and phasic firing of VTA-DA neurons

The contribution of VTA-DA neurons to such adaptive behavior in stressful situations is strongly dependent on the type of activity these neurons display. VTA-DA neurons can be in either an inactive or active state. Active VTA-DA neurons can switch between two neural firing patterns: either asynchronous low-frequency (2–4 Hz) tonic firing with a single action potential discharge or a transient high frequency phasic activity (> 15 Hz), known as burst firing (Fig. 2A) (Cao et al., 2010; Grace and Bunney, 1984; Grace and Onn, 1989; Juarez and Han, 2016; Walsh and Han, 2014). The regulation of tonic and phasic VTA-DA neuron activity is, however, complex (Fig. 2B). Dopaminergic firing patterns are facilitated through presynaptic interactions, with γ-aminobutyric acid (GABA)-ergic and glutamatergic input as main regulators (Bariselli et al., 2016; Belujon and Grace, 2015; Grace and Onn, 1989). Inhibitory control from GABA-ergic neurons can keep VTA-DA neurons in a hyperpolarized, inactive state, while input from excitatory glutamatergic neurons can induce phasic burst-firing patterns. The balance between inhibitory and excitatory input therefore determines the neuronal state of a VTA-DA neuron and its ability to respond to behaviorally relevant stimuli.

Importantly, phasic activity can only occur in VTA-DA neurons where tonic activity is present. Thus, the amount of neurons that express tonic firing represents the degree of potential DA signaling amplification (Belujon and Grace, 2015; Grace, 2016). The tonic neural firing profile sets a low background pacemaker DA activity in a subset of VTA-DA neurons and the number of these spontaneously active DA neurons can be defined as the *population activity* (Belujon and Grace, 2015). In benign, neutral environmental contexts, the number of responding VTA-DA neurons is kept low – approximately half of the neurons in the VTA do not fire. Thus, since phasic burst firing can only occur in tonic firing neurons, the effects of excitatory input from brain regions which actually can initiate VTA-DA phasic activity are restricted to the fraction of responding, tonically firing VTA-DA neurons. In perceived deviant emotional-motivational charged environmental conditions, appraisal processes may alter the population activity (Fig. 2C). Therefore, the responsiveness of VTA-DA neurons to context-dependent salient stimuli can be affected, and thus the way VTA-DA neurons are modulating behavior. This suggests that the regulation from an inactive to an active tonic VTA-DA neuronal state (and vice versa) attaches a certain emotional-motivational load to the role of these neurons in coping with specific environmental situations.

These transitions in VTA-DA neuronal activity are also linked to the type of behavioral strategy animals use in order to cope with acute stressful situations. Specifically, an increased tonic firing population activity is linked to the enhanced use of more active coping strategies, whereas a decrease in the VTA-DA population activity is associated to the use of more passive ones (see Fig. 2C; Cabib and Puglisi-Allegra, 2012; Rincón-Cortés and Grace, 2017; Tye et al., 2013). The direct involvement of VTA-DA neurons in switching between different behavioral coping styles is demonstrated by the use of optogenetic manipulation of VTA-DA neurons (Lammel et al., 2014a,b; Tye et al., 2013). Tye et al. (2013) demonstrated that the inhibition of putative VTA-DA neurons during an acute stressful situation led to the increased use of passive coping strategies, as demonstrated by an increased immobility in a forced swim stress test (Tye et al., 2013). They additionally observed a robust increase in the use of active coping when VTA-DA neurons were optogenetically activated (Tye et al., 2013). Given that these behavioral responses were not time-locked to the administration of the light pulses, these transitions of active to passive coping with stress are most likely supported by changes in the tonic firing VTA-DA neuronal population activity, as confirmed electrophysiologically (Rincón-Cortés and Grace, 2017). Therefore, by supporting the switch between active and passive coping strategies, tonic VTA-DA neuronal

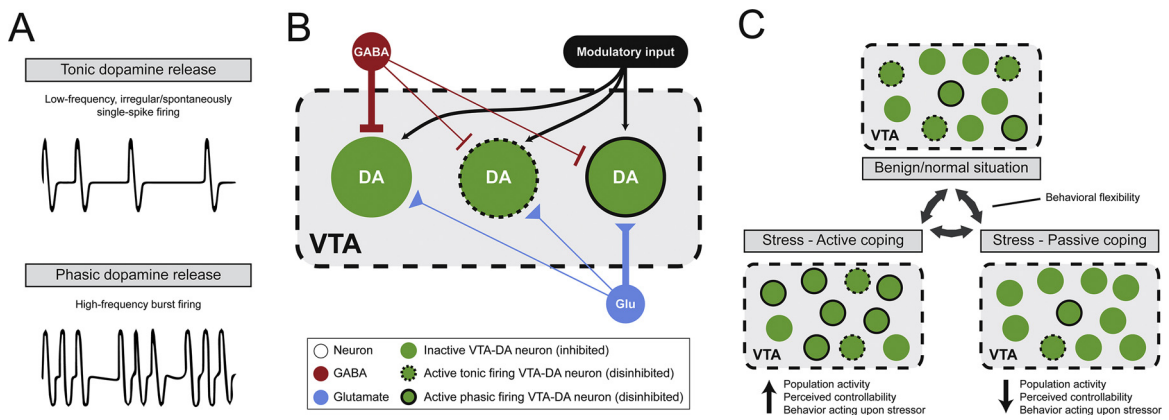

Fig. 2. The VTA-DA neuron.
(A) VTA-DA neurons can display two firing patterns *in vivo*: either low-frequency (< 2–4 Hz) tonic firing or high-frequency (> 15 Hz) burst firing.
(B) Synaptic control of VTA-DA neuron activity. VTA-DA neurons can be in either an inactive or active state, and active neurons can release dopamine in a tonic or phasic manner. While strong inhibitory GABA-ergic input (red) keeps VTA-DA neurons in a hyperpolarized, inactive state (green without outline), disinhibition of the GABA-ergic input releases the inhibitory break, allowing VTA-DA neurons to display tonic firing activity (green with dashed outline). In turn, these activated, tonic firing VTA-DA neurons can display phasic dopamine firing patterns (green with solid black outline) in response to sufficient excitatory glutamatergic input (blue). Phasic activity can only originate in VTA-DA neurons where tonic activity is present. The excitatory and inhibitory synaptic transmission is further affected by modulatory input, which exercises a subtle, fine-tuning influence on neuronal excitability. Modulatory input occurs by *e.g.* the neurotransmitters serotonin, acetylcholine, and noradrenaline; the neuropeptide *e.g.* CRH, the glucocorticoid hormone, and endogenous opioids.
(C) The role of VTA-DA neurons during stress-coping depends on population activity, which is defined as the number of neurons in a disinhibited, active state. An increased population activity in response to stress generally promotes active coping strategies. In contrast, a decreased population activity in response to stress promotes passive coping, which emerges when the stressful situation is appraised as “inescapable” or "uncontrollable". The ability to switch between behavioral strategies, referred to as behavioral flexibility, supports successful adaptive behavior in response to acute stressful situations. See text for further details and references. Figures adapted from (Belujon and Grace, 2015; Grace, 2016; Juarez and Han, 2016). Abbreviations: DA, dopamine; GABA, γ-aminobutyric acid; Glu, glutamate; VTA, ventral tegmental area.

activity is involved in behavioral decision-making.

In conclusion, VTA-DA neurons are responsive to a broad array of behaviorally relevant stimuli, including stimuli related to the seemingly opposite experiences of reward and aversion. These behaviorally relevant stimuli are subjected to appraisal processes and contribute to the complex integration of excitatory and inhibitory input onto VTA-DA neurons. As will be discussed in Sections 4 and 5, the characteristic VTA-DA firing patterns are modulated through these afferent inputs, which are in particular orchestrated by hippocampal and amygdala circuits (Belujon and Grace, 2017). Since these modulating effects are state-dependent and the eventual behavioral outcomes can affect future appraisal processes, the VTA-DA mesocorticolimbic circuitry likely supports adaptive coping strategies.

2.4. Stress-induced changes in VTA-DA activity

In response to *acute stressors* robust increases of extracellular dopamine and its metabolites were found with microdialysis in the most prominent VTA-DA neuron target areas, the N. accumbens (NAc) and the mPFC (Fig. 1) (see Holly and Miczek, 2016). The research by Cabib’s group has shown that stress-induced norepinephrine (NE) release in the mPFC corresponds to an increased DA release in the NAc and that increased mPFC DA is causally related to a decreased NAc DA efflux (Pascucci et al., 2007; Fiore et al., 2015). High DA in NAc supports active coping strategies, goal-directed behavior, and motivational arousal, while a diminished stress-induced DA is linked to passive coping in situations that are uncontrollable (Cabib and Puglisi-Allegra, 2012; Fiore et al., 2015).

In agreement with these microdialysis studies stress-induced increases in tonic firing population activity were observed which facilitated phasic VTA-DA activity (Belujon and Grace, 2015). On the basis of differential responses, other authors proposed two rather than one distinct VTA-DA neuron subpopulations (Lammel et al., 2014a,b; Ungless et al., 2010). The dorsolateral VTA-DA neurons were mainly inhibited by acute stress (Guarraci and Kapp, 1999; Mantz et al., 1989; Mirenowicz and Schultz, 1996; Schultz and Romo, 1987; Ungless, 2004), and most of these neurons showed phasic excitation *upon termination of the stressor* (Brischoux et al., 2009; Navratilova et al., 2012; Tanimoto et al., 2004). In contrast, rapid and potent phasic excitations *at the onset of stressor exposure* were discovered in the ventromedially located “non-conventional” VTA-DA neurons (Anstrom et al., 2009; Anstrom and Woodward, 2005; Cohen et al., 2012; Lammel et al., 2014a,b; Zweifel et al., 2011). Thus, VTA-DA neurons are responsive to acute stress, but phasic activity is differentially expressed in VTA-DA neuron subpopulations at onset and termination of the stressor.

Other studies have shown that the activation of VTA-DA neurons upon acute stress exposure can alter VTA-DA activity responses to later stimulation (Holly and Miczek, 2016; Valenti et al., 2012). Importantly, these alterations in VTA-DA neurons are shown in both tonic and phasic firing patterns, but appear to depend on the experimental conditions. Mild or intermittent stress protocols generally tend to increase VTA-DA population activity, while exposure to prolonged, more severe and uncontrollable/inescapable stress paradigms tend to blunt tonic firing in VTA-DA neurons (Chang and Grace, 2014; Rincón-Cortés and Grace, 2017; Kaufling, 2019). These differences in tonic firing may lead to transitions in the use of active and passive coping strategies in response to acute stressors (Cabib and Puglisi-Allegra, 2012; Lloyd and Dayan, 2016; Tye et al., 2013). Furthermore, when an animal is subsequently exposed to a heterotypic stressor – thus of a different nature than the previous stressor(s) used in the stress paradigm – the phasic responses are generally sensitized and/or amplified (Cuadra, 2001; Cuadra et al., 1999; Di Chiara et al., 1999; Finlay et al., 1995; Gresch et al., 2002; Murphy et al., 2003; Tidey and Miczek, 1997, 1996; Watt et al., 2014).

Thus, VTA-DA neurons are responsive to stressors, and these responses may show spatiotemporal variation. Furthermore, although different stressors can result in diverse VTA-DA neuron activity responses, it is clear that stressor pre-exposure can alter future VTA-DA activity responses to stressful behaviorally relevant stimuli. However, discrepancies between experimental findings make it currently a challenge to determine the exact link between VTA-DA neuron activity and

Table 1
Studies describing chronic stress effects on VTA-DA neurons.

Study	Stress	Paradigm	Animals	VTA-DA neurons	Behavioral effects	Note
Kaska et al. (2017)	CSDS	10 days	Mice	↓ Soma size in "SP"; ↓ Active cofilin		mTOR signaling dependent
Sugama and Kakinuma (2016)	CRS	8 h/day, 16 weeks	Male Wistar rats	↑ VTA-DA neuronal cell loss		
Sugama et al. (2016)	CRS	8 h/day, 16 weeks	Male Wistar rats	↑ VTA-DA neuronal cell loss		↑ Microglial activation; ↑ Oxidative stress
Qu et al. (2017)	CSDS	10 days	Male C57BL/6 mice	↑ Spine density in "SP"	↑ Social avoidance in "SP"; ↓ Sucrose preference in "SP"	
Anacker et al. (2016)	CSDS	10 days	Male C57BL/6 mice	↑ VTA volume in "SP"		
Fitzgerald et al. (1996)	CRS	45 Min/day for 10 days	Male Sprague-Dawley rats	↑ GluR1 expression		
Fitzgerald et al. (1996)	CUS	10 Days	Male Sprague-Dawley rats	↑ NMDAR1 and GluR1 expression		
Toth et al. (2008)	CUS	4 Weeks	Male & Female Spraque-Dawley rats	↔ GluR1 levels (aVTA and pVTA); ↔ BDNF levels (aVTA and pVTA)	↓ Sucrose preference; ↓ Exploration	
Stelly et al. (2016)	CSDS	10 Days	Male Sprague-Dawley rats	↑ NMDAR-mediated LTP	↑ Cocaine-induced CPP	LTP promoted by mGluR/IP3-induced intracellular Ca^{2+}-release; GR signaling dependent
Whitaker et al. (2013)	SI	P21-P42	Male Sprague-Dawley rats	↑ NMDAR-mediated LTP	↑ Amphetamine- and ethanol-induced CPP	LTP promoted by mGluR/IP3-induced intracellular Ca^{2+}-release
Covington et al. (2008)	ISDS	4 x SDS in 10 days	Male Long-Evans rats	↔ NMDAR expression; ↑ GluR1 expression	↑ Cocaine self-administration	
Nikulina et al. (2005) and Nikulina et al. (2008)	CSDS	5 Days	Male Sprague-Dawley rats	↑ MOR mRNA expression; ↓ GABAergic transmission	↑ MOR agonist-induced locomotor activity	
Der-Avakian et al. (2017)	CSDS	3 days	Male Wistar Rats	↓ Fos mRNA levels	↓ Response bias toward frequently rewarded stimulus (blunted reward learning)	N/OFQ peptide and NOPR mRNA levels in VTA inversely related to reward learning; ↑ N/OFQ in striatum
Krishnan et al. (2008b)	CSDS	10 Days	Male Sprague-Dawley rats	↓ p-Akt in "SP"; ↓ GABAergic transmission	↑ Social avoidance; ↑ Immobility in forced swim stress; ↓ Sucrose preference	Involves PI3K/Akt/mTOR signaling
Warren et al. (2013)	CSDS	10 Days	Male C57BL/6 J mice	↓ Gabrd (δ-$GABA_A$R) expression; ↑ GABAergic transmission	↑ Social avoidance; ↑ Immobility in forced swim stress; ↓ Exploration in EPM	In VTA-GABA interneurons; regulated by neurosteroids
Holly et al. (2016)	ISDS	4 x SDS in 10 days	Male Long-Evans rats	↑ Phasic CRF in pVTA (acute stress); ↑ Phasic CRF in aVTA (chronic stress); ↑ Tonic CRF (aVTA & pVTA)	↑ Cocaine self-administration (CRF-R1 dependent in pVTA; CRF-R2 dependent in aVTA)	
Fanous et al. (2010)	ISDS	4 x SDS in 10 days	Male Sprague-Dawley rats	↑ BDNF expression		
Krishnan et al. (2007)	CSDS	10 Days	Male c57bl/6 mice	↑ BDNF in "SP"; ↑ K^+- channels in "RP"	↑ Social avoidance in "SP"; ↓ Sucrose preference in "SP"	
(Miczek et al., 2011)	ISDS	4 x SDS in 10 days	Male Long-Evans rats	↑ BDNF expression	↑ Cocaine-induced locomotion; ↑ Cocaine self-administration; ↔ Exploration in OFT; ↔ Sucrose preference	
Miczek et al. (2011)	CSDS	36 Days	Male Long-Evans rats	↓ BDNF expression	↔ Cocaine-induced locomotion; ↓ Cocaine self-administration; ↓ Exploration in OFT; ↓ Sucrose preference	
Gersner et al. (2010)	CUS	38 Days	Male Sprague-Dawley rats	↔ BDNF levels	↔ Locomotion; ↓ Exploration; ↔ Immobility in forced swim stress; ↓ Sucrose preference	

Footnote: Abbreviations: "RP", Resilient phenotype; "SP", susceptible phenotype; Akt, thymoma viral proto-oncogene/protein kinase B; aVTA, anterior VTA; CPP, conditioned place preference; CRS, chronic restraint stress; CSDS, chronic social defeat stress; CUS, chronic unpredictable stress; DA, dopamine; EPM, elevated plus maze; ISDS, intermittent social defeat stress; LTP, long term potentiation; MOR, μ-opioid receptor; NOPR, N/OFQ receptor; OFT, open field test; p-Akt, phosphorylated Akt; pVTA, posterior VTA; SDS, social defeat stress; SI, social isolation; VTA, ventral tegmental area.

Table 2
Studies describing chronic stress-induced effects on VTA microglia.

Study	Stress	Paradigm	Animals	VTA microglia	Behavioral effects
Sugama and Kakinuma (2016)	CRS	8 h/day, 16 weeks	Male Wistar rats	↑ Microglial soma size	
Tanaka et al. (2012)	CSDS	10 Days	Male c57bl/6 mice	↑ Iba-1 immunoreactivity	↑ Social avoidance; ↓ Exploration in EPM
Tynan et al. (2010)	CRS	2 x 30 min/day, 14 days	Male Sprague-Dawley rats	↔ Iba-1 immunoreactivity	↓ Sucrose preference

Footnote: Abbreviations: CRS, chronic restraint stress; CSDS, chronic social defeat stress; EPM, elevated plus maze; VTA, ventral tegmental area.

specific behavior modulating effects. A further complication in interpreting data on VTA-DA neuron stress responses is the divergence in methodological procedures; the nature, schedule, and intensity of the stressor matters, and stressors can be novel and may be promoted by conditioned or unconditioned stimuli (Cabib and Puglisi-Allegra, 2012; Holly and Miczek, 2016). Consequently, in response to stressors both increases and decreases in VTA-DA neuron activity have been observed (see Holly and Miczek, 2016).

2.5. VTA circuit and social competence

A recent series of experiments place GABA-ergic control of VTA-DA neurons in a novel perspective. It was discovered that the local infusion of the benzodiazepine diazepam, a $GABA_A$ receptor ($GABA_AR$) agonist, in the VTA exerted anxiolytic activity in rats and, surprisingly, also increased the rewarding experience of social competitiveness (van der Kooij et al., 2018a,b). Further study showed that intra-VTA diazepam administration increased DA release selectively from its NAc terminals, and not from innervations in the mPFC, hippocampus, and amygdala. Upon stimulated DA release c-fos protein was induced in NAc target neurons that expressed D1 rather than D2 receptors. Accordingly, social dominance was also promoted by local administration of a D1 agonist in the NAc. In agreement with a previous observation by the same group (Hollis et al., 2015) mitochondrial activation in the NAc target neurons appeared causal to improved social competence. Intra-VTA diazepam infusion increased NAc adenosine triphosphate (ATP) production and post-mortem mitochondrial O_2 consumption. Blockade of mitochondrial respiration and function with rotenone reversed the VTA-DA effects on anxiety and social competitiveness (van der Kooij et al., 2018a,b). So, social interaction depends on VTA-DA activity.

The findings are supported by a companion paper of the same authors that demonstrated the engagement of GABA-α2 rather than the GABA-α1 receptor subunits linked to addiction, by using selective benzodiazepine agonists for each receptor type (van der Kooij et al., 2018a). Recently, Rincón-Cortés et al. (2018) showed that a low systemic dose of diazepam could alleviate the negative symptoms of amphetamine withdrawal by ameliorating anxiety-like and social behavior (Rincón-Cortés et al., 2018). This treatment attenuated inhibitory GABA-ergic control, thereby increasing the number of spontaneously firing VTA neurons. As has been examined in detail by Antony Grace's group, the number of cells showing this firing pattern represents tonic activity of the VTA neurons as a determinant of the gain of phasic DA bursts during amphetamine withdrawal (Belujon and Grace, 2017). The discovery has important implications for the potential of benzodiazepine analogs to increase social competence and to attenuate anhedonic symptoms in patients suffering from anxiety- and depressive disorders (Soria et al., 2018).

In conclusion, the findings rekindle the scheme by Belujon and Grace on the prefrontal-limbic-VTA circuitry with its activating hippocampal and inhibiting amygdala inputs. The new experiments suggest that local manipulation of GABA-ergic interneurons in the VTA as well as the utilization of energy substrates in the NAc has profound consequences for mesolimbic DA activity, and its function in the rewarding, emotional, and motivational aspects of social interaction. Interestingly, a recent study demonstrated a role for CRH in the modulation of social interaction in GABA-ergic terminals (Dedic et al., 2019). However, the underlying mechanism of GABA-ergic control of VTA-DA excitability requires further study. For instance, it is unclear to what extent the GABA-dependent suppression of the inhibitory afferent input *versus* potentiation of the GABA-ergic interneuron input is involved.

3. Chronic stress and VTA-DA activity

Acute stress responses trigger powerful adaptive reactions in order to protect and to prepare body and brain for coping with similar environmental challenges in the future. In this section, the effects of chronic stress on excitatory and inhibitory transmission in the VTA-DA circuit will be discussed (see Tables 1 and 2; Fig. 3). It appears that neurons in the VTA may be lost and we highlight the role of microglia in this neurodegenerative process.

3.1. Structural plasticity

Chronic stress exposure can induce morphohological changes in VTA-DA neurons, as demonstrated in a study by Kaska et al. (2017) who reported that in mice susceptible to chronic social defeat stress (CSDS) the VTA-DA neuron soma size decreased (Kaska et al., 2017). In this study, western blot analysis on micro-dissected VTA tissue revealed a decreased level of phosphorylated cofilin – a protein which can disassemble cytoskeletal actin filaments. Therefore, the authors hypothesize that chronic stress may alter – amongst many other effects – the cytoskeleton of VTA-DA neurons. Moreover, the chronic stress-induced shrinkage of neuronal soma sizes may be related to the diminished availability of neurotrophic factors (Chu et al., 2007; Stockmeier et al., 2004).

Furthermore, chronic stress exposure can additionally result in excessive loss of dopaminergic neurons in the VTA (Sugama and Kakinuma, 2016). By using immunohistochemical and *in situ* hybridization techniques, Sugama and Kakinuma (2016) showed that a 16-week chronic restraint stress (CRS) paradigm can induce dopaminergic neurodegeneration in male Wistar rats (Sugama and Kakinuma, 2016). They demonstrated that the number of tyrosine hydroxylase (TH)-immunoreactive and mRNA expressing neurons in the VTA were decreased down to 40 percent as compared to control animals after 16 weeks of CRS. The TH positive cells were also positive for the neurodegeneration marker Fluoro-Jade B in the CRS exposed animals (Sugama et al., 2016). Together, these studies imply that chronic stress exposure can induce profound morphological changes and, if extended to a longer time, may cause loss of VTA-DA dopaminergic neurons. The stress-induced loss of dopaminergic neurons awaits further confirmation, however.

In support, male Wistar rats exposed daily for 3.5 h to a combination of chronic unpredictable stressors during three weeks showed *in vivo* under urethane anesthesia with magnetic resonance imaging (MRI) a decreased volume of VTA, NAc, hippocampal, and cortical regions. This decrease in VTA volume was accounted for by rats that were highly responsive to the stressor. However, connectivity was found increased between VTA and the ventral subiculum of the hippocampus, with an inflection at day 7 of stress exposure (Magalhães et al., 2017). The findings on chronic-stress-induced VTA degeneration align with parallel decreases in population activity (see Belujon and Grace, 2015; Grace,

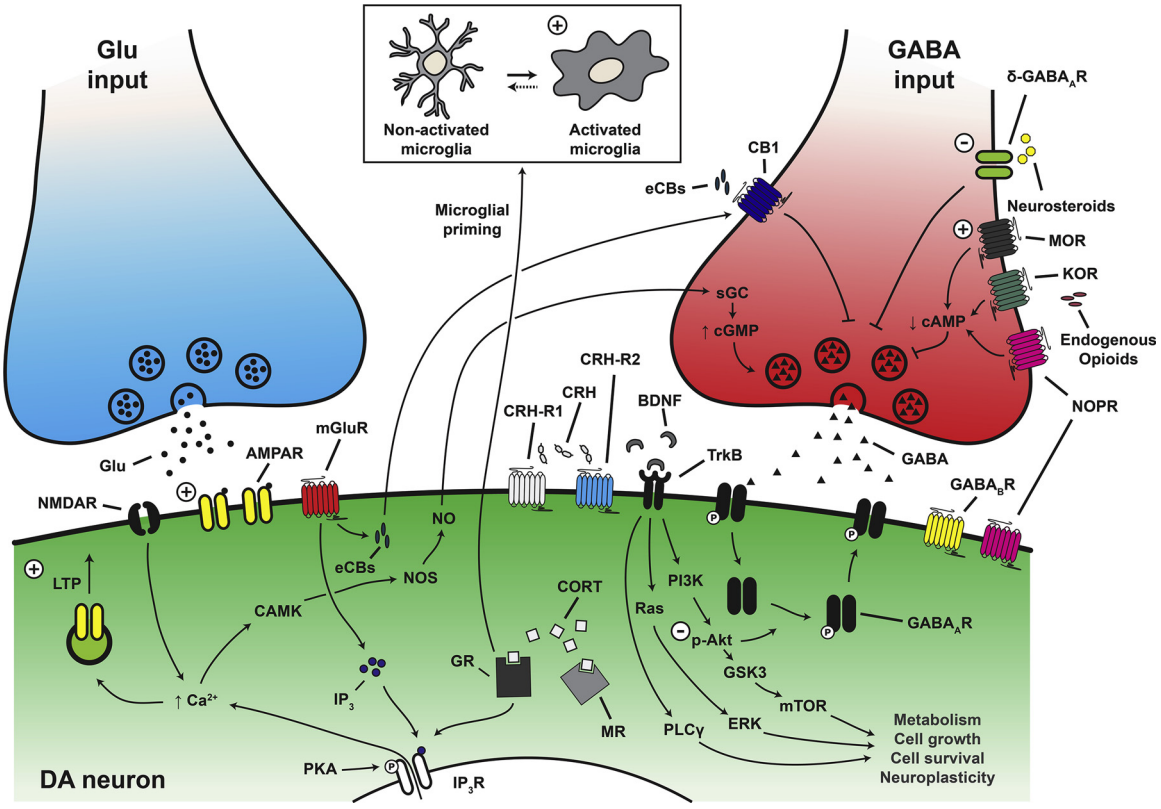

Fig. 3. Major biomolecular pathways involved in VTA-DA neuroadaptive changes during chronic stress exposure. See text for further details and references. Certain intermediates and other details are left out for clarity. Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; CAMK, Ca^{2+}/calmodulin-dependent protein kinase; CB1, cannabinoid receptor type 1; cGMP, cyclic guanosine monophosphate; CORT, glucocorticoids; CRH, corticotrophin releasing hormone; CRH-R1, corticotrophin releasing hormone receptor 1; CRH-R2, corticotrophin releasing hormone receptor 2; DA, dopamine; eCBs, endocannabinoids; ERK, extracellular signal-regulated kinase; GABA, γ-aminobutyric acid; $GABA_AR$, $GABA_A$ receptor; $GABA_BR$, $GABA_B$ receptor; Glu, Glutamate; GR, glucocorticoid receptor; GSK3, glycogen synthase kinase 3; IP_3, inositol 1,4,5-triphosphate; IP_3R, IP_3 receptor; KOR, κ-opioid receptor; LTP, long-term potentiation; mGluR, metabotropic glutamate receptor; MOR, μ-opioid receptor; MR, mineralocorticoid receptor; mTOR, mammalian target of rapamycin; NMDAR, N-methyl D-aspartate receptor; NO, nitric oxide; NOPR, nociceptin/orphanin FQ receptor; NOS, nitric oxide synthase; pAkt, phosphorylated protein kinase B; PI3K, phosphatidilinositol 3 kinase; PKA, protein kinase A; PLCγ, phospholipase C-γ; sGC, soluble guanylyl cyclase; TrkB, tropomyosin-receptor kinase B.

2016); the reduced amount of tonic firing neurons can be explained by the possible VTA-DA neuronal cell loss.

In contrast, using 10-day CSDS the "susceptible" (the defeated) rather than the resilient mice showed increased spine density of VTA and NAc neurons, as opposed to decreased spine density in the prelimbic PFC and hippocampal CA3 and DG neurons. In the same mouse CSDS paradigm, using *ex vivo* structural imaging, the volume of the VTA was found increased, while that of the NAc was decreased in correlation with the severity of social avoidance used as a criterion for susceptibility (Anacker et al., 2016; Chaudhury et al., 2012).

It cannot be excluded therefore that the presumed neuronal loss is preceded by an overexcitation of VTA-DA neurons, however, because of the transiently increased spine density (Hausknecht et al., 2013; Christoffel et al., 2011; Qu et al., 2017), the enhanced firing of the ventral subiculum-mesolimbic DA connection, and the increased BDNF expression (Krishnan et al., 2007) in the CSDS susceptible animals (see also Sections 2.2, 2.5, 4.1, and 5). If this increase in spine density also occurs in the face of neuronal loss during prolonged stress, this may indicate that the connectivity patterns in the remaining VTA-DA neurons are strengthened which, in turn, may have consequences for VTA-DA dependent modulation of behavioral patterns (Magalhães et al., 2017). However, it is unclear to what extent these structural changes are linked to pathology or whether they reflect an adaptive response. In the next sections, the role of excitatory and inhibitory transmitters will be examined.

3.2. Excitatory synapse plasticity

In addition to structural plasticity of VTA-DA neurons, chronic stress exposure can promote long-lasting functional changes at the synaptic level. These include changes at excitatory synapses and, since excitatory input guides the switch from tonic firing to phasic firing activity, these synapses largely determine the eventual dopaminergic output. The main source of excitatory input onto VTA-DA neurons derives from glutamatergic innervation of the pedunculupontine tegmentum (PPTg) and habenular nucleus, targeting the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and *N*-methyl D-aspartate receptors (NMDARs).

Only few studies have addressed the effects of chronic stress exposure on the modulation of glutamatergic synaptic transmission. Yet, even though diverse stress paradigms were used, the results of these studies are fairly in harmony and are implying that chronic stress exposure induces an enhanced excitability of VTA-DA neurons. This is demonstrated by early work showing that both 10 days of chronic unpredictable stress (CUS) or CRS increased the global expression of GluR1 (an AMPAR subunit) and NMDAR1 (a NMDAR subunit) in the VTA (Fitzgerald et al., 1996), but see Toth et al. (2008), who did not see such changes after 4 weeks of CUS. In addition, other studies, using CSDS and social isolation stress paradigms, demonstrated chronic stress-enhanced long-term potentiation (LTP) of NMDAR-mediated glutamatergic synaptic plasticity in the VTA, which was also shown in animals with a history of social isolation (Stelly et al., 2016; Whitaker

et al., 2013). NMDAR LTP is facilitated by protein kinase A (PKA)-dependent and metabotropic glutamate receptor (mGluR)-mediated inositol 1,4,5-triphosphate (IP_3)-induced Ca^{2+} signaling (Stelly et al., 2016): mGluRs mediate the generation of IP_3, leading to IP_3-induced Ca^{2+} signaling. This is gated by phosphorylation of the IP_3 receptor (IP_3R) by PKA, which increases the IP_3 sensitivity of this receptor. In the same study, however, Stelly et al. (2016) found, in contrast to Fitzgerald et al. (1996), no CSDS-induced changes in global NMDAR-mediated excitation. In another study, GluR1 subunit protein expression levels in the VTA were increased 10 days after the final defeat of an intermittent social defeat stress (ISDS) paradigm, while NMDAR1 expression levels were unaffected (Covington et al., 2008).

Interestingly, enhanced afferent glutamatergic innervation from the ventral hippocampus to the NAc determined the phenotype of the susceptible animals in the 10-day CSDS model. The phenotype is reversed by evoking long-term depression (LTD) to attenuate the excitatory input. This effect is specific for the hippocampal input, since opposite effects are observed after optogenetic stimulation of mPFC and basolateral amygdala (BLA) (Bagot et al., 2015). The data support the finding that in the 10-day CSDS model phasic rather than tonic optogenetic stimulation of the VTA-DA neurons rapidly induced a susceptible phenotype characterized by reduced sucrose preference and social avoidance. The effect of optogenetic stimulation was mediated by the mesolimbic- rather than the mesocortical DA pathway (Chaudhury et al., 2012) (see Sections 2.1, 2.5 and 5).

Overall, only few studies have addressed how exposure to chronic stress affects glutamatergic synaptic plasticity onto VTA-DA neurons. These studies, however, are relatively congruent and imply that chronic stress exposure may result in a *transient* increased excitability of VTA-DA neurons. However, in one CUS stress paradigm no changes in GluR1 and NMDAR1 expressions were found (Toth et al., 2008). This paradigm of Toth et al. (2008) lasted four weeks, while in all other studies stress exposure lasted for a maximum of 10-12 days (Covington et al., 2008; Fitzgerald et al., 1996; Stelly et al., 2016; Whitaker et al., 2013).

3.3. Inhibitory synapse plasticity

Inhibitory synaptic transmission in the VTA is also susceptible to undergo plasticity (Xin et al., 2016). While excitatory input is essential for the transition from tonic to phasic firing activity, GABA-ergic inhibition can keep VTA-DA neurons in a hyperpolarized, inactive state, thereby silencing these neurons. Moreover, this inhibitory synaptic transmission is thought to underlie extinction of learned behaviors and to moderate excessive VTA-DA neuron excitability (Xin et al., 2016). Inhibitory input onto VTA-DA neurons is mediated by $GABA_A$Rs and $GABA_B$ receptors ($GABA_B$Rs). While the postsynaptic ionotropic $GABA_A$Rs act by fast synaptic transmission, presynaptic $GABA_B$Rs are slower metabotropic channels linked to G-protein coupled inwardly rectifying potassium channels (GIRKs) (Lüscher et al., 1997). In addition to excitatory synaptic plasticity, the importance and prevalence of inhibitory plasticity is becoming increasingly apparent (Xin et al., 2016).

The mechanisms by which inhibitory synapses on VTA-DA neurons can strengthen or weaken activity are mainly derived from studies in the field of addiction. Increase in inhibitory synaptic strength is a result of LTP of $GABA_A$ currents. While for LTP of AMPA currents AMPAR activation is required, activation of $GABA_A$Rs is not required for LTP of $GABA_A$ currents (Nugent et al., 2007; Nugent and Kauer, 2008). Instead, as demonstrated in *ex vivo* experiments in tissue slices, GABA-ergic synaptic plasticity derives from glutamatergic terminals, and is driven by NMDARs located on the VTA-DA neurons. Upon NMDAR activation, the induced rise in postsynaptic calcium levels results in the Ca^{2+}/calmodulin-dependent protein kinase (CAMK)-mediated activation of nitric oxide synthase (NOS), thereby catalyzing the synthesis of nitric oxide (NO). In turn, by traveling retrogradely to the presynaptic GABA-ergic neuron, where it increases the levels of cyclic guanosine monophosphate (cGMP) by activating soluble guanylyl cyclase (sGC), NO is able to mediate long-term enhancement of GABA release onto dopamine neurons (Nugent et al., 2007; Nugent and Kauer, 2008). Thus, this enhancement of GABA-ergic input can decrease the excitability of VTA-DA neurons.

Similar to LTD in excitatory glutamatergic synapses, inhibitory synaptic strength can decline. This is also the case for VTA-DA neurons (Xin et al., 2016). Repeated cocaine administration can result in a decreased $GABA_A$R-mediated inhibition of VTA-DA neurons, thereby facilitating LTP at glutamatergic synapses onto these neurons, as demonstrated in tissue slices (Liu et al., 2005). In the decrease of GABA-ergic postsynaptic responses the activation of group I mGluRs on the postsynaptic VTA-DA neurons may be involved (Quraishi and Paladini, 2017). The activation of these mGluRs leads to the synthesis of endocannabinoids, which bind to the G protein-coupled cannabinoid receptor type 1 (CB1) located on presynaptic GABA-ergic neurons (Chevaleyre and Castillo, 2004, 2003). Therefore, endocannabinoids show trans-synaptic retrograde signaling in a similar manner as NO in GABA LTP processes, causing a decrease of GABA-ergic input to VTA-DA neurons.

Moreover, endocannabinoid signaling interacts with opioids in the modulation of the VTA circuit underlying reward processing and reinforcement behavior (Wenzel and Cheer, 2017). However, this interaction is very complex and to date there is very little work on linking these three signaling systems, let alone linking stress to their interaction. The role of the endogenous opioid system in (stress-related) VTA-DA neuron activity is discussed in more detail in Section 4.3. Nevertheless, endogenous opioid and endocannabinoid signals are predominantly involved in the suppression of presynaptic GABA-ergic input to VTA-DA neurons, which results in enhanced excitability of the VTA-DA neurons (Van't Veer and Carlezon, 2013; Polter and Kauer, 2014; Covey et al., 2017).

Only few studies have addressed chronic stress-induced changes in GABA-ergic synaptic strength. Krishnan et al. (2008a, 2008b) used a 10-day CSDS paradigm and found significant decreases in Akt (thymoma viral proto-oncogene) phosphorylation in the VTA of susceptible rats (Krishnan et al., 2008b). Since Akt can increase membrane insertion of $GABA_A$Rs by β2-subunit phosphorylation, the inhibition of Akt is sufficient to increase VTA-DA neuron excitability through $GABA_A$-dependent mechanisms (Krishnan et al., 2008a,b; Wang et al., 2003). In addition, Akt is involved in the phosphatidylinositol 3 kinase (PI3K)/Akt/glycogen synthase kinase 3 (GSK3)/mammalian target of rapamycin (mTOR) pathway in cell signaling. The PI3K/Akt/GSK3/mTOR signaling pathway is important in subcellular integration of synaptic neurotransmission, and its function is linked to the regulation of metabolism, cell growth, cell survival, and thus neuronal excitability (Abelaira et al., 2014; Kitagishi et al., 2012; Polman et al., 2012). Together, these results are in line with a chronic stress-induced increased excitability of VTA-DA neurons.

To our knowledge, no direct evidence for strengthened GABA-ergic synapses on VTA-DA neurons upon chronic stress-exposure has been reported. Interestingly, however, Warren et al. (2013) found with a 10-day CSDS paradigm a long-lasting significant decrease in δ-$GABA_A$R expression in the VTA (Warren et al., 2013). δ-$GABA_A$Rs mediate extrasynaptic tonic inhibition and are strongly regulated by neurosteroids – which are synthesized de novo in the brain from progesterone or deoxycorticosterone precursors (Reddy, 2010; Brickley and Mody, 2012). While one study implies an indirect mechanism that may increase inhibitory synaptic transmission, most studies hint that exposure to chronic stress weakens inhibitory synaptic strength onto VTA-DA neurons, thereby contributing to an increased excitability of these neurons.

3.4. Microglial cells

In order to form a proper behavioral response to stress and to

prioritize metabolic needs, neural, immune, and endocrine products of the stress response need to be integrated. Microglia, the main cellular actors of the brain's immune defense network (Ransohoff and Cardona, 2010), have the necessary repertoire of receptors to serve such an integrative role on a local neuronal level (Frank et al., 2019). Moreover, by secretion of cytokines, prostaglandins, and growth factors, microglia can shape neuronal networks and contribute to modulation of synaptic function including that of the VTA-DA neurons (Delpech et al., 2015). The midbrain contains 4.5 times more microglial cells than other brain regions (Kim et al., 2000; Sugama and Kakinuma, 2016) and DA neurons show higher susceptibility to neuroinflammatory signals than other brain cells (Block and Hong, 2007; Gao et al., 2003). While most of glial functions are health-promoting, their neuroinflammatory reaction to insults may overshoot and cause exacerbation of neuronal damage (Block and Hong, 2007).

Various studies have demonstrated that acute and chronic stress exposure can affect inflammatory processes (Dowlati et al., 2010; Gilman et al., 2013; Kendler et al., 1999; McLaughlin et al., 2010; Miller et al., 2008; Frank et al., 2019). Chronic stress exposure showed profound effects on microglia in the VTA, both in structural and functional ways (Table 2). In the previously described study where a 16-week CRS paradigm induced VTA-DA neuronal cell loss, it was found that stress increased intra-VTA microglial cell body sizes significantly (Sugama and Kakinuma, 2016). Enlarged microglial body sizes imply an activated status, and these enlargements were observed both after acute prolonged (8 h session) stress and, although relatively lesser, after chronic (16-weeks) stress. Furthermore, Tanaka et al. (2012) showed a CSDS-induced increase in reactivity of ionized calcium-binding adaptor protein-1 (Iba1), which is a marker of morphological changes in activated microglia (Tanaka et al., 2012; but see Tynan et al., 2010).

In the study by Sugama and Kakinuma (2016), the possible comorbidity between neuronal cell loss and increased microglial activation may imply a role for microglial neuroinflammatory mechanisms in chronic stress-induced adaptations of VTA-DA neurons (Sugama and Kakinuma, 2016). Moreover, since microglial-induced inflammatory mediators, including cytokines, can orchestrate physiological and behavioral responses (Dantzer et al., 2008), these modulations may have consequences for stress-induced behavior during health and disease. Various studies, indeed, have implicated elevated cytokines in stress-related disorders or their symptoms (Dowlati et al., 2010; Felger and Miller, 2012; Dantzer et al., 2008).

Moreover, chronic stress-induced alterations in microglial neuroinflammatory functionality is implicated in neurodegenerative diseases (Lull and Block, 2010; Réus et al., 2015). In this link between microglia and the vitality of (dopaminergic) neurons, the involvement of microglia in regulating homeostatic processes of local brain environments may be of crucial importance (Colonna and Butovsky, 2017). As discussed in Section 3.2, mGluR/IP_3-enhanced promotion of intracellular Ca^{2+}-release is involved in synaptic plasticity processes (Stelly et al., 2016; Whitaker et al., 2013). Increased intracellular Ca^{2+} concentrations are featured in pathological cellular states associated with oxidative stress and excitotoxicity, processes known to promote apoptosis (Radley and Morrison, 2005; Salido, 2009; Dantzer and Walker, 2014; Pan et al., 2017). Thus, the enhanced neuronal reactivity may occur at the expense of intra-cellular mechanisms, putting their homeostatic limits to the test and ultimately may result in neuronal degeneration. Consequently, this may lead to a structural decrease in tonic firing population activity, and therefore produce a structural decrease in vigor of VTA-DA neuron behavior modulating effects. Accordingly, the degenerated VTA-DA neuronal network may be causal to depressive pathology, if translated to humans (Belujon and Grace, 2017; Cabib and Puglisi-Allegra, 2012; Tye et al., 2013; Wood and Bhatnagar, 2015).

Interestingly, glucocorticoids regulate neuroinflammation controlled by microglial cells in a sequential pattern. First, *via* MR the hormone acts initially pro-inflammatory (Brocca et al., 2017; de Kloet et al., 2018). Next, *via* GR the well-known anti-inflammatory and recuperative phase occurs. Finally, microglial cells can be primed in their response by the inflammatory experience (Frank et al., 2015). Specifically, during inflammation the recuperative anti-inflammatory action of glucocorticoids *via* GR can leave a footprint, the so-called inflammasome. This 'memory' of the brain's immune response ensures that microglia are prepared for a next time and can support an immediate pro-inflammatory response to damage and infections in the future (Frank et al., 2015). Such adaptive changes of microglial neuroinflammatory activity support optimal allocation of energy resources when faced with stressful environmental challenges (McNamara, 2005; Rauw, 2012).

In conclusion, a role of microglial activation and cytokines in VTA-DA function during chronic stress cannot be excluded and requires further study. It should be noted, however, that besides the locally produced inflammatory signals, peripheral inflammatory responses can exert profound effects on (dopamine-related) motivated behaviors as well (Felger and Treadway, 2017; Stanton et al., 2019).

3.5. Synthesis: from excitation to neurodegeneration

The response of the VTA-DA neurons to stressors is context-dependent and is generally implicated in emotional-motivational appraisal processes for assessment of valence. The activity of the VTA-DA neurons can guide and modulate various coping responses and adaptive behaviors, including reinforcement learning and behavioral flexibility. Given that VTA-DA neurons are highly innervated by afferents from various brain regions, particularly of mPFC and limbic origin (Belujon and Grace, 2017), the VTA-DA-mediated behavioral effects are dependent on the balance of specific excitatory, inhibitory, and modulatory inputs. In response to acute stressors, such an integration of presynaptic inputs leads eventually to fluctuations in both tonic and phasic VTA-DA activity. In general, tonic firing population activity reflects the state and can be affected by acute stress, while phasic responses, on the other hand, are more spatiotemporal specific and may vary over different stressors and stressor intensities. These VTA-DA responses to stress are thought to result in increased vigilance and to support behavioral activation, with the goal to attain control over the stressor by using one's own resources.

Chronic exposure to stress, however, can lead to profound changes in VTA-DA neuron activity, not only in response to the stressors, but also to other behaviorally relevant stimuli. Such chronic stress-induced changes in VTA-DA reactivity vary over methodological procedures, especially with respect to the tonic firing population activity. When an animal has been exposed to chronic stress and is subsequently facing a stressor of a different nature, phasic responses generally appear sensitized. These changes in VTA-DA activity are promoted by plasticity induced by glutamatergic excitatory and GABA-ergic inhibitory synaptic input. The reported synaptic adaptations show that chronic stress exposure mainly alleviates the GABA-ergic inhibitory input onto VTA-DA neurons and facilitates excitatory synaptic transmission, which is in line with the sensitized VTA-DA activity responses.

The chronic stress-induced alterations in VTA-DA neurons rather reflect vulnerability. However, although current knowledge is far from complete, one can conclude that chronic exposure to stress is capable of causing long-lasting changes, and may lead, after possibly an initial transient activation (Krishnan et al., 2007; Chaudhury et al., 2012; Magalhães et al., 2017) over time to degeneration or perhaps even loss of VTA-DA neurons, a process in which microglia activation participates (Tables 1 and 2, and Fig. 3). These neuroadaptations involve both functional changes, predominantly leading to a transiently increased VTA-DA neuron excitability, morphological changes, and altered connectivity, potentially increasing the risk for stress-related and neurodegenerative diseases (Abelaira et al., 2014; Ceretta et al., 2012; Hoyo-Becerra et al., 2014; Iseme et al., 2014; McInnis et al., 2014). The exact link between increased VTA-DA neuron excitability, neuroinflammatory responses, and neurodegeneration is, however, not yet well

understood.

4. BDNF, CRH, and opioids

The excitation-inhibition balance is crucial for the function of the VTA-DA circuit and can be modulated by a variety of local and systemic factors that are induced by stress. While these stress-induced factors are essential in neuroadaptive processes, each one by itself is believed to be insufficient to cause the behavioral changes seen after (chronic) stress exposure. Moreover, these stress mediators act conditionally and presumably rely on the nature and integration of excitatory input (Joëls and Baram, 2009). We will discuss four classes of mediators: BDNF, as an example of a locally acting trophic factor, the CRH neuropeptide, as the central organizer of the stress response, the endogenous opioid system, having addictive properties while also released as a consequence of stressors, and the glucocorticoid hormones. The latter will be addressed in a separate section (Section 5).

4.1. Brain-derived neurotrophic factor (BDNF)

The structure and function of VTA-DA neurons is affected by neurotrophins, which are key mediators of growth and neuronal plasticity (de Azevedo Cardoso et al., 2014; Russo et al., 2009). Although there are four neurotrophin family members (nerve growth factor (NGF), neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), and BDNF) expressed in the brain, we focus on the action of BDNF (Nikulina et al., 2014), which is best investigated in the hippocampus and the VTA-DA system.

The expression of BDNF is activity-dependent and is affected by stress and glucocorticoids. For instance, if coping is successful, glucocorticoids are permissive and hippocampal BDNF expression is increased, but downregulated after exogenous glucocorticoids or chronic stress (Schaaf et al., 1998, 2000). Its downregulation in hippocampus has been implicated in stress-related mood disorders, and many current antidepressant drugs, that are used to treat these disorders, promote BDNF expression and signaling (Calabrese et al., 2009; Hashimoto et al., 2004; Post, 2007). BDNF binds to the tropomyosin-receptor kinase B (TrkB) receptor and TrkB signaling leads to the activation of multiple intracellular signaling cascades, including PI3K/Akt/GSK3/mTOR, Ras/extracellular signal-regulated kinase (ERK), and phospholipase C-γ (PLCγ) (Nikulina et al., 2014). Chronic stress-induced alterations in BDNF activity vary over stress paradigms and show regionally different response patterns in the brain. After ISDS (Fanous et al., 2010), BDNF expression was decreased in hippocampus. Using CSDS, BDNF was also decreased in hippocampus, but increased in the VTA and NAc of rats and mice (Krishnan et al., 2007).

In the latter study a 10-day CSDS paradigm was used to differentiate male C57Bl6 mice in susceptible and resistant phenotypes as judged from their performance in a social interaction test (Krishnan et al., 2007; Berton et al., 2006). The susceptible mice showed social avoidance towards a conspecific control, a passive coping style in the forced swim test, and reduced preference for sucrose. In susceptible mice, BDNF expression is increased in the VTA-NAc circuit, rather than the decrease commonly observed in hippocampus. The susceptible phenotype could be reversed to a resistant variant with deletion or suppression of BDNF expression in the VTA (or alternatively by stimulating its overexpression in hippocampus) (Berton et al., 2006). In the studies by Miczek et al. (2011) a 10-day ISDS also produced increased DA release and BDNF expression in the VTA-NAc system (Miczek et al., 2011), while a continuous CSDS paradigm (36 days) showed the opposite down-regulatory effect. In contrast to the various social defeat stress paradigms, a four-week as well as a 38-day lasting CUS paradigm left BDNF expression levels in the VTA unchanged, however (Gersner et al., 2010; Toth et al., 2008).

BDNF is considered as critical for survival and function of VTA-DA neurons, but the effects of chronic stress exposure are diverse and vary over stress procedure and susceptibility of the animals. While after stress BDNF expressions levels are initially rising, there is some evidence that prolonged stress exposure may curtail the BDNF increase. Moreover, BDNF increases seem to be dependent on disinhibition of VTA-DA neurons, as VTA μ-opioid receptor (MOR), see Section 4.3, knockdown blocks induction of VTA BDNF expression and prevents social defeat-induced cross-sensitization to amphetamine (Johnston et al., 2015). Furthermore, since BDNF activity is dependent on inhibitory control (Johnston et al., 2015) and strongly associates with enhanced (ERK activity dependent) stimulus-response behavior (Grimm et al., 2001; Lu et al., 2009, 2004; Neisewander et al., 2000), the effects of BDNF on VTA-DA neuron excitability seem to be stimulus-dependent and rely on the integration of excitatory input (Leonard et al., 2017). Nevertheless, although the effects of chronic stress exposure on BDNF-mediated signaling are complex, the growth factor appears to be an important permissive mediator of neuronal remodeling.

High VTA and low hippocampal BDNF expression in post-mortem tissue of depressed patients matched the opposite BDNF levels in these two brain regions of the male susceptible CSDS mice (Krishnan et al., 2007). Moreover, the *Bdnf* G196A (Val66Met) single nucleotide polymorphism (SNP) impairs BDNF signaling and contextual learning, and is associated with psychopathology (Chen et al., 2014), a finding that probably refers to hippocampal BDNF expression. In translational studies with these SNPs, transgenic BDNF Met/Met mutants appeared resilient to CSDS and expressed 50 % of the BDNF found in the ventral striatum of the Val/Val mutants (Krishnan et al., 2007). Interestingly, a similar CSDS-induced pattern was recently found for the induction by NGF of the *Vgf* gene and its C-terminal AQEE-30 and TLQP-62 neuropeptide (Lin et al., 2014; Mo et al., 2015). Although these data are very interesting, they add to the conundrum that increased bio-availability of the growth factors and enhanced VTA-DA activity would predispose for susceptibility in the CSDS model, while exposure to chronic unpredictable stressors produces a similar susceptible phenotype, but is characterized by decreased VTA-DA function.

In conclusion, BDNF is an important regulator of VTA-DA function; its effects are conditional and seem related to the extent of controllability, duration, and severity of the stressor.

4.2. Corticotropin releasing hormone (CRH)

CRH orchestrates the autonomic and neuroendocrine response to stress and coordinates the various emotional expressions as part of the behavioral adaptation. These actions exerted by CRH occur widespread in the brain and are mediated by CRH-R1 and the lower affinity CRH-R2 receptors; the latter receptors actually respond predominantly to urocortin (Hsu and Hsueh, 2001; Reyes et al., 2001). Using *in situ* hybridization of mRNA expression or autoradiography of radioligand binding, CRH-R1, but not CRH-R2, was found co-localized with DA markers in neurons of the VTA (Van Pett et al., 2000; Tan et al., 2017; Kelly and Fudge, 2018). Yet, acute activation of VTA-CRH-R2 receptors amplified NMDA excitatory currents (Ungless et al., 2010). Furthermore, CRH strongly affects the excitability of VTA-DA neurons upon stress exposure (Holly et al., 2016; Korotkova et al., 2006; Leonard et al., 2017; Wang, 2005). With *in vivo* microdialysis, phasic release of CRH was demonstrated in the posterior VTA during the acute stress of social defeat, but when stress exposure is repeated CRH is also recruited in the anterior VTA (Holly et al., 2016). This effect of CRH exerted on VTA-DA neuronal firing involves protein kinase C (PKC)- rather than cAMP–protein kinase A (PKA)-dependent enhancement of I_h currents (Korotkova et al., 2006; Wanat et al., 2008).

The chronic stress paradigm also increased cocaine self-administration, which could be prevented by antagonism of CRH-R1 in the posterior VTA and of CRH-R2 in the anterior VTA prior to each stress session (Holly et al., 2016). Leonard et al. (2017) studied cocaine-taking behavior and compared the effects of repeated CRH microinjections in the VTA of male rats with a CSDS paradigm (Leonard et al., 2017). They found that both protocols produced intense, but slightly

different, patterns of drug taking behavior. The authors of this recent study suggest that the effects of CRH in the VTA may be stimulus-dependent, and that the chronic stress-induced increase in drug bingeing behavior is independent of reward valuation. Instead, chronic stress exposure impairs inhibitory control and therefore empowers the stimulus-dependent effects of CRH (Leonard et al., 2017).

Besides effects on addiction, reward, and locomotion (Wang, 2005; Kalivas, 2009), the best known action of CRH is on fear-motivated behavior. This effect on fear expression involves the recently discovered GABA-ergic neurons that co-express CRH in the extended amygdala – comprising the BNST and central amygdala – that has mono-synaptic projections to the VTA (Dedic et al., 2018). Stimulation of this subpopulation of CRH neurons appeared to increase dopamine release from VTA-DA neurons and to exert anxiolytic effects (Dedic et al., 2018). Under stressful conditions and during the withdrawal phase of addictive behavior, CRH, however, aggravates anxiety (Lemos et al., 2012; Wanat et al., 2013). Recent research has demonstrated that trait anxiety is actually a determinant in the outcome of VTA-CRH-R1 stimulation by either stress exposure or exogenous local CRH application. In rats selected for low anxiety these manipulations improved motivation to collect a reward, while behavior of the high anxious rat was impaired. Intra-VTA infusion of CRH in the low anxious rats evoked a larger DA response than in their high anxious littermates (Zalachoras et al., 2018).

It is noteworthy that Lemos et al. (2012) revealed in male mice the importance of CRH in stress responses at the terminal level of VTA-DA transmission (Lemos et al., 2012). While CRH results in increased VTA-DA release in the NAc, a two day repeated forced swim stress paradigm abolished this effect for at least 3 months. Furthermore, in naïve animals (pre-stress) intra-NAc microinjections with CRH promoted conditioned place preference behavior (indicated as *appetitive*), while after the swim stressor the CRH effect switched to conditioned place *aversion*. Interestingly, treatment with the GR antagonist prior to the forced swim reinstated the appetitive CRH effect (Lemos et al., 2012). Although the effect of CRH seemed to involve co-activation of both CRH-R1 and CRH-R2 receptors in the NAc, the precise mechanism underlying this stress-induced switch in function of CRH has yet to be fully elucidated. It might be linked to the stress-induced increase in use of habitual (stimulus-response) instead of cognitive behavioral strategies, which may occur after blockade of GR when MR activation is privileged (Dias-Ferreira et al., 2009; Leonard et al., 2017; Wanat et al., 2013; Schwabe et al., 2013) (see Section 5.3).

In conclusion, the effects of CRH on VTA-DA neuron excitability seem to be conditional and, therefore, stimulus-dependent (Leonard et al., 2017; Wanat et al., 2013). Although these CRH-DA interactions are best studied in locomotion, addiction, and reward, recent research highlights emotionally valenced social behaviors driven by CRH expressing GABA-ergic projections from the extended amygdala. Since glucocorticoids induce amygdala CRH and can modulate VTA-DA function it is of interest to examine how these hormones are implicated in control of VTA-DA function (see Section 5).

4.3. Opioids

Besides BDNF and CRH, we also wish to highlight the role of the endogenous opioid system in VTA control. While this neuromodulatory system, which is famously known for its abuse liability, is involved in widespread physiological processes, including pain modulation, respiratory function, and gastrointestinal transit, the endogenous opioids are also linked to motivated behavior and, specifically, the modulation of VTA-DA activity in stressful situations (Miller et al., 1984; Kalivas and Abhold, 1987; Cabib et al., 1989; Latagliata et al., 2014; Margolis and Karkhanis, 2019). Moreover, endogenous opioids are massively released during stressful situations (Latagliata et al., 2014). We will not elaborate on the endogenous opioid system in full detail, since excellent articles have appeared, including their interaction with glucocorticoids (Witkin et al., 2014; Benarroch, 2012; Henry et al., 2017; Szklarczyk et al., 2016).

Briefly, the endogenous opioid system consists of four major subtypes of G protein-coupled opioid receptors, the MOR, the δ-opioid receptor (DOR), the κ-opioid receptor (KOR), and the nociceptin receptor (NOPR), which can be targeted by four families of opioid peptides, *viz*. β-endorphin, enkephalins, dynorphins, and nociceptin/orphanin FQ (N/OFQ). These opioid peptides derive from four different precursor proteins: POMC, which is the same precursor protein as for ACTH, proenkephalin, prodynorphin, and prepronociceptin, respectively. Current literature suggests that DA and opioid stimulation have similar behavioral effects (Callaghan et al., 2018). While acting on various intracellular signaling cascades (Al-Hasani and Bruchas, 2011), all opioid receptors share that they inhibit cAMP formation upon receptor agonist stimulation. While opioids may act on VTA-DA neurons directly, at the cell bodies within the VTA, or at terminals at projection areas, the most profound effects of the endogenous opioid system on VTA-DA dynamics are pathway specific and act indirectly (Langlois and Nugent, 2017; Thomas et al., 2018; Callaghan et al., 2018). Stress-induced alterations within the endogenous opioid system may contribute to changes in VTA-DA dynamics, ultimately supporting the development of maladaptive behavior, but stress-induced changes in VTA-DA dynamics can also be modulated by opioids (Callaghan et al., 2018; Przewlocki and Almeida, 2017). In this section we will describe the effects of the endogenous opioid system on VTA-DA neuron dynamics and discuss how stress can alter these dynamics.

Various studies show that stress-induced alterations in dopamine activity and behavioral outcome can be modulated by opioids (Kalivas and Abhold, 1987; Latagliata et al., 2014; Callaghan et al., 2018; Tejeda and Bonci, 2019; Kalivas et al., 1988; Przewlocki and Almeida, 2017). For example, daily exposure of mild footshock stress enhances the motor stimulatory effect of intra-VTA administration of an enkephalin analog, and daily intra-VTA administration of this opioid receptor agonist led to an elevated dopaminergic response in the NAc. Interestingly, pre-stress treatment with naltrexone, a competitive antagonist for opioid receptors, augmented these dopaminergic responses (Kalivas et al., 1988).

More specifically, MOR activation is linked to changes in VTA-DA responses to stress (Latagliata et al., 2014; Nikulina et al., 2008). In a study where an acute restraint stress paradigm was combined with microdialyis, Latagliata et al. (2014) showed that MOR activation can reduce NAc DA tone *via* enhancement of DA transmission in the mPFC (Latagliata et al., 2014). In studies from Nikulina et al. (2005, 2008), 5 days of CSDS exposure increases mRNA expression of MOR in the VTA for up to 14 days after the last episode of stress (Nikulina et al., 2005, 2008). Predominantly, the effects of MOR activation on VTA-DA neuron activity are indirect, as they act presynaptically on GABA-ergic afferents derived from the ventral pallidum and RMTg, and result in tonic inhibition of this input onto VTA-DA neurons (Steffensen et al., 2006; Chieng et al., 2011; Hjelmstad et al., 2013; Matsui et al., 2014; but see Margolis et al., 2014). However, NAc-derived MOR sensitive GABA-ergic afferents to the VTA can have opposing actions on VTA-DA neurons, as NAc-derived GABA-ergic input primarily synapse to non-dopaminergic neurons in the VTA (Xia et al., 2011). Thus, while intra-VTA treatment with MOR agonists can inhibit GABA-ergic input directly synapsing onto VTA-DA neurons, it can also disinhibit the same GABA-ergic neurons *via* NAc afferent MOR activation. Consequently, MOR agonist studies will predominantly address the most prominent MOR sensitive inhibitory neuronal populations to the VTA, presumably the RMTg, thereby overshadowing projection-specific and subtle MOR-induced modulation of VTA-DA neuron activity (Thomas et al., 2018). Moreover, given the indirect nature of VTA-DA modulation *via* MOR, eventual dopaminergic and behavioral output relies on integration of excitatory input.

In addition, stressors potently activate KORs within the VTA. KORs inhibit excitatory and inhibitory transmission onto VTA-DA neurons,

somatodendritic dopamine release, and dopamine release in dopaminergic terminals at the NAc and mPFC (Margolis et al., 2003, 2005; Margolis et al., 2006; Ford, 2006; Tejeda and Bonci, 2019). However, VTA-DA modulating effects of VTA KOR can be species specific as in rats KOR agonists do hyperpolarize VTA-DA neurons that project to mPFC but not NAc, while in mice KOR agonists were able to inhibit dopaminergic input onto the NAc as well (Ford, 2006; Baimel et al., 2017). However, a KOR agonist in striatal slices reduced DA release *via* blockade of presynaptic nicotinic receptors (nAChRs) by inhibiting striatal cholinergic interneurons (Mamaligas and Ford, 2016), which can explain the ability of KOR to inhibit DA transmission at dopaminergic terminals in the NAc. Sex differences may complicate the above described findings, however, since female mice show relatively less KOR inhibition of dopamine release (Abraham et al., 2018). Nevertheless, KOR and stress are linked and stress can alter the way KORs modulate dopamine release (Bruchas et al., 2010; Van't Veer and Carlezon, 2013; Karkhanis et al., 2016; Polter et al., 2017). This is demonstrated by Graziane et al. (2013), showing that acute stress blocks synaptic plasticity at GABA-ergic input onto VTA-DA neurons (Graziane et al., 2013), and post-stress treatment with a KOR antagonist can rescue stress-induced behavioral effects (Polter and Kauer, 2014). Moreover, a single exposure to a brief cold-water swim stress induces prolonged KOR activation in VTA-GABA neurons synapsing on VTA-DA neurons (Polter et al., 2017).

While the link between DORs and dopamine dynamics is less studied than the above described opioid receptors, the most recently discovered member of the opioid receptor superfamily, the NOPR, can regulate DA transmission and is highly linked to stress (Driscoll et al., 2019; Khan et al., 2018). The VTA expresses NOPRs in a high density (Ikeda et al., 1998) and, additionally, high levels of TH-containing neurons in the VTA co-express NOPR mRNA, but not N/OFQ mRNA (Norton et al., 2002). Although this nociceptin-ergic DA modulation derives from various sources (Khan et al., 2018), it is notable to highlight that in a recent paper by Parker et al. (2019) a nociceptin-ergic population of neurons within the VTA is identified – thereby emphasizing the heterogeneity of the midbrain once again. These neurons contain the precursor peptide for N/OFQ, the protein called prepronociceptin, they project directly to VTA-DA neurons, and are linked to motivation in a reward-seeking behavioral paradigm (Parker et al., 2019). Moreover, their data suggest that the input of these neurons constrain VTA-DA neuron activity and that the NOPR is at least partially responsible for this dopaminergic modulation. Nevertheless, the effects of N/OFQ on dopaminergic transmission are evident, as N/OFQ inhibits dopamine transmission in striatal brain slices (Flau et al., 2002), antagonism of NOPRs demonstrates enhancement of dopaminergic transmission (Marti, 2004, 2005), and downregulation of NOPR has neuroprotective effects on dopamine neurons (Arcuri et al., 2016). In addition, Olianas et al. (2008) found that striatal NOPR activation inhibits TH phosphorylation, thereby limiting its potency in dopamine synthesis (Olianas et al., 2008). Besides these presynaptic effects, the same authors found that postsynaptically D1R signaling was inhibited as well. Furthermore, NOPRs have a modulatory role on the HPA-axis, suggesting that N/OFQ signaling may play a role in HPA-axis feedback mechanisms (Khan et al., 2018).

In a study by Der-Avakian et al. (2017) NOPR mRNA was found increased in the striatum and Fos mRNA, a molecular marker for neuronal activity, decreased in the VTA of rats after exposure to a 3-day SDS paradigm (Der-Avakian et al., 2017). Thus, although the link with stress requires further elucidation, literature suggest a role for N/OFQ signaling in dopaminergic regulation, with NOPR activation generally inhibiting dopaminergic transmission.

In conclusion, various studies show that stress-induced alterations in dopamine activity and dopamine-related behavioral outcome can be modulated by opioids. However, due to a lack of studies it is currently unclear how – especially after chronic stress exposure – the post-stress dynamics in levels of endogenous opioids affect VTA-DA neuronal excitability and plasticity. The above described dopamine neurotransmission modulatory role of the endogenous opioid system, however, suggest that the most prominent effects by MOR and KOR on VTA-DA dynamics are regulated in an indirect manner in inhibitory presynaptic input or at dopaminergic terminals. This would suggest that in the case of opioid regulation of dopaminergic terminals, activity of VTA-DA neurons would remain unperturbed and, although effects can be significant, local control is the main influence of the opioid system. The described N/OFQ modulation of dopaminergic neurons suggests a more direct influence on dopaminergic transmission. The link with stress, however, requires more investigation.

5. Glucocorticoids

It is well-established that glucocorticoids increase dopamine-dependent motivation and psychostimulant intake and, in excess, may cause psychotic and depression symptoms (Schatzberg et al., 1985; Marinelli and Piazza, 2002), while these effects can be attenuated by GR antagonists (DeBattista and Belanoff, 2006; Block et al., 2018) (see Section 2.1). In the first section we will review the role of the glucocorticoid hormone and its receptors, MR and GR, in the function and regulation of the VTA-DA circuit. Then, the action mediated by these receptors in limbic afferents to the VTA circuit is discussed. In the third section, glucocorticoid action is highlighted in the coordination of VTA-DA and limbic-prefrontocortical circuitry during stress-coping and adaptation. The hormone feeds back for this purpose on the very same brain circuitry that initially produced the stress response and thus attenuates its own secretion. Best known are the genomic actions mediated *via* MR and GR. Recently non-genomic MR- and GR-mediated actions have been discovered and identified in limbic, hypothalamic and prefrontal cortex, the immune system and other peripheral target tissues (Lösel and Wehling, 2003; Groeneweg et al., 2012), but need to be demonstrated still in VTA-DA neurons.

5.1. VTA-DA circuit

Strong GR-immunoreactivity was found in the medial parts (nucleus interfascicularis and nucleus linearis caudalis; see Holly and Miczek, 2016) of the VTA along its entire rostro-caudal extent in 61 ± 9 % of all TH-immunoreactive cells (Härfstrand et al., 1986). This medial part of the VTA projects to the mPFC and is involved in cognitive aspects of reward processing and strongly responds to stress (Thierry et al., 1977) . Besides GR, the VTA circuit and its NAc and mPFC target regions do express MR as well, but in lower abundance than GR. MR and GR occur both abundantly in limbic afferents of the hippocampus, amygdala, and lateral septum (Arriza et al., 1988; van Eekelen et al., 1991; Ahima et al., 1991; Diorio et al., 1993; Brinks et al., 2007; Caudal et al., 2014).

Only few experiments were directed to explore the role of MR and GR within the VTA-DA system. Firstly, pharmacological experiments in urethane anesthetized rats showed that under basal conditions MR and GR cooperate in sustaining a circadian pattern in release of dopamine from the NAc core (Tye et al., 2009). The authors conclude that this MR/GR cooperation stabilizes tonic meso-accumbens dopaminergic transmission and ensures maintenance of NAc dopamine activity in the face of changing glucocorticoid levels over the circadian cycle. Other experiments suggested that the corticosterone action becomes apparent in the VTA when glutamatergic afferents are activated (Overton et al., 1996). In addition, intra-VTA, but not intra-BLA, infusion of the MR antagonist spironolactone attenuated a conditioned fear response but did not affect locomotion and exploration in an open field test condition. This intra-VTA treatment with the MR antagonist decreased DA release within the BLA. In these experiments the GR antagonist neither was anxiolytic nor prevented dopamine release from the VTA efferent projections to the amygdala (de Oliveira et al., 2014). Thus, the glucocorticoid action is conditional, and MR- and GR-mediated actions cooperate with the goal to maintain VTA-DA activity.

During acute stress, a GR-mediated action activates the VTA-DA neurons. Hence, the effect of stress exposure on dopamine can be altered by antagonizing GR function (Chen et al., 2016; DeBattista and Belanoff, 2006; Goshen et al., 2008; Gourley and Taylor, 2009; Kvarta et al., 2015; Wu et al., 2007). On the cellular level, CSDS-induced facilitation of LTP of NMDAR-mediated transmission in VTA-DA neurons requires GR activation (Stelly et al., 2016). The GR antagonist mifepristone administered prior to each defeat session prevented inositol IP_3R sensitization – which was otherwise necessary to increase VTA-DA neuron excitability. Interestingly, various studies suggest that this glucocorticoid-mediated regulation of VTA-DA neuron excitability is not regulated by GR expressed in VTA-DA neurons, but by GR expressed in the VTA's main projection areas, *i.e.* the dopaminoceptive neurons in prefrontal cortical areas and ventral striatum (Ambroggi et al., 2009; Barik et al., 2013; Butts et al., 2011).

In the study by Barik et al. (2013), adult mice exposed to three weeks CSDS showed symptoms of anxiety and social aversion (Barik et al., 2013). Genetic deletion of the GR in the dopaminoceptive neurons rather than in the DA neurons *per se* obliterated stress-induced social aversion – but not anxiety – and a similar result was obtained when mifepristone was given during the repeated defeat experience. Moreover, blockade of the GR in dopaminoceptive neurons of the mPFC attenuated the glutamatergic excitatory feedforward drive to the VTA-DA neurons (Butts and Phillips, 2013). Their finding is in support of a positive feedback loop under control of these postsynaptic GRs that maintains the firing rate of the VTA during stressful conditions. Interestingly, the dopaminoceptive neurons in the NAc mediate the precipitation of stress-induced addictive behavior (Ambroggi et al., 2009; McEwen, 2013a,b).

Niwa et al. (2013) reported that glucocorticoids also can exert long-term control *via* presumed epigenetic programming. After exposure to three weeks of isolation stress during adolescence, adult mice showed a preferred passive coping response in the forced swim test (Niwa et al., 2013). However, this response was displayed only in animals that carried a *DISC1* allele, of which variants can precipitate a schizophrenia-like phenotype. Chronic stress reduced DA activity in the VTA projection to the frontal cortex, but DA activity was *not* changed in the NAc projection. The programming of this 'low VTA-DA passive phenotype' by chronic stress during adolescence was prevented if stressor exposure was experienced in the presence of the anti-glucocorticoid mifepristone.

In animals subjected to CUS the glucocorticoid response to an acute stressor is prolonged, but the VTA-DA release is diminished. This failure of elevated glucocorticoids to increase DA release in NAc and mPFC during CUS may be the reason for lack of motivation, lack of pleasure, and depressed mood (Chen et al., 2017). Interestingly, chronic exercise also increases circulating glucocorticoid concentrations, but now DA release is increased and the VTA-DA system is functional. Moreover, adrenalectomy (ADX) attenuates the exercise-induced rise in DA, which is reinstated with corticosterone replacement (Chen et al., 2017). There is no answer yet on the mechanism that underlies this glucocorticoid paradox in stimulation *versus* suppression of DA release during either exercise or CUS exposure, respectively. However, it likely refers to the rewarding experience of exercise, which is a stimulus leading to DA release, and associated reinforcement learning.

In sum, GR-mediated glucocorticoid actions sustain VTA-DA activation during stress *via* stimulation of TH in their cell bodies, while promoting motivational arousal particularly under rewarding circumstances of successful coping, winning a contest, and exercise. VTA-DA activity is increased during such acute challenges by a GR-dependent positive glutamatergic feedback loop, but reduced with a prolonged stress experience during failure to cope in the face of elevated circulating glucocorticoids. The few data available suggest that under basal conditions MR and GR seem to be involved in spontaneous firing and thus tonic activity of the VTA-DA system and possibly in promoting DA release from its efferents innervating limbic and cortical regions.

5.2. Limbic afferents to the VTA-DA circuit

Limbic afferents, *e.g.* from hippocampus and amygdala, are considered to be the main determinants of tonic VTA-DA neuronal activity (Belujon and Grace, 2017). It is therefore of interest to briefly summarize the seminal studies with rat hippocampal neurons showing that in these hippocampal cells "*MR-mediated steroid actions enhance cellular excitability, whereas activated GRcan suppress temporarily raised neuronal activity*." (Joëls and de Kloet, 1992).

The results revealed in hippocampal CA1 neurons that these opposing MR- and GR-mediated actions actually produced a U-shaped dose response in a number of cellular responses. The steroid actions, that developed with a delay of 15–30 min, required GR dimer formation and protein synthesis (Karst et al., 2000). Thus, in CA1 neurons MR occupation with low glucocorticoid concentrations caused small Ca^{2+}-currents through L-type Ca^{2+}-channels as a result of transcriptional regulation of the Ca^{2+}-channel β4 subunit (Chameau et al., 2007). Hence, in the pyramidal neurons the slow Ca^{2+}-dependent K^+-conductance (after-hyperpolarization), NE- and current-induced cell firing frequency accommodation, and $5HT1_A$ K^+-hyperpolarization response were all attenuated by MR activation (Joëls and de Kloet, 1989, 1990; Joëls et al., 1991). These currents were increased in absence of steroid by adrenalectomy (ADX) as well as during excess stimulation of GR. The most stable condition occurred with mostly MR and little GR activation, which represents the average receptor occupancy under basal HPA axis conditions throughout the day.

However, glucocorticoids also exert non-genomic actions in hippocampus and BLA *via* MRs and GRs (Groeneweg et al., 2011, 2012). Membrane GRs control the release of endocannabinoids which exert an inhibitory presynaptic action on transmitter release and have effects on appetite and mood (Hill and Tasker, 2012). MRs were found in the hippocampus to promote rapidly the release probability of glutamate from single vesicles. The mechanism involved a fast MAP kinase pathway, which is measured postsynaptically as an increase in the frequency of miniature excitatory postsynaptic currents (mEPSCs) (Karst et al., 2005; Pietranera et al., 2006; Olijslagers et al., 2008). This increased excitability is in hippocampus rapidly suppressed *via* GR.

A similar increased frequency of mEPSCs was observed in the BLA, but this effect persisted because it was sustained rather than inhibited by a GR-mediated genomic effect as observed in hippocampus. This cooperativity of non-genomic MR and genomic GR was termed 'corticosterone metaplasticity' (Joëls et al., 2010). In another series of experiments the neurons of the amygdala were first excited by isoproterenol (a β-agonist) followed 20 min later by exposure to corticosterone in order to mimic *in vitro* the release of the agents under *in vivo* stress conditions. NE-induced mEPSCs were suppressed by moderate concentrations of corticosterone, but with very high concentrations of both hormones, mimicking severe stress, the mEPSCs were enhanced in a long-term manner (Karst and Joëls, 2016). This coordinated glucocorticoid-NE mechanism may explain why emotions are so strongly remembered.

The studies on genomic and non-genomic actions by Marian Joëls and coworkers (Joëls et al., 2012) were performed with slices of the dorsal hippocampus, a region primarily involved in spatial learning and cognitive processes. The ventral hippocampus (vHipp), however, processes information on the stress- and fear-related emotional state of the individual rather than cognitive processes (Moser and Moser, 1998), but here MR activation did not activate EPSCs. Instead, corticosterone acting *via* MR was found to reduce the frequency of inhibitory postsynaptic currents (IPSCs) and suppressed paired pulse of evoked synaptic currents in the vHipp, and this action did not occur in the dorsal part (Maggio and Segal, 2007, 2009). Therefore, in response to MR stimulation, both the increased mEPSCs in the dorsal and the reduced mIPSCs in the ventral part of the hippocampus promote excitability, and thus can enhance excitatory outflow of the hippocampus to the VTA-NAc-DA system, albeit *via* different pathways related to either

emotion in the ventral or cognition in the dorsal part.

Recently, a hippocampal-NAc pathway was firmly established using an electrophysiological approach. It was found that LTP induced in the hippocampal-NAc pathway was required for reward-motivated conditioned place preference. Chronic stress attenuated the hippocampal input and was accompanied by anhedonia. This finding documented that the activity-dependent hippocampal-NAc input can be modulated by contextual aspects of the anticipation or presentation of rewarding stimuli. This suggests the presence of a population of reward associated cells in the hippocampus that is linked to goal-directed reward processing in the VTA circuit (LeGates et al., 2018).

Collectively, these data suggest that MR and/or GR modulation of the hippocampal and amygdala afferent inputs may be a determinant of VTA-DA neuronal firing (Belujon and Grace, 2017). Although speculative, predominant MR activation of excitatory hippocampal outflow could activate *via* the NAc trans-synaptically the gain of the VTA-DA system, which then can be suppressed in an hour or so by subsequent GR activation in this structure. The hippocampal input possibly can be overridden during severe stress by the amygdala upon synergistic MR, GR, and β-adrenergic activation.

5.3. Coping with stress

When a threat is detected, an alarm triggers an immediate defense reaction by activating the sympathetic nervous system and the HPA-axis. At the same time appraisal processes and retrieval of previous experiences are activated, emotions are generated, and decisions are made how to cope with the stressor (Henry and Stephens, 1977). By combining data of human brain imaging and animal experiments, Hermans et al. (2014) identified a frontocortical salience network as substrate for the integration of sensory information with the immediate stress reaction. This salience network innervates the hypothalamus and amygdala for emotional and neuroendocrine responses. The locus coeruleus-based norepinephrine circuit is activated for vigilance and attention. Subsequently, resources are gradually shifted to the executive network which supports contextualization and rationalization of coping with the stressful experience, and ultimately the selected coping style is stored in the memory for future use (Hermans et al., 2014).

Exposure to inescapable stressors such as experienced by animals in the Porsolt swim stress or tail suspension test (see for validity of these tests Molendijk and de Kloet, 2015; de Kloet and Molendijk, 2016; Molendijk and de Kloet, 2019), recent studies have revealed how the mPFC controls *top-down* peri-aquaductal grey (PAG)-mediated behavioral coping. Using optogenetic stimulation or inhibition combined with neuro-anatomical tracing techniques, it was found that activation of the excitatory projection from mPFC neuronal ensembles stimulate GABA-ergic neurons in the anteroventral bed nucleus stria terminalis (avBNST) (Johnson et al., 2016). Then, these GABA-ergic neurons project to the ventrolateral-PAG, which upon activation promotes a passive coping response (Johnson et al., 2016, 2018). Of interest, stimulation of the dorsolateral/lateral-PAG (Keay and Bandler, 2001) evoked an active coping response. Other branches of the avBNST innervate the PVN where – at distinct PVN neurons – stimulation of the GABA-ergic input inhibited either stress-induced HPA axis activity or sympathetic activity (Radley and Johnson, 2018) (Fig. 4). Although not demonstrated, the avBNST likely also conveys information to the VTA.

Studies using a fear conditioning paradigm revealed that the prelimbic PFC activation was linked to expression of fear as shown by increased 'freezing' (Milad and Quirk, 2012), while such downstream emotional expressions were suppressed from the infralimbic PFC. Other studies demonstrated that the switch from prelimbic-dorsomedial striatum to infralimbic-dorsolateral striatum neuronal ensembles actually serves to attenuate overactivation of the salience network (Fiore et al., 2015) thereby acting in the same direction as the dampening effects of glucocorticoids.

Glucocorticoids modulate *bottom-up* the large scale dynamics in the shift from the salience to the executive neuronal networks (de Kloet et al., 2019). The hormones support the reallocation of energy resources and coordinate in a conditional and time-dependent manner the central and peripheral demands *via* MR and GR. Thus, *the high affinity genomic MRs* are occupied by basal glucocorticoid levels and signal a tonic influence over brain functions which is as a determinant in the threshold and responsivity of the neuroendocrine, autonomous, and behavioral stress response. Next with rising hormone levels, the *non-genomic* MRs are involved in regulation of attention, vigilance and appraisal processes, retrieval of previous experiences from memory, and the selection of an appropriate coping response followed by encoding of the experience for learning (Schwabe et al., 2010; Joëls et al., 2012; Schwabe et al., 2013; Vogel et al., 2016). fMRI and EEG measurements confirmed that MR activation promoted the switch towards amygdala-dorsolateral striatum (DLS) at the expense of amygdala-hippocampal connectivity (Schwabe et al., 2013). The bias towards habit learning was also privileged by a gain in function polymorphism of the MR (Wirz et al., 2017, 2018). Moreover, MR antagonists could block the amygdala switch, and re-introduce hippocampal declarative learning, but performance was found diminished, though MR manipulation affected risk assessment and choice of coping style in a Morris maze, during object recognition, and in an olfactory fear conditioning task (Oitzl and de Kloet, 1992; Souza et al., 2014; ter Horst et al., 2013; Harris et al., 2013). Fear and aggression is amplified by MR activation and can be attenuated by MR (Korte et al., 1995; Kruk et al., 2013). Again, how the VTA-DA circuit is integrated in the MR-mediated selection of coping style needs further investigation.

The rapid membrane GR-endocannabinoid mechanism attenuates the initial stress reactions. Membrane GRs are activated to attenuate the immediate stress reactions (Hill and Tasker, 2012). Then, after ten minutes the rising glucocorticoid concentrations progressively activate the lower affinity genomic GR. This action is aimed to dampen stress-induced cascades, including those in the salient network, which are essential for the initial defense reactions, but may become harmful if not controlled *via* GR. (Munck et al., 1984; Sapolsky et al., 2000; McKlveen et al., 2013). The stressful experience is contextualized by recruitment of specific co-regulator cocktails with the GRs (Meijer et al., 2018). Transactivation of GR promotes subsequently the memory storage of the experience (De Kloet et al., 1998; Maier and Watkins, 2010; Frank et al., 2015; Harris et al., 2013). The GR-dependent actions in the VTA mesocortico-DA system supporting reward processing and motivation also are under genomic control by glucocorticoids (Barik et al., 2013; Piazza and Le Moal, 1996), but see Imperato et al. (1991) who did not observe effects of glucocorticoids on striatal DA dopamine release (Imperato et al., 1991).

The pattern of glucocorticoid secretion reflects how the individual has managed to cope. Thus, a rapid rise in circulating glucocorticoid is a sign of a resilient individual in coping with stress as long as its secretion is also readily terminated. It follows that if coping is less successful this can be read from the slower rate the stress reaction is terminated: glucocorticoid secretion remains elevated for a prolonged period of time. The selected coping style is meant to gain control over the stressor. This is a rewarding experience, produces incentive motivation, and increases social competitiveness. In social competition the active coping style is often termed *pro-active* to indicate a phenotype that is inclined to take control before the confrontation evolves. The "losing" opponent is labeled with a *reactive* phenotype whose response characteristics are driven by environmental stimuli. The two phenotypes show extreme differences in physiological and behavioral response patterns (Koolhaas et al., 1999, 2010; de Boer et al., 2017).

The pro-active dominant individual is characterized by a high sympathetic tone and low HPA-axis activity. Interestingly, the high sympathetic tone corresponds to high noradrenergic activity of the locus coeruleus driven by a CRH input from the central amygdala. The re-active subordinate individual displays the opposite phenotype showing high HPA-axis activity (de Boer et al., 2017). In a similar

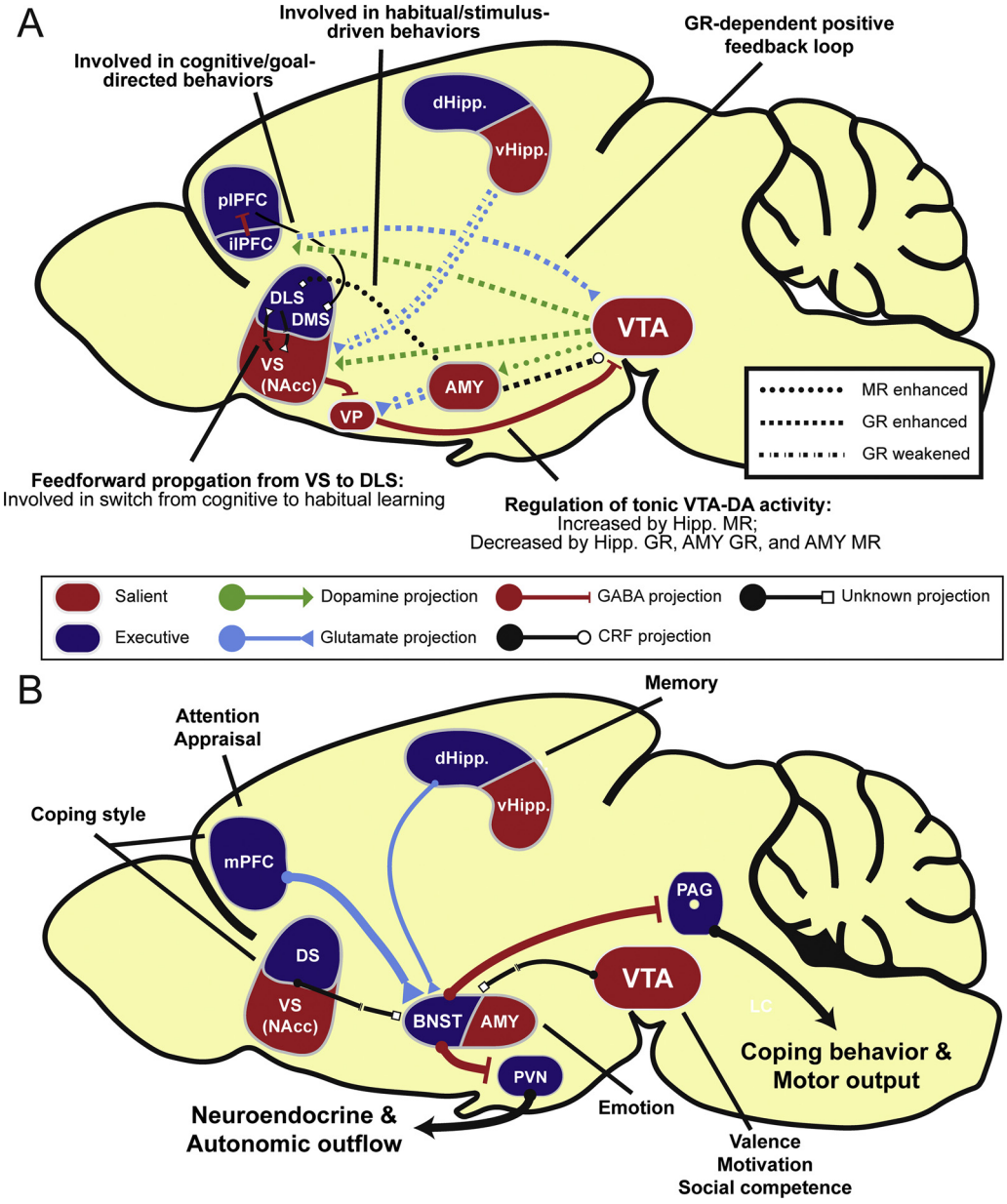

Fig. 4. Glucocorticoid control of VTA function and stress-coping.
The VTA is thought to be involved in the assessment of valence during appraisal of a salient stimulus and subsequently in motivation to pursue goals in the executive phase as part of reward processing and reinforcement learning. VTA function is also regulated in feedforward fashion by prefrontal cortex afferents and modulated by emotional and contextual limbic inputs inputs. During stress-coping the function of the VTA and its afferent inputs is coordinated top-down by prefrontal cortex circuits and bottom-up by glucocorticoid signaling that is mediated in a complementary fashion by MR and GR (de Kloet et al., 2019). Fig. 4A and B are sagittal sections of the rat brain with some selected regions involved in processing of salient information (red) and others in executive control (blue).
(A) Glucocorticoid responsive VTA circuitry and afferent projections. Three modes are distinguished. (i) Limbic MR activation facilitates a stress-induced switch from a (amygdala-hippocampus-dependent) flexible/cognitive/goal-directed to a (amygdala-dorsal striatum-dependent) rigid/habitual coping style (Fiore et al., 2015; Wirz et al., 2018). How the VTA is implicated requires further investigation (ii) MR/GR responsive limbic control of tonic VTA-DA activity involved in reward processing, motivation and social interaction. (iii) GR-dependent promotion of the ventral striatum/prefrontocortical/hippocampal feedforward cascade to support motivation and effort during *e.g.* social interaction, reward processing and excitatory central-amygdala CRH driven emotional input that in turn can suppress VTA activity *via* the ventral pallidum hub (Bagot et al., 2015; Barik et al., 2013; Belujon and Grace, 2017).
(B) Glucocorticoid responsive coping circuit. In case of inescapable stressors the switch from PL- to IL-PFC activates downstream circuits aimed to restrain excessive emotional and physiological responses; passive, energy-conserving – rather than active – coping strategies are promoted involving a pathway from the mPFC *via* the BNST to the periaquaductal grey (PAG) (Keay and Bandler, 2001; Cabib and Puglisi-Allegra, 2012; Radley and Johnson, 2018; Wood et al., 2018). Glucocorticoids acting progressively *via* GR promote the re-allocation of energy to executive circuits underlying rationalization (mPFC), motivation and social competence (ventral striatum), fear (amygdala) and contextualization (hippocampus) to facilitate memory storage of the experience for future use, in coordination with *e.g.* noradrenaline (Oitzl and de Kloet, 1992; Roozendaal and McGaugh, 2011; Hermans et al., 2014; Zalachoras et al., 2016; Vogel et al., 2016; Picard et al., 2018; Ghosal et al., 2019).
Abbreviations: AMY, amygdala; BNST, Bed nucleus of the stria terminalis; CRF, corticotropin-releasing factor; dHipp., dorsal hippocampus; DLS, dorsal lateral striatum; DMS, dorsal medial striatum; DS, dorslal striatum; GABA, γ-aminobutyric acid; GR, glucocorticoid receptor; ilPFC, infralimbic prefrontal cortex; mPFC, medial prefrontal cortex; MR, mineralcorticoid receptor; NAcc, nucleus accumbens; PAG, periaqueductal gray; plPFC, posterior lateral prefrontal cortex; PVN, paraventricular nucleus of hypothalamus; vHipp., ventral hippocampus; VP, ventral pallidum; VS, ventral striatum; VTA, ventral tegmental area.

protocol Reyes et al. (2015) distinguished rats based on time to defeat. The authors reported that – in both male asfemale rats – this criterion for social competition revealed that after a single challenge the rapidly defeated animal showed a higher locus coeruleus noradrenergic activity driven by a central amygdala CRH input, which was counteracted by an activated enkephalin afferent from the nucleus gigantocellularis. Upon repeated defeat the CRH-induced locus coeruleus activity persisted. The findings led to the recognition of the CRH/enkephalin balance at the locus coeruleus as a determinant in the neurobiology of social competition, and thus are relevant for VTA function. There are no sex differences identified (Reyes et al., 2015, 2019).

A striking example of the role of GR in expressing VTA-DA-dependent social competition was recently uncovered by Carmen Sandi's laboratory in rats that were selected for high and low corticosterone levels during puberty. They found large differences in aggressiveness at adulthood, which could be prevented not only by treatment with anti-glucocorticoids at puberty, but also by anti-glucocorticoid treatment at a time outside the context of the social interaction test (Papilloud et al., 2018). This finding adds to a growing database showing that anti-glucocorticoids can *reset* the activity of the stress system (Dalm et al.,

2018) with consequences for VTA-DA function.

In conclusion, there is evidence that MR and GR coordinate in complementary fashion during stress the action of glucocorticoids from modulation of appraisal processes and selection of coping style to facilitation of memory storage of the experience, respectively. MR activation causes a bias towards activation of amygdala-striatal pathway associated with habit learning and active coping, while MR blockade rather promotes hippocampal passive coping albeit with poorer performance. The role of MR activation in VTA-DA function is still poorly understood, but likely involves potentiation of limbic inputs. GR activation promotes memory storage and boosts VTA-DA function as can be learned from the increased motivation and reward processing under a variety of conditions (Fig. 4).

6. Vulnerability to VTA-DA neuron dependent disorders

As is previously highlighted in this review, VTA-DA activity in the mesocorticolimbic DA circuitry is involved in the formation of subjective emotional-motivational values for particular behavioral options – rather than objective properties about distinctions between "good and bad" (Burke et al., 2014; Lak et al., 2014; Papageorgiou et al., 2016). These valuations, which are based on the integration of internal and external states, are experience-dependent and lead, depending on an animal's specific situation and associated needs, to subjective preferences for the selection of specific behavioral choices (Burke et al., 2014; Papageorgiou et al., 2016). Mesolimbic DA responds to rewards, contributes to stress-coping, and promotes social interactions. The release of DA promotes reinforcement learning, increases motivation to acquire anticipated rewards, and the drive to succeed in stress-coping. VTA-DA activity-dependent reinforcement learning processes may promote repetition of behavioral preferences during goal-directed behaviors, thereby contributing to the formation of habitual behaviors in particular situations with associated needs. The mesocortical branch rather mediates computational aspects of the cost and benefit, thereby investing in effort and motivation to acquire a 'feel good' sensation as expressed in planning and decision-making during anticipation of rewards *versus* facing the challenge to cope with stress (Ironside et al., 2018; Weger and Sandi, 2018; Stanton et al., 2019; Hauser et al., 2017).

Acute stress enhances attention and vigilance. The sensitivity to perceive rewards is augmented and motivational arousal is increased. At the same time the stressor may signal danger and evoke fear and emotion. It is the role of the mPFC to guide decision-making in the trade-off between a threat and the pursuit of a reward. Glucocorticoids act in such circumstances as a double edged sword. They increase motivation to win a social competition or collect a reward *via* VTA-DA GR, while on the other hand, and also *via* GR, fear-motivated behavior is enhanced by increased *e.g.* amygdala CRH expression involving the VTA. This contrast is most striking when it concerns the need for life-sustaining food *versus* coping with a life threatening situation. There are surprisingly few studies available on the topic except for excellent books and overviews (Sapolsky, 1994; Denton, 1984; Krause and Sakai, 2007; de Kloet and Herman, 2018).

Thus, these VTA-DA neuron-dependent processes are essential for adaptive behavior in an ever-changing environment (Lloyd and Dayan, 2016). In this review we have reported evidence that a chronic stress experience may compromise the role of the VTA-NAc circuit to pursue rewards and social interactions as well as the ability of the VTA-mPFC to cope cognitively with flexible adjustments to environmental demands. Fundamental to the behavioral consequences of chronic stress-induced neuroadaptive changes is the bias towards more habitual control of instrumental rather than goal-directed behavior (Dias-Ferreira et al., 2009; Schwabe et al., 2011; Schwabe and Wolf, 2013) as is applicable to both addictive (Section 6.1) and low-risk/low-effort (Section 6.2) behaviors. In the case of addictive behaviors, this VTA-DA neuron-dependent bias may contribute to an acceleration in the switch from initial voluntary use to habitual-like addictive behaviors. In the case of behavioral changes towards low-risk and low-effort, which are in animal studies frequently referred to as "depression-like behaviors", the habitual bias contributes to *"the generalization between environments"*, as argued by Dayan and colleagues (Huys and Dayan, 2009; Lloyd and Dayan, 2016). In both cases, when environmental challenges are appraised as such, the initial responses may rapidly shift towards experience-based habitual behavioral patterns in a manner that favors low-risk and/or low-effort behavioral solutions and without re-updating or devaluating learned associations between contextual stimuli and responses. This rapid switching towards habitual behaviors increases an animal's behavioral efficiency in certain environmental situations, while it may come at the expense of its behavioral flexibility in fluctuating, natural environments (Dias-Ferreira et al., 2009; Sousa, 2016). Therefore, the essential issue in the contribution of chronic stress-induced VTA-DA neuronal plasticity to the etiology of stress-related disorders is whether they affect an animal's ability to change behaviors when contexts change.

Hence, the VTA-DA neurons may contribute to maladaptive modulation of emotional-motivational behavioral patterns of which we will address below a few specific manifestations.

6.1. Addiction

VTA-DA neuron-dependent reinforcement learning processes are involved in facilitating the development and consolidation of habitual behaviors (Schwabe et al., 2011; Lloyd and Dayan, 2016) and a chronic stress-enhanced influence of excitatory input onto VTA-DA neurons may contribute to alterations in an animal's behavioral response towards addictive substances. Indeed, the link between (chronic) stress exposure and addictive behaviors is evident (Chen et al., 2010; Koob and Volkow, 2016) and *"the VTA is required for stress-induced reinstatement of drug-seeking behaviors"* (Polter and Kauer, 2014). Furthermore, VTA-DA dependent development and consolidation of addictive behaviors are associated with the well-described chronic stress-induced bias towards more habitual control of instrumental behavior (Dias-Ferreira et al., 2009; Schwabe et al., 2011). This link between chronic stress, VTA-DA adaptation, and addictive behavior has received substantial support (Table 1). The studies demonstrate increases in stress- and drug-induced conditioned place preference (Stelly et al., 2016; Whitaker et al., 2013), locomotor activity (Nikulina et al., 2005, 2008; Miczek et al., 2011), and cocaine self-administration (Covington et al., 2008; Holly and Miczek, 2016). Moreover, these processes may be modulated by CRH and BDNF (Holly and Miczek, 2016). In addition, the pioneering research by Piervi Piazza and colleagues in the 1990s (Piazza and Le Moal, 1996) has demonstrated in rodent studies that the enhanced VTA-DA activity induced *via* GR by glucocorticoids and stress can increase dopamine release particularly from the NAc shell. This action of the glucocorticoid hormone has a facilitatory role in the behavioral effects of psychostimulants on locomotor activity, self- administration, and relapse, and can be blocked by GR antagonists (Marinelli and Piazza, 2002).

GR rather than MR activation by corticosterone replacement of ADX animals enhanced amphetamine sensitization (Rivet et al., 1989). Using cocaine, it appeared to be the initiation rather than the expression of psychostimulant-induced sensitization of the locomotor response in the ADX-corticosterone replaced rats, although co-administration of epinephrine was required (De Jong et al., 2009). Likewise, mifepristone given to intact animals blocked psychostimulant sensitization only in the initiation phase (van der Veen et al., 2013). Glucocorticoid-dependent sensitization was strain-dependent and occurred in DBA, and not in C57Bl mice (de Jong et al., 2008). Moreover, for cocaine intake at adulthood, maternal environment experienced as pups appeared crucial for these DBAs (van der Veen et al., 2008).

Differential sensitivity to psychostimulants such as amphetamine is often used as an indication of psychosis susceptibility in humans. In the search for the involved common genes and pathways, DBA2 mice were

divided by their locomotion response to amphetamine in sensitized and resistant animals. Subsequently, transcriptome analysis of the NAc, prefrontal cortex, and the hippocampal CA1 regions revealed a large number of uniquely responsive gene patterns in each region. By far the most profound and reproducible differences between the sensitized and resistant animals were observed in the hippocampus: many of the validated genes in CA1 are members of the cAMP response element (CRE) family and targets of GR and myocyte enhancer factor 2 (Mef2) transcription factors. Hence, these genes were postulated to contribute to susceptibility to amphetamine-induced psychotic symptoms (Datson et al., 2011).

Together, these studies support the notion that chronic stress exposure may contribute to addictive-like behaviors by adaptive changes of VTA-DA neurons. The studies also show the complexity of glucocorticoid involvement. The hormones were found to potentiate particularly the initial phases of drug addiction implying a role in sensitization of the VTA-DA reward and motivation circuitry.

6.2. Depression

Chronic stress-induced changes in VTA-DA activity may lead to changes in effort- and value-based decision-making in a manner that behavior which minimizes contact with aversive environmental input is prioritized. Accordingly, counterproductive behavioral strategies are usually avoided. Hence, chronic stress may compromise the involvement of the VTA neurons in translation of emotional-motivational valuations to approach – or withdrawal – as well as explorative or exploitative behaviors (Lloyd and Dayan, 2016; Pizzagalli, 2014). Specifically, the stress-induced enhancement of excitatory input of VTA-DA neurons may facilitate reinforcement learning of value representations, and therefore support such shifts in behavioral prioritization. This is well-supported by symptomatology of major depressive disorder, such as *e.g.* anhedonia, which represents devaluation of rewarding substances, and reduced motivation for explorative behaviors (Der-Avakian and Markou, 2012; Treadway and Zald, 2011; Venzala et al., 2013).

The effects of chronic stress on shifts in behavioral prioritization involving VTA-DA are listed in Table 1. CSDS exposure resulted in an increased social avoidance, decreased sucrose preference and decreased explorative behavior (Krishnan and Nestler, 2011; Warren et al., 2013; Qu et al., 2017). Additionally, an animal's history of repeated exposure to uncontrollable stress, where the use of active coping strategies repeatedly have failed to control the environmental challenges, may facilitate a switch in coping strategy towards more passive ones as is supported by an increased immobility in the forced swim stress test upon chronic stress exposure (Krishnan et al., 2008a; Cabib and Puglisi-Allegra, 2012; de Kloet and Molendijk, 2016).

The influence of prolonged stressors appears variable, however. A predictable stressor such as studied in the CSDS model was shown to enhance the phasic firing rate of the VTA-DA system in the defeated animals (Krishnan et al., 2007; Barik et al., 2013). Alternatively, chronic stress leads to a reduced spontaneous firing and atrophy of the VTA-DA system (Chang and Grace, 2014; Sugama and Kakinuma, 2016; Belujon and Grace, 2017). This reduced spontaneous (tonic) firing may be due to the high DA activity in the mPFC which feeds back on the NAc as was demonstrated by a series of highly interesting studies of Simona Cabib's group (Pascucci et al., 2007; Fiore et al., 2015). Yet, both the increased as well as the decreased VTA-DA activity displayed a phenotype characterized by social withdrawal, anxiety, and decreased sucrose appetite, that was investigated mechanistically in great detail (see Section 3). Moreover, optogenetic manipulation of the DA neurons could reverse these phenotypes either produced by social defeat or CMS (Tye et al., 2013; Chaudhury et al., 2012). To explain this conundrum of opposing outcomes by exposure to different repeated stressors a role fort the I*h* current was suggested (Friedman et al., 2014). Also the nature of the stressor, the time of measurement during the circadian cycle, and the heterogeneity of the VTA-DA cells involved in the various stressors may play a role and of course the characterization of either tonic *versus* phasic firing in each model.

Nevertheless, the involvement of VTA-DA neurons in the symptomatology of major depressive disorder is evident. Causality, however, may be linked to the higher mPFC top-down control of stress-coping and behavior as reviewed in more detail in Section 5.3. Eventually, degeneration of hippocampal, VTA-DA, and pre-frontal cortex circuits may occur after chronic stress exposure as is demonstrated by MRI (Magalhães et al., 2017). This breakdown of the stress-coping network is facilitated by the elevated glucocorticoids linked to chronic stress, in a manner that involves increased emotional expression generated by the hypertrophied extended amygdala (McEwen et al., 2016).

7. Sex differences

Most studies on the plasticity and functioning of the VTA have been performed with males. However, the relatively few animal studies available point to a sex differences in VTA-DA dynamics and function (Russo et al., 2003; Shansky et al., 2010; Bale and Epperson, 2015; Gillies et al., 2014). Females show higher VTA-DA turnover and release than males, particularly in response to psychoactive drugs such as amphetamine (Becker and Chartoff, 2019). These differences may be due to sex steroids. Estradiol was found to stimulate dopamine function and estrogen receptors are expressed in dopaminergic neurons of the VTA that project to the NAc (Kritzer and Creutz, 2008). However, androgen receptors occur in dopaminergic neurons that project to the mPFC (Kritzer and Creutz, 2008). Such hormonal effects are achieved either by genomic actions, although also recently discovered rapid membrane effects cannot be excluded (Gillies et al., 2014).

In addition to these direct effects of the steroids also the afferents to the VTA are sexual dimorphic and thus may contribute to the sex difference in dopamine function (Bale and Epperson, 2015). This is exemplified by the inputs from the mPFC and limbic regions which underly the very different strategies males and females use to cope with stress. The preferred coping strategy of males is the well-known 'fight-or-flight' response in attempts to gain control. As pointed out previously social defeat increases dopamine turnover in the ventral striatum. In contrast, females rather rely on a more passive strategy that can be characterized by 'tend-and-befriend' (Taylor et al., 2000), which relies on social support involving the mesolimbic dopamine system (Weger and Sandi, 2018).

The above 'activational' actions of the steroids are superimposed on their 'organizational' effects during perinatal life. It is well established that during early-life testosterone masculinizes the brain (Bangasser and Shors, 2008). Subsequently, at puberty these masculinizing effects are further potentiated by the androgens (Ahmed et al., 2008). The female brain becomes around puberty responsive to estrogens and progestins (Becker, 2009). Accordingly, given the profound differences in brain organization, it is perhaps not so surprising that sexual dimorphisms of the VTA system has evolved.

Superimposed on the these perinatal organizational actions of the sex steroids are the programming effects of adverse early-life experiences. It is well established that early-life adversity, lack of care, immune activation by infections, and emotional neglect have profound effects on the organization of limbic and cortical brain circuits underlying stress-coping and adaptation, including the dopamine circuitry (Bilbo and Schwarz, 2012; Daskalakis et al., 2013). The studies generally agree that a history of early-life adversity increases emotional responding – generated by a hypertrophied amygdala – and impairs cognitive performance as reflected by reduced dendritic branching of hippocampal and mPFC neurons. Early-life adversity reduces VTA-DA mesocorticolimbic function and causes a bias towards an anhedonic phenotype (Moriceau, 2009; Marusak et al., 2017). However, whether such programming effects reflect maladaptive or adaptive value should be discussed with caution. The outcome of these effects may affect

vulnerability and resilience differentially for better or worse. It provides an advantage in certain contexts, but in others it may contribute to the etiology of neuropsychiatric disorders (Champagne et al., 2008; Ellis et al., 2011; Nederhof and Schmidt, 2012; Daskalakis et al., 2013; Nesse et al., 2016). Relevant for this review is that in rats genetically selected for a high striatal DA responsiveness, exposure to stressors in early as well pubertal life had a particular negative outcome. This combination of genetic load and early-life adversity is the basis of the 'three-hit hypothesis' for the study of vulnerability to stress-related disorders (see Daskalakis et al., 2013).

In an intriguing series of experiments, Soares-Cunha et al., 2014 showed that intra-uterine treatment of the rat fetus with dexamethasone impaired dopamine function in the offspring's later life (Soares-Cunha et al., 2014). This was shown in behaviors interpreted as impairment of salient incentives and motivational drive. Gillies et al. (2016) demonstrated sexual dimorphic effects of perinatal treatment with the potent synthetic glucocorticoid dexamethasone. This treatment is known to affect cognitive functions and behavior in later life, although the outcome is dependent on context. Antenatal dexamethasone profoundly increased DAT expression in male offspring, while it was decreased in females. This observation was confirmed with amphetamine, which increased dopaminergic function in males and decreased it in females. Behavioral studies provided support. The male antenatal dexamethasone rats displayed a profound pre-pulse inhibition of a startle response. The females showed a diminished locomotor response to amphetamine stimulation (Virdee et al., 2014; Gillies et al., 2016).

These findings led to the hypothesis that sexual dimorphic responses of the mesocorticolimbic system to stress and stress hormones, in particular glucocorticoids, during adulthood or development represents a mechanism which may contribute to sex biases in common DA-dependent-associated disorders (Gillies et al., 2014). These include deficits in decision-making (Georgiou et al., 2018), risk assessment, and resilience (Wellman et al., 2018). Stress- and dopamine-related brain disorders are female prevalent as is the case in addictive behaviors, anxiety, and depression (Bale and Epperson, 2015, 2017; Kessler et al., 2003; Bangasser and Valentino, 2014).

If patients suffering from these disorders are subjected to stressors, males and females show profound differences in HPA-axis reactivity, with males having a higher cortisol secretion in anxiety and depression. In healthy individuals androgens are known to stimulate and estrogens to inhibit HPA-axis activity, and this difference is sustained and apparently amplified during depression. This finding suggests that there is a sex difference in glucocorticoid feedback (Kudielka and Kirschbaum, 2005; Goel et al., 2014; Zorn et al., 2017). Interestingly, glucocorticoid action is sexual dimorphic. Duma et al. (2010) showed profound sex differences in genome wide transcriptional response to dexamethasone in the liver. Glucocorticoid responsive genes were overrepresented in males *versus* females suggesting that males are more susceptible to *e.g.* the anti-inflammatory actions of dexamethasone. In fact, according to Cidlowski (personal communication) such profound sexual dimorphism in glucocorticoid action is a common phenomenon, and is also observed in brain (Duma et al., 2010).

In conclusion, the VTA-DA and the stress response systems are sexual dimorphic. The sex differences originate from genetic background and organizational actions of sex hormones. Glucocorticoid actions are sexual dimorphic. These findings warrant further research into the sexual dimorphic function of the VTA during stress.

8. Concluding remarks

One of the messages conveyed in this review is that the VTA circuit harbors a mechanism that enables an individual to predict outcome valuation of a salient experience or a social interaction, while taking emotional and contextual inputs into account. Predictability manages a sense of control, which is the determinant of the severity of a psychogenic stressor. In first instance, the stressor triggers immediate behavioral, autonomous, and neuroendocrine defense reactions. At the same time, appraisal processes, memory retrieval, and emotional aspects bias decision-making how to cope with the stressor in order to prevent the initial defense reactions from overshooting. The substrate for decision-making is in mPFC ensembles that inform *via* the BNST either the dorsal or ventrolateral PAG divisions about the selected behavioral coping strategy and the hypothalamus about control of the autonomic and neuroendocrine response patterns (Keay and Bandler, 2001; Mcklveen et al., 2015; Johnson et al., 2018).

How the VTA-DA circuit is embedded in this stress-coping circuitry is not precisely known. In this review we focused on the role of the excitation-inhibition balance in control of VTA-DA function as it was modulated by BDNF, CRH, opioids, and in particular the glucocorticoid master regulator. Fig. 4A provides a schematic overview of the glucocorticoid action on VTA-DA and its limbic-prefrontocortical afferents that is mediated in a complementary fashion by MR and GR. Fig. 4B shows how these same regions are implicated in the stress-coping circuit. In the representation it is understood that acute stressors first cause a state of ***alarm*** that energizes immediate coping responses. Next, the stressful experience is rationalized and contextualized as a prelude to executive functions that serves recovery and behavioral adaptation. Finally, the experience is stored in memory for future use. Outstanding questions are *e.g.* how the VTA-DA circuit links valence assessment with coping style and how VTA-DA-dependent functioning contributes to psychosocial resilience. Actually, a recent study in rats demonstrated that mesolimbic DA circuitry links the position in a social hierarchy with alertness in response-reward behavior (Lozano-Montes et al., 2019).

A second message concerns the role of the VTA during chronic stress. Initially, repeated exposure to stressors generates a state of ***resistance,*** which requires additional resources (allostatic load) for maintenance of an altered homeostatic state (allostasis) (Selye, 1946; McEwen and Wingfield, 2010). From the VTA-DA perspective motivation is enhanced to either pursue rewards and social relationships or to withdraw and conserve energy resources in a process that depends on mPFC-based computation of cost and benefit that is affected by the mesocortical dopaminergic input (Ulrich-Lai and Herman, 2009; Radley and Johnson, 2018; Weger and Sandi, 2018). Fundamental for these processes are the number of spontaneously active (tonic firing) VTA-DA neurons that depend on limbic input as a determinant of the magnitude of the phasic bursts in response to excitatory inputs (Belujon and Grace, 2015, 2017). A future challenge is how precisely the excitation-inhibition balance in the VTA is regulated. For instance, is the enkephalin-CRH balance implicated as it is in the regulation of locus coeruleus neurons (Reyes et al., 2015; Hupalo et al., 2019) or for that matter to what extent is the tonic and phasic VTA-DA activity under control of this CRH-driven locus coeruleus mechanism or how does MR/GR control of limbic afferents contribute?

Finally, with continuous chronic stress, the energy resources that drive coping and adaptation may become ***exhausted***. The mPFC, hippocampal circuits, and VTA circuits show atrophy *versus* the hypertrophy of the extended amygdala (Sousa, 2016; Magalhães et al., 2017). mPFC circuits meant to provide flexibility are becoming 'locked' (McEwen et al., 2015). The role of the microglia is increasingly recognized in this process (Frank et al., 2019). However, the nature of the stressor is important. For instance, the outcome of CUS and CSDS is opposite for the VTA-DA activity, while anhedonia and passive coping styles are the outcome in both models. Various explanations for this conundrum have been offered including the involvement of mesocortical- and/or mesolimbic pathways, the day or night phase the experiments were performed, and, of course, the nature and severity of stressor, particularly in view of the 'predictability' in social interactions of the animals in the CSDS model (Muir et al., 2019).

The three stage process of ***alarm, resistance, and exhaustion*** is recapitulated during addiction with reference to the VTA-DA circuit

(Koob, 2015; Koob and Volkow, 2016; Kwako and Koob, 2017). Briefly, the *binge* phase depends on the VTA-DA system regarding positive reinforcement of impulsive drug intake. The *withdrawal* phase causes a dysfunctional VTA-DA system that impose a dysphoric stressed-out phenotype. And the *craving* phase is characterized by a dramatic reorganization of the salience and executive network with profound consequences for the VTA-DA circuitry. The mPFC and hippocampal inputs are uncoupled, implying a severe deficit in decision-making, planning, cognitive flexibility, and declarative/spatial cognitive function. Compulsivity is the main driver of habit behavior, and the functioning and plasticity of mPFC control over the emotional extended amygdala is compromised. The features of drug addiction are reminiscent to VTA-DA involvement in the pathogenesis observed in increased vulnerability to obsessive compulsive disorder, obesity, major depressive disorder, and post-traumatic stress disorder.

With our current understanding of the mechanisms and signals involved in mental states, the question can be raised whether there are options for preventive or curative treatment. CRH antagonists have met success as anxiolytics and anti-depressant in animal studies and probably involve a VTA-DA component as well in their action (Holsboer and Ising, 2010). MR antagonists have not been tested yet, but the reports with GR antagonist and modulators are encouraging. In experiments in animals and humans GR antagonists were effective in blocking the withdrawal/negative affect phase of alcohol dependence (Vendruscolo et al., 2015), likely by interfering in the CRH-VTA-DA cascade. Local manipulation of GABA-ergic interneurons and energy metabolism in the VTA circuitry also holds promise because of the positive outcome for social competence and resilience (Ghosal et al., 2019).

Currently, chemogenetic and optogenetic technology combined with live-imaging methods offer an unprecedented opportunity to examine plasticity and connectivity of the limbic-VTA-striatal-cortical stress and reward network (Muir et al., 2019). The single cell RNA sequencing is beginning to provide the precise topography and diversity of the VTA neurons (Tiklová et al., 2019). If combined with tracing techniques, Allen Brain Connectivity Atlas data-mining will allow to combine cytoarchitectonic data and unique molecular-genetic blueprints with circuits dedicated to VTA function. The coordinating and integrating role of *e.g.* BDNF, CRH, opioids, and glucocorticoids from gene to behavior provides in this respect an excellent opportunity towards understanding the functioning of this VTA-DA circuit in limbic-forebrain management of stress-coping and adaptation. Moreover, how VTA-DA function is being affected by early-life adversity is also an important topic for further research. A sobering thought is, however, that the sexual dimorphism of the stress-reward system is still poorly documented. This lack of knowledge of VTA-DA sex differences hampers progress in the translation to clinical understanding of female prevalence in vulnerability to stress-related brain disorders.

Declaration of Competing Interest

EHD is PhD student at Macrobian-Biotech. ERdK owns stock of Corcept Therapeutics.

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