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The ventral pallidum: Subregion-specific functional anatomy and roles in motivated behaviors

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Abstract

The ventral pallidum (VP) plays a critical role in the processing and execution of motivated behaviors. Yet this brain region is often overlooked in published discussions of the neurobiology of mental health (e.g., addiction, depression). This contributes to a gap in understanding the neurobiological mechanisms of psychiatric disorders. This review is presented to help bridge the gap by providing a resource for current knowledge of VP anatomy, projection patterns and subregional circuits, and how this organization relates to the function of VP neurons and ultimately behavior. For example, ventromedial (VPvm) and dorsolateral (VPdl) VP subregions receive projections from nucleus accumbens shell and core, respectively. Inhibitory GABAergic neurons of the VPvm project to mediodorsal thalamus, lateral hypothalamus, and ventral tegmental area, and this VP subregion helps discriminate the appropriate conditions to acquire natural rewards or drugs of abuse, consume preferred foods, and perform working memory tasks. GABAergic neurons of the VPdl project to subthalamic nucleus and substantia nigra pars reticulata, and this VP subregion is modulated by, and is necessary for, drug-seeking behavior. Additional circuits arise from nonGABAergic neuronal phenotypes that are likely to excite rather than inhibit their targets. These subregional and neuronal phenotypic circuits place the VP in a unique position to process motivationally-relevant stimuli and coherent adaptive behaviors.

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1.0. Introduction

More than four decades ago, the ventral pallidum (VP) was delineated from the subcommissural part of the substantia innominata by Heimer and colleagues (Heimer, 1972; Heimer and Wilson, 1975; Switzer et al., 1982; Heimer et al., 1982). In early discussions, Mogenson et al., (1980) proposed that the VP integrated limbic/emotionally salient signals from the nucleus accumbens (Acb) to brain motor systems. Swerdlow and Koob (1987) furthered this hypothesis with studies showing how the Acb to VP projection links the mesoaccumbal dopamine system to motor circuitry. At the time, dopamine was already well-known to be involved in reward-motivated behavior (Wise, 1980). Soon after, it was revealed that the VP is innervated by dopamine inputs from the midbrain and that dopamine directly alters VP neuronal firing (Napier and Potter, 1989). As early as 1991, Napier and colleagues (1991a) put forth the concept that in addition to integrating various inputs from Acb, the VP incorporates reward-related signals carried by midbrain dopaminergic neurons. This concept was quickly expanded to encompass the idea that dopamine transmission within the VP regulates a collection of behaviors, including locomotion and cognition (Napier 1992c). Building on the role of VP dopamine, and Mogenson's original concepts involving the VP in brain circuits that direct “motivation to action” (Mogenson et al., 1980), it was subsequently proposed that the VP forms part of a “final common pathway” for drug-seeking behavior (Kalivas and Volkow, 2005) and for reward processing in general (Smith et al., 2009). These concepts served as modern-day assessments of the ventral striatopallidal system. As our understanding of this system has grown, the importance of subregional circuits involving the ventromedial VP (VPvm) and dorsolateral VP (VPdl) with the Acb shell (AcbSh) and Acb core (AcbC) has become apparent. Furthermore, although considered a largely inhibitory structure, a substantial proportion of neurons residing in VP express vesicular glutamate transporter 2 (VGluT2) mRNA (Hur and Zaborszky, 2005), indicating subpopulations of VP neurons have the capacity for glutamatergic neurotransmission. In addition, the cholinergic neurons residing within VP receive GABAergic input from the Acb (Zaborszky and Cullinan, 1992), make local connections within VP as well as extrinsic projections to the prefrontal cortex and the basolateral amygdala. Therefore, the goal of this review is to provide a new conceptual framework for the VP that incorporates current understanding of its subregional afferents, efferents and neuronal function and the roles for its subregions and neuronal phenotypes in behavior.

We put forth that the contribution of VP towards a variety of motivated behaviors is dependent upon the participation of GABAergic neurons belonging to individual VP subregions, as well as from nonGABAergic neurons, which affect discrete neuronal circuits. GABAergic VPvm neurons, with AcbSh afferents and thalamocortical, dopaminergic, and hypothalamic targets, are involved in discriminating the stimulus conditions of reward/drug acquisition, consumption, and working memory. NonGABAergic VP neurons, with dopaminergic and cortical targets, provide excitatory signals that likely oppose the VPvm-mediated signals. GABAergic VPdl neurons innervated by AcbC neurons and projecting to motor-related structures including subthalamic nucleus (STN) and substantia nigra pars reticulata (SNr), are involved in mediating reward motivated behavior (e.g., drug-seeking responses). These circuits adapt to repeated exposure to reward-related stimuli (e.g., repeated drug use), and these adaptations alter the integrative capacity of the VP which can lead to deficits in the output of motivation and reward. Thus, understanding the subregional neuroanatomy of the VP, and its related circuits, will broaden our understanding on the underpinnings of such behavioral dysfunctions.

2.0 Neuroanatomy

2.1. Boundaries of the ventral pallidum and its subregional compartmentation

Pallidal brain structures are linked to basal ganglia circuitries. In the basal ganglia, pallidal structures include the globus pallidus (GP), the rodent homolog of the external pallidal segment in higher species, and the entopeduncular nucleus (EPN), the rodent homolog of the internal pallidal segment. The VP occupies the rostral, subcommissural part of the area historically known as the substantia innominata, a major component of the ventral striatopallidal system that is ventral to the anterior commissure, and together with the ventral striatum belongs to the ventral striatopallidal system (Heimer, 1972; Heimer and Wilson, 1975; Haber et al. 1983; Heimer et al. 1997).

Outside of the VP, groups of cells and fibers in the caudal (sublenticular) substantia innominata that bridge the centromedial amygdala to the bed nucleus of stria terminalis were named the ‘extended amygdala’ (Alheid, 2003; de Olmos and Heimer, 1999). The more or less continuous collection of large, corticopetal neurons, consisting of primarily cholinergic and GABAergic neurons, stretching from the diagonal band area in the rostral forebrain to the level of the caudal part of the globus pallidus, is called the basal nucleus of Meynert in the clinical literature (Zaborszky et al., 2008; 2012, 2015a,b). The neurons of the basal nucleus of Meynert (basal forebrain magnocellular complex) intermingle with neurons of the ventral striatopallidal system and the extended amygdala.

In rodents, the boundaries of the VP are defined by “wooly fiber”-like elements that originate from the Acb and express substance P-immunoreactivity (IR) and enkephalin-IR (Haber and Nauta 1983; Hill and Switzer, 1984; Groenewegen and Russchen, 1984; Zahm and Heimer, 1990; Heimer et al., 1991, 1997; see **Figure 1A-D** for four anteroposterior planes of VP). Substance P-IR is more strongly expressed and selective for VP than enkephalin-IR because enkephalin-IR is also observed in neighboring structures, such as bed nucleus of the stria terminalis (Haber and Nauta, 1983). Unfortunately, current brain atlases have not utilized these markers to delineate the VP boundaries.

The boundaries of the VP in the primate are more difficult to delineate. We follow the same convention used for the rodent, as described by Haber and colleagues (1990). Accordingly, the primate VP is a crescent-shaped structure ventral to the anterior commissure expressing both enkephalin-IR and substance P-IR wooly fibers. The VP in primates has common features of both the external and internal segments of the globus pallidus; the external, enkephalin rich component of the VP lies ventral and adjacent to the anterior commissure. The internal, substance P component of the ventral pallidum, lies as a ventral and rostral extension of the internal segment of the globus pallidus, often interdigitating with finger-like processes of the ventral striatum. Delineation of primate VP also has come from tracing studies (Hreib et al., 1988; Russchen et al., 1985; Haber et al., 1990), which are consistent with the rodent (sections 3.0 and 4.0). For the remainder of the review, we will refer to studies within the rodent VP unless explicitly stated otherwise.

Several "neurochemically distinct" subregions of the VP have been delineated, all of which exhibit substance P-IR and enkephalin-IR wooly fibers (**Figure 2A,D**). The largest VP subregion, VPvm, receives projections from AcbSh, and exhibits fibers with neurotensin-IR but not fibers with calbindin-d28k-IR (**Figure 2B-C, E-F**; Zahm and Heimer, 1988, 1990; Zahm 1989; Zahm et al., 1996; Geisler and Zahm, 2006a). Conversely, the crescent-shaped VPdl receives projections from AcbC (**Figure 1E-H**) and exhibits fibers with calbindin-d28k but not fibers with neurotensin-IR (**Figure 2B-C, E-F**; Zahm et al., 1996; Riedel et al., 2002; Tripathi et al., 2010, 2013). The ventrolateral VP subregion (VPvl), exhibits little to no neurotensin-IR or calbindin-d28k-IR (**2B-C, E-F**). The rostral VP subregion (VPr, following the convention of Mengual and colleagues (Tripathi et al., 2010, 2013), best appreciated in sagittal sections, is described as finger-like extensions dorsal to the olfactory tubercle and ventral to Acb that lack neurotensin-IR and calbindin d28k-IR (**Figure 1A**; Heimer, 1978; Haber and Nauta, 1983; Zaborszky et al., 1986; Tripathi et al., 2010, 2013). The afferent/efferent connections of the VP subregions will be further delineated in sections 3.0 and 4.0.

2.2. Neuronal morphology, phenotypes, and functional subpopulations

VP neurons typically exhibit oval-, fusiform-, or triangle-shaped somata measuring 15-30 μm in diameter (Young 1984; Záborszky et al., 1986; Pang et al., 1998) with two to four thick, long, sparsely ramified smooth dendrites emerging from the cell body, covered by axon terminals (Heimer and Wilson, 1975; Young 1984; Zahm et al., 1985; Záborszky et al., 1986). A subset of VP neurons rostral to the crossing of the anterior commissure (both VPvm and VPdl) exhibits spiny dendrites (Kupchik and Kalivas, 2013).

VP GABAergic neurons that express GAD65 and/or GAD67 mRNA are the major neuronal population in every VP subregion (**Figure 3A-B**). VP neurons also express calretinin, calbindin, parvalbumin, neuropeptide Y, or somatostatin (Zaborszky et al., 2012), although it remains for future studies to identify their colocalization with GAD or VGluT2. GABAergic neurons are covered extensively by GABAergic boutons, mostly from the Acb or local connections (Zahm et al., 1985, **Figure 4**). GABAergic neurons in the VP receive both GABAergic and nonGABAergic input from ventral striatal areas (Zaborszky and Heimer, 1986). Within GAD-IR terminals, symmetrical synapses are established on both perikarya and dendrites, typical of inhibitory neurotransmission.

The vesicular transporters for glutamate are differentially expressed by VP glutamatergic neurons. Most VP glutamatergic neurons express VGluT2 mRNA (**Figure 3C-D**; Hur and Zaborszky, 2005; Geisler et al., 2005, 2007), while a small population expresses VGluT3 mRNA (Poulin et al., 2006), and none express VGluT1 mRNA (Hur et al., 2009). The number, electrophysiological properties and morphological characteristics of VP glutamatergic neurons are unknown, although some of the VGluT3-expressing cells are cholinergic (Poulin et al., 2006). While not empirically determined, it appears that the VPvm is dense in VGluT2-expressing neurons, while VPdl and VPvl subregions contain only few such cells (Hur and Zaborszky, 2005).

Cholinergic neurons residing within VP typically have large (~30 μm in diameter) multipolar somata with four to seven thick tapering dendrites (Bengtson and Osborne, 1999) (**Figure 3E-F**). Axons of cholinergic neurons give rise to abundant local collaterals (Duque et al., 2007) and project to the cerebral cortex and the amygdala (Groenewegen and Russchen 1984; Carlsen et al., 1985: Záborszky et al., 1986, 1992, 2005, 2012). Cholinergic neurons are found in each VP subregion, but most are within VPvm, and their total numbers are small (Gritti et al., 1993; Záborszky et al., 1999). Cholinergic neurons residing in the VP receive dopaminergic, noradrenergic, adrenergic, GABAergic, and glutamatergic inputs (for review, see Zaborszky et al., 2012) and receive topographically organized input from the Acb (Záborszky and Cullinan, 1992). Outputs from cholinergic neurons residing in the VP project to the prefrontal cortex (Gritti et al., 1997, 1999; Zaborszky et al., 2012; Zaborszky, unpublished observations), the basolateral amygdala (Carlsen et al., 1985), and also establish local synapses onto VP GABAergic neurons (Záborszky et al., 1986). In light of recent studies showing that dorsal pallidal cholinergic cells are integrated in basal ganglia circuitry (Saunders et al., 2015a,b), it will be important to conduct similar cell-type specific studies to determine if this is the case with VP cholinergic neurons as well.

Numerous attempts have been made to sort VP neurons electrophysiologically into different categories based on action potential characteristics, responses to pharmacological agents, anatomical location and phenotypes. Emerging evidence points to functionally relevant neuronal subpopulations within the VP. Whether recording from awake behaving rodent or nonhuman primate preparations, *in vivo* anesthetized preparations, or *in vitro* preparations in rodents (Mitchell et al., 1987; Wilson and Rolls, 1990; Yang and Mogenson, 1989; Napier and Potter, 1989; Napier et al., 1991a,b; Chrobak and Napier, 1993; Lavin and Grace, 1996; Pang et al., 1998; Turner, Mignon, Napier, 2002; Heidenreich et al., 2004; Tindell et al., 2005; Root et al., 2010, 2013; Avila and Lin, 2014a), it has long been known that VP neurons exhibit great variability in their basal firing rates and spiking patterns. While firing rate or pattern do not tightly co-vary with particular action potential characteristics (e.g., Turner et al., 2002), correlations are reported for electrophysiological characteristics that are subthreshold to spiking, as well as to morphology and transmitter phenotypes (Lavin and Grace, 1996; Pang et al., 1998; Kupchik and Kalivas, 2013). For example, “Type l” neurons of Pang and colleagues (Pang et al., 1988) and “Type B” neurons of Lavin and Grace (1996), both recorded *in vivo*, approximated the noncholinergic neuron characteristics obtained during *in vitro* recordings (Bengtson and Osborne, 2000). Type I neurons exhibit few or no axon branches near the soma suggesting these cells were projection neurons (Pang et al., 1998). Type B neurons of Lavin and Grace (1996) encompassed 27% of the recorded cells and these exhibited a ramp-like depolarization preceding spike discharges with prominent afterhyperpolarizations in a 1.3 ms waveform. “Type II” neurons described by Pang et al. (1998) approximate the characteristics of “Type A” VP neurons described by

Lavín and Grace (1996). Type A neurons were the most common cell (53%) in the latter study, and these neurons exhibited no afterhyperpolarizations in their long duration (2.8 ms) waveforms. Type II neurons of Pang et al. (1998) were determined to be noncholinergic, and these neurons exhibited extensive axonal arborizations that did not extend past their dendritic arbor, suggesting they were interneurons, though extra-VP termination cannot be ruled out. In either case, the results of Pang and colleagues (1998) indicate that Type II neurons, and not type I neurons, affect local VP processing.

Using awake behaving recordings and analyzing firing patterns across discrete behavioral events from neurons in several basal forebrain regions (e.g., substantia innominata, medial and lateral parts of the horizontal diagonal band, ventral globus pallidus, caudal VP, etc), Avila and Lin (2014a) observed three general types of neurons that also differed in electrophysiological characteristics (e.g., baseline firing rate, inter-spike intervals, waveform complexity). Most neurons were categorized as Type I (46%), which belong to a group of motivational salience-encoding neurons observed throughout all basal forebrain regions (Lin and Nicolelis, 2008; Avila and Lin, 2014b). The Type I neurons of Avila and Lin (2014a) are highly sensitive to cues predicting the start of a reward trial as well as conditioned stimuli and the reward itself, especially when predicted rewards are comparatively robust. The motivational salience signaling of Type I neurons is correlated with faster decision speed (Avila and Lin, 2014b) and a short latency frontal cortex potential (Nguyen and Lin, 2014). Together, Type I neurons were interpreted as non-cholinergic corticopetal basal forebrain neurons (Avila and Lin, 2014a). In contrast, Type II (14%) and type III (16%) neurons do not change firing rates following cue-presentation but are modulated during discrete behaviors involved in obtaining rewards (e.g., fixation as a response requirement to obtain rewards, behaviors related to approaching the reward (fixation port exit, reward port entry), and consumption (onset of licking)). The Type II and Type III neurons of Avila and Lin (2014a) are separated by their increasing or decreasing firing rate changes during fixation and movement events and were interpreted as belonging to the VP.

Using *in vitro* slice methods, Kupchik and Kalivas (2013) reported a neuronal subtype located in VP subfields rostral to the crossing of the anterior commissure that exhibits electrophysiological characteristics similar to ventral striatal and extended amygdala neurons. This neuronal subtype exhibits a more hyperpolarized membrane potential with no spontaneous action potentials, and is comparatively more sensitive to glutamatergic influences than other VP neurons. The richness of the morphological and functional characteristics of VP neurons point to heterogeneity of the structure and to the diversity of processes that these neurons likely integrate. These concepts are explored in subsequent sections of this review.

3.0. Afferent inputs and changes in firing rates induced by these inputs

In the following subsections we review the afferent connections to the VP subregions and responsiveness of VP neurons to these inputs (**Figure 5**). While most of the afferent (and efferent) projection patterns of VP subregions are well delineated, few studies have considered whether or not neurons belonging to distinct VP subregions exhibit differential sensitivity to various afferent-associated transmitters. As such evaluations are critical to understanding the functional circuits in which the VP participates, these studies are highlighted.

3.1.1. Inputs from the nucleus accumbens: GABA

The largest input to VP is from the Acb. This input has been detailed by lesion degeneration (Williams et al., 1977; Haber and Nauta, 1983; Zahm and Heimer, 1987), anterograde and retrograde tracer methods (Swanson and Cowan 1975; Powell and Leman 1976; Conrad and Pfaff 1976a; Williams et al., 1977; Troiano and Siegel 1978a; Nauta et al., 1978; Mogenson et al., 1983; Haber and Nauta, 1983; Groenewegen and Russchen 1984; Lu et al., 1988; Churchill et al., 1990; Maurice et al., 1997, 1998; Zahm and Heimer 1990; Heimer et al., 1991; Záborszky and Cullinan 1992; Usuda et al., 1998) and with electrophysiological approaches (Chrobak and Napier, 1993). The Acb projection typically exits the Acb caudally (Tripathi et al., 2010) via the medial forebrain bundle (Conrad and Pfaff 1976a; Troiano and Siegel, 1978a) but on occasion can extend rostrally before hooking caudally towards VP (Chang and Kitai, 1985). Surprisingly, definitive evidence that Acb neurons establish synapses onto GABAergic VP neurons is lacking in the literature. Using lesion degeneration and immunoelectron microscopy, we reveal here that AcbSh and AcbC neurons establish symmetric synapses (characteristic of inhibitory GABAergic neurotransmission) onto GAD-IR VP neuron dendrites (**Figure 4**).

Acb projections to VP are topographically organized (**Figure 6**). The medial AcbSh projection is contained within the neurotensin-immunoreactive VPvm subregion (Zahm and Heimer, 1988; Zahm, 1989; Zahm and Heimer, 1990; Heimer et al., 1991; Zahm and Brog, 1992). Neurotensin-IR within the VPvm depends on the integrity of the Acb, as lesions of this structure reduce neurotensin-IR in VPvm (Geisler and Zahm, 2006a). Anterograde tracers injected in AcbSh produce an abundance of labeled terminals within the VPvm, which continue as a broad column through the rostrocaudal extent of VPvm and into the sublenticular regions beyond VP, such as extended amygdala and lateral hypothalamus (LH) (Zahm and Heimer 1990; Heimer et al., 1991, 1997). The lateral AcbSh as well as the lateral olfactory tubercle innervates the VPvl, which is devoid of neurotensin-IR (Heimer et al., 1987; Heimer et al., 1991; Groenewegen et al., 1993). Consistent with the innervation topography of neurotensin-containing inputs to the VPvm, but not VPvl, neurotensin reduces VP firing rates in two-thirds of VPvm neurons, but has no effect on VPvl neurons (Michaud et al., 2000). The AcbC projection is contained within the calbindin-d28k- immunopositive VPdl subregion (Zahm and Brog 1992; Zahm et al., 1996; Tripathi et al., 2010). These anatomical observations are supported by functional characterizations of the AcbC to VP projection topography, wherein electrical activation of the AcbC evoked short-latency responses consistent with monosynaptic inputs in 74% of the accumbal-sensitive neurons within the VPdl, but only 43% of responding neurons recorded from the VPvm (Chrobak and Napier, 1993). Single-axon tracings have shown that a minority of core neurons that project to the VPdl collateralize within the lateral VPvm (Tripathi et al., 2010), suggesting that the accumbal-sensitive neurons in lateral parts of the VPvm received axon collaterals from core neurons that targeted VPdl. Finally, a sparse Acb projection, but large projection from the olfactory tubercle, terminates within the “finger-like” VPr (Zahm and Heimer, 1987; Tripathi et al., 2010).

Early anatomical and functional studies on Acb to VP projections documented the involvement of GABA in these inputs (Walass and Fonnum, 1979; Jones and Mogenson, 1980; Zaborszky et al., 1986; Chrobak and Napier, 1993). The number of GABAergic synapses on VP neurons has been estimated to be greater than 80% (Zahm et al., 1985), most likely reflecting Acb and local GABAergic connections. Neurochemical studies have shown that the VP contains high concentrations of extracellular GABA (Bourdelais and Kalivas, 1990, 1992; Xi and Stein, 2000; Lawrence et al., 2003; Tang et al. 2005; Li et al., 2009; Wydra et al., 2013) and intense immunoreactivity for the GABA synthesizing enzyme, GAD (Oertel et al., 1984; Mitrovic et al., 1999). AcbSh and AcbC projections synapse onto both GABAergic and cholinergic VP cells (Grove et al., 1986; Záborszky et al., 1991; Záborszky and Cullinan, 1992). Cholinergic neurons receive prominent GABAergic inputs to their cell bodies and proximal dendrites (Zaborszky, 1989), and those from the Acb establish symmetric synapses, characteristic for inhibitory terminals (Zaborszky and Cullinan, 1992).

VP exhibits intense immunoreactivity for ionotropic GABA-A receptors (Zilles et al., 1991; Henderson, 1995; Hartig et al., 1995) and low immunoreactivity for metabotropic GABA-B receptors (Margeta-Mitrovic et al., 1999). Consistent with high expression levels of ionotropic GABAergic receptors, early studies in anesthetized rats verified that local applications of GABA dramatically decrease firing in nearly all neurons tested (e.g., Jones and Mogenson, 1980; Lamour et al., 1986; Napier et al., 1991b; Chrobak and Napier, 1993). Local application of the GABA-A receptor antagonist bicuculline increases firing in most tested VP neurons (Yang and Mogenson, 1985; Chrobak and Napier, 1993; Turner et al., 2001) presumably by displacing endogenously released GABA. This tonic GABAergic inhibition involves Acb inputs, as intra-Acb infusions of the local anesthetic, procaine, can robustly increase VP firing (Napier 1992), and applications of GABA-A antagonists onto VP neurons nullify the suppression in firing rate that occurs with electrical stimulation of the Acb (Chrobak and Napier, 1993).

3.1.2. Inputs from the nucleus accumbens: GABA co-localized with peptides

GABAergic fibers within VP are often co-localized with enkephalin, dynorphin or substance P (Reiner and Anderson, 1990; Zahm, 1985, 1989). Enkephalin and GABA are typically observed in boutons that make symmetrical synapses on VP somata and proximal dendrites (Zahm et al., 1985; Bolam et al., 1986), indicative of a strong inhibitory transmission unto VP neurons.

Enkephalin and dynorphin are natural ligands of the *mu* and *kappa* opioid receptors. All three major types of opioid receptors are identified within the VP (Lahti *et al.*, 1989; Moskowitz and Goodman, 1984; Pilapil *et al.*, 1987), with *mu* receptors having the highest levels (Lahti *et al.*, 1989; Moskowitz and Goodman, 1984). The functional pharmacology of VP responses to opioids is complex, and includes the modulation of several other VP transmitters (for review, see Napier and Mitrovic, 1999). Local *in vivo* application of agonists pharmacologically verified to be specific for their respective subtype have revealed that approximately 50-70% of VP neurons exhibit sensitivity to one type of opioid receptor agonist (Napier et al., 1992a; Chrobak and Napier, 1993; Mitrovic and Napier, 1996;

Johnson and Napier 1997; Mitrovic and Napier, 1998). In a study that directly compared *mu*, *kappa* and *delta* opioid agonists (Mitrovic and Napier, 1995), agonists for *mu* and *kappa* receptors predominantly decreased VP firing (52% and 41% of tested neurons, respectively) while *delta* receptor agonists had slightly more decreases than increases (24% *vs*. 13%). As a significant portion of VP neurons did not respond to any opioid agonist (e.g., 61 out of 191 neurons tested, Mitrovic and Napier, 1995) these electrophysiological observations concur with anatomical observations by Zahm et al., (1985) that some VP neurons do not receive inputs from opioid-containing fibers.

VP neurons exhibit moderate levels of tachykinin receptors (Danks et al., 1986; Shults et al., 1984; Rothman et al., 1984), and it has been verified that cholinergic neurons that reside within VP are included in those VP cells that express substance P receptors (Chen et al., 2001). Substance P or the metabolically stable substance P analog, DiMeC7 (pGlu5,MePhe8,MeGly9)-substance P5) increases firing of approximately 40-50% of tested VP neurons (Mitrovic and Napier, 1996, 1998; Napier et al., 1995) and substance P antagonists block increases in firing rate induced by Acb stimulation (Mitrovic and Napier, 1998). Suggesting that the cholinergic neurons residing within VP may be engaged, cultured cholinergic neurons from the basal forebrain show significant depolarization and spike facilitation to bath applied substance P, and these effects are related to the ability of the tachykinin to suppress inwardly rectifying potassium channels (for review, see Nakajima et al., 1991).

3.1.3. Inputs from the nucleus accumbens: Integration of firing

A wealth of information regarding the functional consequences of activating Acb-VP pathways, and how the major transmitter systems interact at the level of postsynaptic VP neurons, was provided by early electrophysiological studies. Electrical stimulation of the rat Acb can evoke short latency (2-6 ms) inhibition of VP spiking (Chrobak and Napier, 1993; Mitrovic and Napier, 1998), which likely reflects endogenously released amino acids acting on pallidal ionotropic receptors. However, accumbal-evoked VP responding often exhibits comparatively longer latency (>7 ms) (Mogenson, Swanson, Wu, 1983; Chrobak and Napier, 1993; Lavín and Grace, 1996; Mitrovic and Napier, 1998), indicative of metabotropic receptor activation and/or integration of substance P, enkephalin, and GABA influences. Indeed, most *in vivo* studies show that VP neuronal firing exhibits both increases and decreases in response to Acb stimulation (Mogenson, Swanson and Wu, 1983; Chrobak and Napier, 1993; Mitrovic and Napier, 1998) (but see Lavín and Grace (1996)). Moreover, Acb evoked VP responses are antagonized by microiontophoretically applied antagonists of GABA-A, opioid (Chrobak and Napier, 1993) and substance P (Mitrovic and Napier, 1998) receptors.

The concept that VP neurons can integrate various accumbal influences fits with anatomical and electrophysiological descriptions of the Acb to VP projections (Groenewegen and Russchen, 1984; Bolam et al., 1986; Heimer et al. 1991; Zahm and Heimer, 1990, 1993; Záborszky and Cullinan 1992; Chrobak and Napier, 1993; Napier et al., 1995; Mitrovic and Napier, 1996; Johnson and Napier 1997; Mitrovic and Napier, 1998; Pickel et al., 2012). One third of VP neurons sampled *in vivo* were observed to be sensitive to both the *mu* agonist DAMGO and substance P (Mitrovic and Napier, 1996). In these neurons, DAMGO antagonized substance P-evoked increases in firing and conversely substance P antagonized decreases in firing rates induced by DAMGO (Mitrovic and Napier, 1996). Local (microiontophoretic) application of another *mu* opioid agonist, morphine, was shown to *reduce* Acb-evoked VP inhibition (Chrobak and Napier, 1993) as well as the inhibitory effects of GABA on VP activity, and this latter effect occurred at local concentrations that were not sufficient to directly alter firing (Johnson and Napier, 1997) consistent with a modulatory role for *mu* receptor activation (for review, see Napier and Mitrovic, 1999).

Neurotransmitters released into the VP upon Acb activation also modulate input influences from non-Acb afferents. For example, the amygdala provides a glutamatergic input to the VP (described below), and in spite of the ability of substance P to increase spontaneous firing rates, the neuropeptide *attenuates* amygdala-evoked increases in VP firing rate, without altering firing rate increases caused by iontophoretically-applied glutamate (Mitrovic and Napier, 1998). This profile suggests that substance P acts presynaptically to reduce glutamate release, an effect that is bypassed by exogenous glutamate. In contrast, DAMGO potentiates VP firing increases induced by both amygdala stimulation and glutamate iontophoresis (Mitrovic and Napier, 1998), consistent with the idea that *mu* receptors can act both pre- and post-synaptically to modify the excitatory effects of glutamate. These functional studies concur with the anatomical observations that *mu* opioid receptors are located on both presynaptic and postsynaptic elements in the Acb-VP pathway (Olive et al., 1997). Similar functional analysis was used to show that *mu* opioid receptors can presynaptically regulate endogenous dopamine at the level of the VP (Mitrovic and Napier, 2002). Thus, both substance P and opioid neuropeptides released from Acb to VP projections are positioned to regulate the influences of several VP afferent systems, including Acb GABAergic, amygdala glutamatergic and midbrain dopaminergic inputs. Indeed, intra-VP activation of *mu* opioid receptors presynaptically reduces the release of VP dopamine subsequent to VTA activation (Mitrovic and Napier, 2002). This suggests that significant integration of a diversity of inputs occurs at the level of VP neurons, a concept that deviates from the classic basal ganglia model where VP is simply inhibited upon Acb activation (Alexander et al., 1986).

3.2. Dopaminergic inputs

Early predictions that the VP is an important dopaminoreceptive brain region (Napier et al., 1991a) are validated by numerous laboratories using a variety of techniques. The dopaminergic inputs are topographically oriented with the lateral VTA (parabrachial pigmented nucleus) projecting to VPr, VPvm, VPdl, and VPvl and the midline VTA projecting to medial parts of VP (Zahm and Heimer, 1988; Klitenick et al., 1992; Groenewegen et al., 1993; Del-Fava et al., 2007; Taylor et al., 2014). VP afferents arising from the substantia nigra (pars compacta or pars reticulata) are sparse (Beckstead et al., 1979; Prensa and Parent, 2001). Dopaminergic projections from the VTA or SN synapse onto multiple neuronal types in the VP including parvalbumin-immunoreactive, nonparvalbumin-immunoreactive, and cholinergic neurons (Zaborszky, 1989; Gaykema and Záborszky 1996, 1997a,b). Indirect evidence for dopaminergic regulation of forebrain cholinergic function is lent by the robust increase (>200%) in acetylcholine turnover (i.e., hemicholinium binding) seen in terminal regions for these cholinergic neurons (the prefrontal cortex and amygdala) in rats after 6-hydroxydopamine-induced lesions of the dopaminergic inputs (Muma et al., 2001).

The dopaminergic projection to VP is not dense (Beckstead et al., 1979; Klitenick et al., 1992); relatively few fibers in VP exhibit tyrosine hydroxylase-IR (**Figure 3E**; Seifert et al., 1998; Prensa and Parent, 2001) and the concentration of dopamine and its metabolites is low (Napier and Potter, 1989; Muma et al., 2001). Nonetheless, intra-VTA infusion of the glutamate receptor agonists NMDA and AMPA clearly increases extracellular dopamine levels in the VP (Kretschmer et al., 2000) and electrical activation of the VTA/medial SNc results in profound, dopamine-mediated effects on VP neuronal function (Maslowski-Cobuzzi and Napier 1994; Mitrovic and Napier, 2002). For example, stimulation of the VTA/medial SNc produces short latency changes in firing rate of almost 90% of recorded VP neurons, and of these, roughly 60% show decreases and 30% show increases in firing rate (Maslowski-Cobuzzi and Napier 1994; Mitrovic and Napier, 2002). This multifunctional response profile is recapitulated by locally (microiontophoretically) applied dopamine (Napier and Potter, 1989; Napier et al., 1991; Johnson and Napier 1997a; Mitrovic and Napier, 2002) and likely reflects both direct and indirect effects. Local application of dopamine antagonists attenuate the ability of VTA/medial SNc stimulation to alter VP neuronal firing, consistent with the conclusion that VTA/medial SNc activation releases dopamine from terminals within the VP (Maslowski-Cobuzzi and Napier 1994; Mitrovic and Napier, 2002).

D_1, D_2, and D_3 receptors are localized within the VP (Contreras et al., 1987; Beckstead et al, 1988; Richfield et al., 1989; Mansour et al., 1990; Tziortzi et al., 2010) and application of agonists for these receptors directly onto VP neuronal elements is sufficient to alter VP firing (Napier and Maslowski-Cobuzzi, 1994). Systemic administration of the non-selective DA agonist, apomorphine alters VP firing by activating both D_1 and D_2 receptors (Maslowski and Napier, 1991a; Napier et al., 1991), and systemic administration of agonists with a preference for activating D_1 receptors (Maslowski and Napier, 1991b; Heidenreich et al., 1995) or D_2 receptors (Maslowski and Napier, 1991b) all alter VP firing in doses that also alter behavior in rats. Locally (microiontophoretically) applied DA agonists result in response profiles that differ from those observed with systemic administration of the drugs (e.g., Napier and Maslowski-Cobuzzi, 1994; Heidenreich et al., 2004 *versus* Napier and Maslowski 1991b; Heidenreich et al., 1995, respectively). These differences reflect the ability of systemically administered agonists to influence brain regions that subsequently input the recorded VP neurons, whereas microiontophoretically applied agonists only activate receptors within a restricted, local milieu of the recorded VP neurons.

The particular neuronal elements on which the various dopaminergic receptors are located are becoming apparent, and it is clear that both presynaptic and postsynaptic locales are involved. Ultrastructural immunocytochemical analysis shows that a few of the D_2-receptor labeled axons in the VP contained tyrosine hydroxylase, suggesting only a small proportion of dopamine terminals exhibit D_2 autoreceptors (Mengual and Pickel, 2002). This is consistent with *in vivo* microdialysis findings which show some, but minimal, D_2 autoreceptor regulation of extracellular dopamine in the VP (Melendez et al., 2005). D_2

autoreceptors are physiologically relevant as *in vivo* studies show that up to 43% of the VP neurons responding to VTA/medial SNc stimulation with a monosynaptic profile are antagonized by local applications of D_2 receptor blockers (Maslowski and Napier, 1994). There is no evidence that dopaminergic neurons express D_1 receptors; thus, it is unlikely that D_1 receptors are located on dopaminergic terminals within the VP. Consistent with this assumption, the ability of D_1 agonists to alter VP neuronal activity is not diminished by removal of endogenous dopamine (Heidenreich et al., 2004). Interestingly, however, intra-VP application of SCH-23390, a D_1-like receptor antagonist, increases extracellular levels of dopamine up to approximately 600% of baseline, suggesting that D1 receptors in the VP are substantially involved in regulating extracellular dopamine (Melendez et al., 2005). D_1 receptor mRNA has been found in the amygdala, a major glutamatergic input to the VP (Fremeau et al., 1991), and D_1–mediated VP firing is under the control of amygdala inputs (Napier, 1992b), suggesting that the excitatory input to the VP from the amygdala may be regulated by tonic D_1 receptor inhibition. Therefore, it is possible that intra-VP SCH-23390 may increase excitatory (potentially amygdaloid) transmission on dopaminergic terminals, which would enhance terminal dopamine release.

In situ hybridization studies demonstrate both D_1 and D_2 receptor mRNA in GABAergic projections from the Acb to the VP (Lu et al., 1997, 1998), and while these studies have not been verified with assessments of receptor protein, they do suggest that some dopaminergic receptors in the VP may be located on presynaptic GABAergic terminals. DA does modulate the inhibitory effects of GABA at the level of the VP (Johnson and Napier, 1997a). However, responding by VP neurons to D_1 or D_2 receptor-preferring agonists is maintained following pharmacologic inactivation of the Acb (Napier 1992b), functionally demonstrating the presence of some dopamine receptors that are downstream to Acb GABAergic inputs.

3.3. Glutamatergic inputs

VP receives comparatively less glutamatergic input than does the Acb; however, locally applied glutamate robustly increases firing of almost all recorded VP neurons (Napier et al., 1991, 1995; Mitrovic and Napier, 1998; McDaid et al., 2005, 2006). Glutamate can be consistently measured within the VP using *in vivo* microdialysis (Chapman and See, 1996; Kretschmer et al., 2000; Kemppainen et al., 2010). Although significant concentrations of extracellular glutamate are observed in VP dialysates, the bulk of the measured concentrations are insensitive to local application of potassium chloride (Kemppainen et al., 2010). This is consistent with glutamate microdialysis studies performed in the striatum, Acb, and PFC, each showing that basal extracellular glutamate is derived primarily from non-synaptic (glial) origins (Baker et al., 2002, 2003; Melendez et al., 2005).

Glutamate acts on ionotropic and metabotropic receptors. NMDA and AMPA receptors are ionotropic receptors and evaluations of mRNA, protein, and ligand binding reveal the presence of NMDA and AMPA receptors in the VP (Page and Everitt, 1995). AMPA receptors are hetero-oligomers, or tetramers, composed of GluR protein subunits 1-4. Immunoblotting and immunohistochemistry have determined that GluR1 and GluR2 subunits are located within the VP (Martin et al., 1993; Mickiewicz and Napier, 2011;

Herrold et al., 2013). GluR1 is selectively expressed within the majority noncholinergic neurons of the VP (Martin et al., 1993). VP neurons are sensitive to NMDA or AMPA, and most (82%) are sensitive to both (Turner et al., 2001). Intra-VP infusions of low to moderate doses of NMDA (0.23 or 0.45 μg) increases Fos-like immunoreactivity within the VP as much as five fold (Turner et al., 2008). Metabotropic glutamate receptor subunit proteins are also observed within the VP (Shigemoto et al., 1992; Herrold et al., 2011, 2013). The neuronal consequences of activating these receptors have not yet been determined for the VP.

A major source of glutamatergic inputs to the VP is from the medial STN. These projections target the VPdl and appears to extend into the dorsolateral portions of VPvm (Ricardo et al., 1980; Groenewegen and Berendse 1990; Turner et al., 2001), primarily terminating on distal dendrites (Záborszky et al., 1991). Most VP firing rates are altered by STN stimulation, with 69% of neurons exhibiting excitation and 31% exhibiting inhibition (Turner et al., 2001). Since the excitatory latency is roughly half (5 ms) of the inhibitory latency (10.8 ms), the excitatory and inhibitory effects of STN stimulation likely arose from monosynaptic glutamate and polysynaptic lateral inhibition routes, respectively.

VP receives light projections from infralimbic but not prelimbic cortex (Sesack et al., 1989; Takagishi and Chiba 1991; Vertes, 2004). The cortical projection to VP is glutamatergic, typically synapsing onto dendritic spines or dendritic shafts of noncholinergic, parvalbumin-immunoreactive neurons (Záborszky et al., 1997; Gaykema and Zaborszky, 1997). Although direct cortical projections to VP are significantly less substantial than other afferents, these projections are sufficient to modulate VP activity. For example, medial prefrontal cortex lesions decrease VP firing rates and reduce the occurrence of particular subtypes of VP neuron by 70% (i.e., the electrophysiologically-classified Type B cells; Lavín and Grace, 1998). These outcomes may reflect a loss of direct excitatory prefrontal inputs; however, indirect effects from mPFC-Acb-VP or mPFC-amygdala-VP pathways cannot be excluded.

Anatomical evaluations show that the amygdala projects to cholinergic neurons that reside within the VP (Záborszky et al., 1984, 1986; Carlsen et al., 1985; Poulin et al., 2006). Functional evaluations of the amygdala-VP projection shows that short latency evoked responses (likely monosynaptic) are seen in 54-98% of recorded VP neurons (Maslowski-Cobuzzi and Napier 1994; Mitrovic and Napier, 1998), suggesting that other VP neuronal phenotypes are also innervated by the amygdala. Although the amygdala projection is predominantly glutamatergic (Fuller et al., 1987), amygdala stimulation produces both short latency inhibition and excitation in separate populations of VP neurons; with excitation observed more in the medial than lateral VP (Yim and Mogenson 1983; Maslowski-Cobuzzi and Napier 1994; Mitrovic and Napier, 1998). The short latency excitation is antagonized by local applications of glutamatergic ionotropic receptor antagonists (Mitrovic and Napier, 1998), modulated by dopamine from projections arising in the VTA/medial SNc (Napier 1992b; Maslowski-Cobuzzi and Napier, 1994), and modulated by substance P and opioid projections from Acb (Mitrovic and Napier, 1998). A GABAergic projection to the basal forebrain, including the VP, originating from somatostatin-containing GABAergic neurons of the amygdala has been described (McDonald et al., 2012), suggesting this separate population of amygdala neurons provides an inhibitory influence onto VP.

Recent reports describe ascending glutamatergic and GABAergic projections that arise within the VTA (Hnasko et al., 2012; Taylor et al. 2014; Root et al., 2014a,b). Glutamatergic VTA neurons have a heterogeneous molecular composition (Yamaguchi et al., 2011; Li et al., 2013; Morales and Root, 2014) and additional anatomical evaluations will be necessary to identify the glutamatergic VTA phenotypes innervating VP.

3.4. Serotonergic inputs

Serotonergic systems have long been viewed as playing a crucial role in forebrain function. VP exhibits serotonin transporter-IR (Sur et al., 1996) and the dorsal raphe (DR) projects to VP (Semba et al., 1988; Jones and Cuello, 1989; Vertes, 1991; Hermann et al., 1996). *Post mortem* VP tissue contains high concentrations of 5-HT and its metabolites (Napier and Potter, 1989), and 5-HT is detected *in vivo* using microdialysis in rats (Sizemore et al., 2000). Although the morphological location is not well-characterized, high densities of several 5-HT receptor subtypes have been detected in the VP (Appel et al., 1990; Waeber et al. 1996; Sari et al. 1999; Chen and Lawrence, 2000; Murrough et al. 2011). The few functional evaluations of VP 5-HT that have been conducted thus far point to complex and potentially phenotype–selective effects. Intravenous administration of 5-HT_{1A} (but not 5-HT_{1B}) agonists alters firing of two-thirds of the recorded VP neurons, with increases and decreases in activity equally observed (Heidenreich and Napier, 2000). Intravenous administration of a 5-$HT_{2A/2C}$ agonist alters firing in 92% of the recorded VP neurons, with rate increases occurring in 58% of the responding cells (Napier and Istre, 2008). An *in vitro* electrophysiological study of VP slices from neonatal rats revealed that 5-HT depolarizes noncholinergic neurons and hyperpolarizes cholinergic neurons (Bengtson et al., 2004). Future studies on the potential for specific receptor subtypes to be expressed in a neuronal phenotypic manner would shed important new light on the consequences of VP 5-HT transmission. Serotonin-containing axons apparently do not enter into synaptic connections with VP cholinergic neurons based on electron microscopic studies (Hajszan and Zaborszky, 2000).

3.5 Comparing ventral and dorsal striatopallidal systems: possible direct and indirect circuits

Within the basal ganglia, interspersed medium spiny neurons of the dorsal striatum form a "direct" pathway to the internal GP/SNr or an "indirect" pathway consisting of the striatum-external GP-STN-internal GP/SNr. Whether or not the ventral striatum/Acb is also organized into 'direct and indirect pathways' is not clear. On the basis of connectivity, Sesack and Grace (2010) suggested two circuits: AcbC-SNr-mediodorsal thalamus (MD) direct and AcbC-VPdl-STN-SNr-MD indirect pathways, as well as AcbSh-VTA-MD direct and AcbSh-VPvm-VTA-MD indirect pathways. Direct and indirect activation was proposed to activate or inhibit motor plans related to goal-directed behavior, respectively. Alternatively, on the basis of single axon tracings Tripathi et al. (2010, 2013) suggested two direct pathways, AcbSh-VPvm-MD and AcbC-VPr-MD, and an indirect AcbC-VPdl-STN-VPvm-MD pathway. Thus, there appears to be several possible direct or indirect pathways involving VP, which may play a role in the involvement of the VP in a wide array of motivated behaviors (Section 5.0).

In the dorsal striatum, direct pathway neurons express D_1 receptors and preprotachykinin mRNA (substance P) whereas neurons in the indirect pathway express D_2 receptors and preproenkephalin mRNA. At least in rats (discussed below), distinctions of direct vs. indirect pathways based on Acb D_1/D_2 expression or opioid/tachykinin expression are not as compelling as they are for the dorsal striatum. For example, of AcbSh neurons projecting to VP, between 44.32% (Lu et al., 1998) and 75.52% (Lu et al., 1997) express D_1 and 33.71% express D_2 receptor mRNA (Lu et al., 1988). Of AcbC neurons projecting to VP, 31% express D_1 and 45% express D_2 receptor mRNA. Thus, significant numbers of Acb neurons that express D_1 or D_2 receptor mRNA project to VP. Results are similar with respect to substance P and enkephalin expressing neurons. Of AcbSh neurons projecting to VP, 39% express preprotachykinin mRNA (substance P) and 36% express preproenkephalin (Lu et al., 1998). Of AcbC neurons projecting to VP, 33% express preprotachykinin mRNA (substance P) and 55% express preproenkephalin (Lu et al., 1998). Thus, similar to dopamine receptor expression, significant numbers of Acb neurons that express substance P or enkephalin project to VP. These results suggest that an indirect pathway from Acb to VP cannot be determined by methods used to delineate the dorsal striatum indirect pathway.

With respect to a ventral striatal direct pathway, D_1 receptors are largely expressed on AcbSh neurons projecting to VTA (76%) and D_2 receptors are rarely expressed in these neurons (2%; Lu et al., 1998). Furthermore, preprotachykin mRNA is often observed in AcbSh neurons projecting to the VTA (61%) whereas preproenkephalin mRNA is mostly absent from AcbC neurons projecting to VTA (4%; Lu et al., 1998). Recent studies have found differences between D_1/substance P or D_2/enkephalin expressing Acb neurons with regard to drug abuse (MacAskill et al., 2012; Yawata et al., 2012; Bock et al., 2013). Thus, it is possible that indirect D_1/D_2 or substance P/enkephalin expressing neurons involve different circuits (e.g., Kupchik et al., 2014) and effects on behavior, but these circuits are not wholly congruent with the dorsal striatum pathways.

4.0 Outputs and loops

There is a rich literature that demonstrates the wide array of brain regions which are linked to the VP. In the following subsections we review the efferent connections of VP subregions and neuronal phenotypes (**Figures 5-6**).

4.1 Thalamus

4.1.1 Mediodorsal thalamus—One major target of VPvm is the MD (Haber et al., 1985; Zahm and Heimer, 1990; Groenewegen et al., 1993; Kalivas et al., 1993; Zahm et al., 1996; Churchill et al., 1996; Heimer et al., 1997; O'Donnell et al., 1997; Tripathi et al., 2013), and ultrastructural visualization of this projection has identified large terminals that synapse primarily on dendritic shafts (Kuroda and Price 1991). VPr and VPvl also project to the MD (Young et al., 1984; Zahm and Heimer, 1987; Groenewegen et al., 1993; Tripathi et al., 2013) but the VPdl projection to MD is significantly less than that from other VP subregions (Zahm et al., 1996; O'Donnell et al., 1997). The VP projection to MD is predominantly GABAergic and partly cholinergic (Haber et al., 1985; Young et al., 1984; Kuroda and Price 1991; Ray et al., 1992; Mariotti et al., 2001). It is of great interest to ascertain the functions of these two VP-MD projections.

The MD response to electrical stimulation of the VP is predominantly inhibitory, with 83% of recorded cells decreasing, and 13% of cells increasing firing rates within 1-4 ms of VP activation (Vives and Mogenson, 1985; Mogenson et al.1987; Lavín and Grace, 1994, 1998). However, VP-evoked inhibition followed by a rebound excitation is also reported for 76% of recorded MD neurons (Mariotti et al., 2001). These findings are consistent with circuit-related direct and indirect responses.

VPvm efferents terminate onto MD neurons that project to the prefrontal cortex (Vives and Mogenson, 1985; Lavín and Grace, 1996; O'Donnell et al., 1997). The part of MD that receives VP inputs projects strongly to cortical areas that in turn project to AcbC (Zahm and Brog, 1992; Zahm et al., 1996; Zahm, 1999). Therefore, VPvm may be capable of altering AcbC-VPdl processing through a serial, laterally spiraling circuit.

4.1.2 Reticular nucleus of the thalamus—The reticular thalamus contains GABAergic neurons that provide topographic innervation to all thalamic nuclei (Houser et al., 1980). The VP projects to the rostral reticular thalamus (Jourdain et al., 1989; Cornwall et al., 1990; Groenewegen et al., 1993; O'Donnell et al., 1997; Tripathi et al., 2013). VP stimulation evokes IPSPs in roughly 73% of reticular thalamus cells at 2.7 ms latency (Lavín and Grace, 1994). The reticular thalamus projects GABAergic inputs into MD (Ray et al., 1992). The presence of this projection helps explain the small percentage of MD neurons that are excited by VP stimulation, as inhibition of the reticular thalamus disinhibits MD neurons (Mogenson et al., 1987).

4.1.3. Other thalamic targets—The VP has weak projections to several thalamic nuclei, including ventromedial nucleus, nucleus reuniens, paraventricular, intralaminar central medial and paracentral nuclei (Groenewegen et al., 1999). Most of these projections originate within the VPvm (Tripathi et al., 2013). A large VP projection to the paraventricular thalamus has been reported to arise from the anterior VP (Chen and Su, 1990), but thorough examination of paraventricular afferents demonstrated this is likely not to be the case (Li and Kirouac, 2012).

4.2. Lateral habenula (epithalamus)

The VPvm and VPr project to the medial part of the lateral habenula (LHb; Troiano and Siegel 1978b; Ray et al., 1992; Groenewegen et al., 1993; Zahm et al., 1996; Tripathi et al., 2013), and 28% of VPvm and 36% of VPr neurons that project to the thalamus collateralize within the LHb (Tripathi et al., 2013). The mesopontine rostromedial tegmental nucleus (RMTg), a GABAergic structure that is characterized by LHb input, has reciprocal connections with the VP (Jhou et al., 2009a). Thus, the VP is linked with the RMTg directly and polysynaptically through the lateral habenula. Currently no studies have examined the influence of the VP on the RMTg, or *vice versa*. Examination of these pathways will be of interest given that the RMTg projects to VTA, SNc, DR, and pedunculopontine tegmental nucleus (PPTg) (Jhou et al., 2009a; Lavezzi et al., 2012) and such a circuit would have the potential to influence a wide variety of motivated behaviors.

4.3. Dopaminergic mesencephalon

A major output of VP subregions and individual neuronal phenotypes is directed topographically towards the dopaminergic mesencephalon. GABAergic (Kalivas et al., 1993), neurotensinergic (Zahm et al., 2001; Geisler and Zahm, 2006b), and glutamatergic (VGluT2; Geisler et al., 2008) VP neurons project to VTA. The VPvm projects predominantly to the VTA and retrorubral field while the VPdl largely projects to the SNr (Haber et al., 1985; Zahm 1989; Kalivas et al., 1993; Groenewegen et al., 1993; Zahm et al., 1996; Geisler and Zahm, 2005; Colussi-Mas et al., 2007), but also collateralizes within the most lateral portions of VTA (Tripathi et al., 2013). VPvl projects to SNc and retrorubral field, but not VTA (Groenewegen et al., 1993; Oertel and Mugnaini, 1984; Bevan et al., 1996). VP neurons robustly inhibit VTA dopamine and nondopamine neurons *via* GABA release (Hjelmstaad et al., 2013) and this action can reduce the number of VTA neurons that are in an active/firing state (Floresco et al., 2003).

The projection of VP to the dopaminergic mesencephalon is ideally positioned to alter the efficacy of the limbic/cognitive/motor serial spiral loop circuit from AcbSh to putamen (Haber et al., 2000). This is most readily appreciated by VPvm projections to the lateral portions of VTA (lateral parabrachial pigmented nucleus and lateral paranigral nucleus), and these regions of the VTA topographically send dopaminergic projections to Acb shell and core (Haber et al., 2000). Furthermore, as noted above and by Zahm et al., (2011), outputs from the lateral portions of VP (e.g., VPdl and VPvl), exhibit a termination pattern that spreads laterally from the VTA to the SNc, and these midbrain regions send dopaminergic projections to the dorsal striatum (Haber et al., 2000). VP neurons establish synapses with both VTA and SNc dopaminergic neurons (Uchida et al., 2012; Ogawa et al., 2014). Taken together, the subregional VP projections to VTA and SNc likely represent different mechanisms by which the VP may affect both ventral and dorsal striatum.

4.4. Lateral hypothalamus, subthalamic nucleus, and entopeduncular nucleus

A major target of the VP subregions is the LH (Groenewegen et al., 1993; Tripathi et al., 2013). The projection displays a mediolateral topography whereby VPr, VPvm, and VPdl axons target the most lateral, central, and medial portions of LH, respectively (Tripathi et al., 2013).

The VPdl sends GABAergic projections to the dorsomedial STN (Haber et al., 1985; Zahm, 1989; Groenewegen and Berendse 1990; Groenewegen et al., 1993; Bell et al., 1995; Zahm et al., 1996; Bevan et al., 1997), consistent with inhibition observed in this structure in response to electrical VP stimulation (Maurice et al., 1997, 1998). In rats, intra-VP injections of 45 μg/0.5 μl NMDA or 50 ng/0.5 μl bicuculline increases Fos-IR in the dorsomedial STN, while Fos activation is not seen in the lateral STN (Turner et al., 2008). Given that VP outputs are largely GABAergic, the increased activity in this VP projection target may reflect indirectly mediated disinhibitory effects of VP activation, but if so, it is noteworthy that the polysynaptic pathways follow the direct projections of VP outputs. For example, the medial STN, which receives inputs from VPdl is activated, but the lateral STN which receives inputs from GP is not altered by VP stimulation. This observation is particularly interesting as STN dendrites are oriented from medial to lateral zones of VP and

GP projections, receiving synapses from these structures along their dendrites (Bevan et al., 1997); therefore, some integration of GP and VP influences would be expected to occur. Furthermore, the prelimbic and medial orbital cortices project to this STN region, indicating expanded integration within the dorsomedial STN (Kolomiets et al., 2001). Further examination of pallidal to STN systems is needed to more clearly define these relationships.

The VPdl also sends a light GABAergic projection to the EPN (Zahm et al., 1996; Maurice et al., 1997; Bevan et al., 1997) and intra-VP injections of NMDA or bicuculline increase Fos-IR in the EPN (Turner et al. 2008). These VP to EPN projections are largely separate from GP projections, but exhibit some overlap (Bevan et al., 1997). Yet, EPN dendrites are not organized in a similar manner as STN neurons, and receive comparatively less VP input than the STN, suggesting more topographic influence from the GP. Nevertheless, intra-VP NMDA robustly increases Fos-IR in the EPN as well as its ontogenetically linked region, the SNr (Turner et al., 2008), and both are targets associated with projections from the VPdl.

A single-axon tracing study showed that the VP targets the rostral sublenticular extended amygdala and the area of the horizontal limb of the diagonal band and these projections arise from the VPvm and VPr (Tripathi et al., 2013). Given that cholinergic, GABAergic, and glutamatergic neurons reside within these areas, future investigations will be necessary to determine the type of postsynaptic neuron that receives VPvm and VPr projections.

4.5. Nucleus accumbens

Similar to the dorsal pallidostriatal projection (Staines et al., 1981), the VP projects back to its major striatal afferent source, the Acb, but the projection pattern is different for the two pallidal regions. GP neurons selectively innervate parvalbumin-immunoreactive GABAergic interneurons within the dorsal striatum (Bevan et al., 1998). The VP projection to Acb is less specific than GP, and consists of thin branching axons with numerous varicosities suggesting *en passant* synapses onto several Acb dendrites (Haber et al., 1985). In fact, the ventral pallidoaccumbal projection exhibits approximately equal percentages of VPdl and VPvm neurons projecting to either the AcbSh or AcbC (Tripathi et al., 2013; for subregionally nonspecific pallidoaccumbal projections, see also Heimer et al., 1991; Brog et al., 1993; Groenewegen et al., 1993; Spooren et al., 1996). The VPr exhibits a larger percentage of neurons that project to the olfactory tubercle than other striatal subregions (Tripathi et al., 2013). Orthodromic Acb activation from electrical VP stimulation occurs with roughly 7 ms latency and about half of these orthodromically activated neurons respond to hippocampal fimbria stimulation (Hakan et al., 1992; Yang and Mogenson, 1985). In contrast to striatopallidal cells, both dorsal and ventral pallidostriatal neurons exhibit *delta*, but not *mu* opioid receptor expression (Olive et al., 1997). Some parvalbumin-immunoreactive VP neurons project to the Acb (Kuo and Chang, 1992) suggesting the pallidostriatal projection is GABAergic.

4.6. Amygdala and prefrontal cortex

The VP projects to the basolateral amygdala (BLA) (Conrad and Pfaff 1976b; Troiano and Siegel 1978b; Haber et al., 1985; Carlsen et al., 1985; Mascagni and McDonald, 2009). Roughly 75% of VP neurons that project to the BLA are from cholinergic neurons that reside within the VP (Carlsen et al., 1985; Záborszky et al., 1986). Tracer injections in BLA and cortical regions demonstrate scant double-labeling (Záborszky et al., 1986), suggesting cholinergic neurons within the VP send individual, noncollateralized projections. Only 30% of cholinergic neurons that reside within the VP co-express VGluT3 mRNA; within the subset of these cholinergic neurons that also project to the BLA, nearly all (92%) express VGluT3 mRNA (Poulin et al., 2006). Intra-VP injections of *mu*, *kappa*, and *delta* opiate agonists significantly reduce acetylcholine turnover in the amygdala, suggesting that cholinergic neurons within the VP that project to the amygdala are regulated by opioid receptors (**Table 1**).

Some cholinergic neurons that reside within the VP directly innervate the cortical mantle (Rye et al., 1984; Jourdain et al., 1989), including frontal (Woolf et al., 1983), prefrontal (Funahashi 1983), medial prefrontal (Gritti et al., 1997, 1999 (Zaborszky et al., 2012; Zaborszky, unpublished observations), and the entorhinal (Manns et al., 2001) cortex.

Cortical excitability is regulated by local cholinergic receptors (Pirch et al., 1992; Hars et al., 1993) and pallidocortical projections that involve the cholinergic neurons that reside in the VP (Rigdon and Pirch, 1984; Pirch et al., 1985; Rigdon and Pirch, 1986). Intra-VP injections of NMDA increase Fos-like staining in the frontal cortex (Turner et al., 2008) and intra-VP injections of the GABA-A agonist, muscimol suppresses firing of cortical neurons (Rigdon and Pirch, 1984; Pirch et al., 1991). In contrast, cortically projecting cholinergic neurons within the VP are not regulated by intra-VP *kappa* or *delta* opiate agonists; *mu* activation does reduce acetylcholine turnover in the frontal cortex (but notably, this is not blocked by a *mu* antagonist) (**Table 1**). The lack of cortical regulation by at least *kappa* and *delta* opioid receptors in the VP differs from that obtained for VP influences on acetylcholine turnover in the amygdala (**Table 1**) suggesting that the two termination sites may be regulated by separate cholinergic systems emanating from within and around the VP. Collectively, these findings suggest that pallidocortical cholinergic neurons that reside within the VP express ionotropic glutamatergic and GABAergic receptors, and perhaps *mu* opioid receptors.

4.7 Projections to the brain stem

The VP sparsely projects to the PPTg and midbrain extrapyramidal area (Swanson et al. 1984; Haber et al., 1985; Grove 1988; Semba and Fibiger, 1992; Steininger et al., 1992; Tripathi et al., 2013; for review, see Heimer et al., 1997; though see Groenewegen et al., 1993). Albeit sparse, there is a topography in the PPTg projections, wherein axons arising from the VPvm and VPr, but not the VPdl, exhibit collaterals within PPTg (Tripathi et al., 2013). This input, combined with more robust inputs from other nearby regions (e.g., extended amygdala, preoptic-hypothalamic continuum) (Steininger et al. 1992; Semba and Fibiger, 1992) provide influence on PPTg function. The VP may also indirectly influence the PPTg, as the VPdl projects to the SN, and EPN, which in turn project to PPTg and midbrain extrapyramidal area (Haber et al. 1985; Steininger et al. 1992; Semba and Fibiger, 1992). Further examination is necessary to determine the differential extent of PPTg versus midbrain extrapyramidal targeting of VP neurons.

VP has sparse projections to the raphe nuclei (Conrad and Pfaff 1976b; Peyron et al., 1998) and locus coeruleus (Groenewegen et al., 1993), thereby potentially affecting serotonergic and noradrenergic neurotransmitter systems. Little is known regarding the subregional distribution (although it appears that the projection arises from the VPvm), physiology, receptors, or behavioral function of these VP projections. Recent studies have revleaed that VP neurons synapse onto dorsal raphe 5-HT neurons, and to a lesser extent, onto median raphe 5-HT neurons (Dorocic et al., 2014; Ogawa et al., 2014).

5.0. VP influences on behavior

A wealth of information is emerging regarding the roles of VP in behavior and in recent years, subregional dissection of these roles has begun. In the following sections, we overview VP-regulated behaviors, and propose functional roles for the two major VP subregions, VPvm and VPdl. The roles of VPr and VPvl require future investigation. In considering the role of a brain structure in behavior, it is important to be mindful that this may reflect a modulatory function of behaviors that are engendered by other structures or by the circuit in which the VP is embedded. It is also worth considering the possibility that the VP may serve as a generator of particular behaviors, which subsequently may or may not be modified by downstream structures. As such nuances largely remain unclear for the VP, here we attempt to provide an overview of known behavioral readouts that may involve the VP, regardless of the particular role that the VP has in the orchestration of a behavior *per se*.

Of the many methods that examined VP function, most utilized microinjection approaches. Due to the multitude of basal forebrain circuits and neuronal phenotypes, we suggest that future studies using microinjection methods include site injection controls (i.e., evaluating the effects of injecting test compounds into neighboring sites; e.g., Napier and Chrobak, 1992; Robertson and Jian 1995; Gong et al., 1999; Johnson and Napier, 2000; Chrobak and Napier, 2002; Zahm et al., 2014). In addition, our laboratories have found that high doses, large infusion volumes, and faster infusion rates have the potential to confound “inactivation” interpretations due to nonspecific effects in adjacent nuclei. Furthermore, vehicle treatments (saline or artificial cerebrospinal fluid) injected into VP even as slow as 0.1 μl/min for a total volume of only 0.25 μg are sufficient to produce a persistent deficits in radial arm maze performance (Chrobak and Napier, 2002). While motor (e.g., Johnson and Napier, 2000; Skoubis and Maidment, 2003) and place conditioning behaviors (e.g., Nikolaus et al., 1999; Skoubis and Maidment, 2003; Zarrindast et al., 2007) are not altered by intra-VP injections of a variety of treatment vehicles, the observation that radial arm maze performance deficits can occur suggests that at least some VP neurons are sensitive to fluid perturbation and/or that some behavioral readouts are more sensitive to such perturbations.

5.1. Motor behavior

The VP regulates a wide repertoire of motor behavior, including those that are not under conscious control (e.g., startle reflexes), those that are related to volitional actions, those reflecting learning and memory, and those motivated by reward. These point to the likelihood that VP subregions and neuronal subpopulations within them are relatively specialized for different behaviors, and that highly interactive circuits are involved.

Numerous transmitter systems, and interactions among these systems, are involved in VP-regulated motor function (**Table 2**). Examples include the following: Injections of the GABA-A receptor antagonists within VP results in sniffing, gnawing, tongue protrusion, and chewing behaviors in rats (Zahm et al., 2014) and cats (Cools et al., 1989; Spooren et al., 1989). A similar pattern of oro-facial dyskinesia-like behavior also occurs following intra-VP injections of dopaminergic agonists in cats (Spooren et al., 1991) and in rats (**Table 3**). Unilateral injection of the *mu* receptor agonist DAMGO (Hoffman et al., 1991; Napier, 1992a) or injections of the GABAergic agonist muscimol (Kitamura et al., 2001) engender dose-dependent contraversive circling behavior. Intra-VP dopamine also produces a robust activation of motor behavior, the magnitude of which is greater than that obtained with similar injections into the dorsal striatum (Napier and Chrobak, 1992). Intra-VP injections of D_1- or D_2 receptor antagonists (SCH23390 and sulpiride, respectively), block the locomotor effects of subsequent intra-VP injections of *mu* opioid receptor agonist, DAMGO (Napier, 1992), demonstrating an opioidergic and dopaminergic interaction within VP.

VP-regulated motor behavior is influenced by Acb projections. Evidence for the influence of Acb on VP-mediated locomotion includes the following: Intra-VP substance P, a neuropeptide released from Acb projections to VP, increases locomotion (Napier et al., 1995). Injection of the *mu* opioid receptor agonist DAMGO, a receptor activated by enkephalinergic projections from Acb neurons, or injection of GABA-A receptor antagonists increase locomotion (Austin and Kalivas, 1990; Napier 1992a) and simultaneous VP injection of the GABA-A agonist muscimol reduces this effect (Austin and Kalivas, 1990). Intra-Acb-DAMGO, dopamine, AMPA, amphetamine, kainic acid, NMDA, and picrotoxin induced locomotion is blocked by VP muscimol (Wallace and Uretsky, 1991; Churchill et al., 1998; Patel and Slater, 1988). VP lesions decrease locomotion induced by intra-Acb MK801 (a NMDA antagonist) (De Leonibus et al., 2001), though it is not clear why intra-Acb NMDA and MK801 both increase locomotion (see also Ikemoto and Bonci (2014) for a similar discrepancy between intra-Acb NMDA antagonists and optogenetic stimulation of Acb glutamatergic afferents with reward).

Transmitter systems within the VP that are not contained in Acb efferents are also capable of altering motor function. For example, the raphe provides serotonergic inputs to the VP (see section 3.4) and intra-VP injections of the 5-HT_{2C} agonist, MK212 suppresses motor activity (Graves et al., 2013) at doses (1 and 6.6 ng/0.5 μl) that are subthreshold to those needed to alter motor function when injected into the Acb (Filip and Cunningham, 2002). Glutamatergic inputs also arise from non-Acb structures and intra-VP injections of glutamatergic agonists enhance motor output (Churchill and Kalivas, 1999). Likewise, there is a direct dopaminergic input to the VP, and intra-VP injections of dopamine (Napier and Chrobak, 1992), and D_1 or D_2 agonists (Gong et al., 1999; Napier and Rehman, 1992) alter motor activity. Thus, while most VP inputs are from Acb, VP-mediated motor behavior appears to include non-Acb sources as well.

VP-mediated motor behavior involves the VPvm. Cools and colleagues (Kitamura et al., 2001; Uchida et al., 2005) proposed that AcbSh-mediated motor effects are transmitted through the VPvm. AcbSh injections of carbachol, a nonselective acetylcholine receptor agonist, or a combined dopamine D_1/D_2 receptor agonist, produce locomotor effects or repetitive jaw movements which are blocked by VP injection of muscimol (Kitamura et al., 2001). In turn, several regions that are targets of VPvm projections play a role in locomotion. Locomotion induced by intra-VP DAMGO or AMPA is blocked by intra-VTA baclofen administration (Johnson et al., 1996; Churchill et al., 1998), illustrating an extension of the results from Cools and colleagues wherein the locomotor effects of AcbSh stimulation at least partially involve a AcbSh–VPvm–VTA pathway. It is also possible that the AcbSh-VPvm-MD pathway influences locomotion, though mixed results have been reported. Whereas injection of DAMGO into MD produces locomotion (Klitenick and Kalivas, 1994), injection of the sodium channel blocker procaine into MD does not alter spontaneous locomotion (Mogenson et al., 1989; Churchill and Kalivas, 1999) or locomotion induced by VP picrotoxin (Mogenson and Wu, 1988) or VP AMPA (Churchill and Kalivas, 1993). However, intra-MD procaine (Churchill and Kalivas, 1993) or the GABA-B antagonist saclofen (Kalivas et al., 2001) can block locomotion induced by intra-VP DAMGO.

The projection targets of VPdl neurons are also implicated in locomotion. For example, STN and SNr, recipients of VPdl projections, strongly influence PPTg and midbrain extrapyramidal area (Saper and Loewy, 1982; Haber et al., 1985; Rye et al., 1987; Semba and Fibiger, 1992; Steininger et al., 1992), and procaine injections into the midbrain extrapyramidal area blocks locomotion induced by intra-VP AMPA or DAMGO (Churchill and Kalivas, 1999). These outcomes raise the possibility that some locomotor effects are elicited by VPdl-STN or VPdl-SNr pathways that affect midbrain extrapyramidal areas. Taken together, VP-mediated motor behavior likely involves both the VPvm and VPdl subregions.

5.2 Consummatory behaviors

We define consummatory behaviors as those directly involved in mastication, including natural reward consumption and taste reactivity (**Table 4**).

5.2.1 Consumption—Activation of GABA-A receptors in VP decreases food intake. For example, intra-VP injection of the GABA-A receptor agonist muscimol reduces consumption (Shimura et al., 2006; Taha et al., 2009) and conversely intra-VP injection of the GABA-A receptor antagonist bicuculline increases food intake (Stratford et al., 1999; Smith and Berridge, 2005; Inui et al., 2007). Interestingly, rats will selectively increase consumption of fat following intra-VP bicuculline injection, suggesting VP may play a strong role in fat intake (Covelo et al. 2014). Activation of opioid receptors in VP also increases consumption. Intra-VP DAMGO increases consumption (Smith and Berridge, 2005), and there may be a temporal component to this process as intra-VP DAMGO decreases consumption up to one hour following injection but increases consumption two hours following injection (Shimura et al., 2006). *Delta* antagonists injected in VP also increase consumption (Inui and Shimura, 2014).

The AcbSh is capable of influencing consummatory behavior through the VPvm as well as other output pathways, such as the projection to LH and nucleus tractus solitarius (Will et al., 2003; Stratford and Kelly, 1999; Stratford et al., 1997, 1999; Taha et al., 2009). For instance, on the one hand intra-VP muscimol blocks food intake induced by intra-AcbSh DAMGO (Taha et al., 2009). On the other hand, AcbSh injection of DAMGO is still capable of engendering consumption in VP-lesioned rats, suggesting that AcbSh and VP have common convergent projections can individually alter feeding (Taha et al., 2009). This convergent region likely does not involve the MD since lesions to this structure do not affect consumption (McAlonen et al., 1993). The most likely regions of convergence are the LH and VTA, to which both VPvm and AcbSh project (Haber et al., 1985, 2000; Zahm 1989; Kalivas et al., 1993; Groenewegen et al., 1993; Zahm et al., 1996; Sano and Yokoi, 2007) and are involved in consumption (Noel and Wise, 1993, 1995; Hamilton and Bozarth, 1988; Jenck et al., 1987; Mucha and Iverson, 1986; Segall and Margules, 1989; Kim et al., 2009; Echo et al., 2002; Khaimova et al., 2004; Stratford and Kelly, 1999; Will et al., 2003; Turenius et al., 2009; Stratford and Wirtshafter, 2012, 2013). Furthermore, disconnection of VTA and LH antagonizes consumption (Jenck et al., 1986) supporting the idea that both structures are components of AcbSh and VPvm consumption circuitry.

5.2.2 Cue-induced feeding—Cue-induced feeding involves the BLA, as lesions of this structure block the ability of a cue previously paired with meal interruption (Galarce et al., 2010), or food (Holland et al., 2002; Holland and Gallagher, 2003) to increase consumption. The BLA projection to AcbSh is critical for the expression of outcome specific Pavlovian Instrumental Transfer (PIT) (Shiflett and Balleine, 2010). This cue-induced feeding paradigm links Pavlovian cues associated with a specific food with responding on a lever that previously delivered that same food.

AcbSh, but not AcbC lesions, decrease outcome-specific PIT (Corbit et al., 2001). VP-projecting AcbSh neurons exhibit elevated fos-IR during PIT compared to lever pressing or conditioned stimulus controls (Leung and Balleine, 2013). Contralateral disconnection of AcbSh and VP blocks outcome specific PIT (Leung and Balleine, 2013). Given that AcbSh specifically projects to VPvm, it is likely that a BLA-AcbSh-VPvm circuit is critical for outcome specific PIT. Furthermore, it likely that the VPvm projection to MD plays a significant role in mediating this type of PIT (Balleine et al., 2014).

5.2.3 Taste reactivity and food preference—The VP is involved in regulating consumption and taste reactions in response to preferred foods. For instance, intra-VP bicuculline or SCH-23390 injections increased consumption of a preferred saccharine solution but had no effect on water or quinine (Shimura et al., 2006). Consistent with VP activity being associated with preferred tastants, Tindell and colleagues (2006) found that single VP neurons were sensitive to positive (“liking”), but not negative (“disliking”), orofacial taste reactions. An additional report by this group found increased firing rates in response to a conditioned stimulus that predicted salt infusion when under salt-deprived conditions (Tindell et al., 2009), demonstrating that VP neurons are also sensitive to cues related to hedonic taste reactions. Whether VP subregions exhibit differential changes in firing rate during hedonic facial reactions or cues is not known. However, a rostral-caudal gradient in hedonic taste reactivity induced by AcbSh and VP DAMGO injections has been observed (Smith and Berridge, 2005, 2007). A portion of the caudal, sublenticular parts of VP that have been interpreted as a transition zone involving the lateral preoptic area and extended amygdala (Zahm et al., 2013), has been referred as a “hedonic hotspot” (Smith and Berridge, 2005, 2007).

The VP appears capable of regulating negative taste reactions as well. Extracellular VP GABA concentrations are increased following presentation of a saccharine cue that predicts nausea, but not when a saccharine cue predicts saline, or when a quinine cue predicts nausea or saline (Inui et al., 2009). Thus, these scientists hypothesized that VP GABA is involved in mediating perceived shifts from palatability to predicted illness. In support of this interpretation, intra-VP muscimol increases negative taste reactivity in response to saccharine, which normally induces positive taste reactions (Shimura et al., 2006). Conversely, in rats that have learned that a saccharine cue predicts nausea, bicuculline injection in VP prior to sampling the cue results in increased positive taste responses and lower aversive taste responses (Inui et al., 2007; see Yamamoto, 2007 for review). Given that intra-BLA glutamate enhances conditioned taste aversion (Ferreira et al., 2005) and BLA lesions disrupt taste aversion learning (Borsini and Rolls, 1984; Rollins et al., 2001), a BLA-AcbSh-VPvm pathway could potentially mediate some aspects of taste reactivity, such as palatability and learning.

VPdl may be involved in the self-administration of preferred foods, though VPdl has received less attention than VPvm. Intra-VP muscimol decreases the effort emitted by rats for a preferred food while not altering the response-capacity or the original food preferences of the animal (Farrar et al., 2008). This effect may be due to the AcbC influence on the VPdl because disconnection of unilateral AcbC and contralateral VP impaired performance when access to food required ten responses but not when food access required one response (Mingote et al., 2008). However, the VPdl was not explicitly disconnected alone in this experiment, and the influence of the AcbSh and VPvm on food preference performance was not examined.

5.3. Maternal behavior

The integrity of the VTA is critical for maternal behavior (Numan and Smith, 1984; Numan et al., 2009) and dopaminergic VTA projections to AcbSh are involved in a circuit related to these behaviors. AcbSh dopamine concentrations increase prior to the onse of maternal behavior (pup licking/grooming) and the magnitude and duration of these behaviors significantly correlates with extracellular AcbSh dopamine concentrations (Champagne et al., 2004). Intra-AcbSh of D_1 antagonists, but not intra-VP injections, decrease pup retrievals even though rats increase the number of “hovers” over the pups (Numan et al., 2005a). Increasing GABAergic tone by injections of muscimol within VP, but not AcbSh, decreases pup retrievals, increases the latency to sniff pups, and decreases nursing duration of dams (Numan et al., 2005b). It is likely that maternal behavior involves a VTA dopamine – AcbSh GABA – VP pathway (**Table 5**).

Preoptic circuits also interact with the VP to regulate maternal behavior. Disconnection of the VP (via unilateral injections of muscimol) and medial preoptic area (via contralateral lesions), a region that is highly responsive to maternity-related hormones and cues (see Numan and Stolzenberg, 2009 for review), reduces pup retrievals and nursing duration (Numan et al., 2005b). Maternal behavior that involves the medial preoptic area and VP likely engage the VTA because both medial preoptic area and VPvm project to VTA (Geisler and Zahm, 2005) and unilateral medial preoptic lesions coupled with contralateral VTA lesions disrupt maternal behavior (Numan et al., 2009). These outcomes led Numan and colleagues (Numan, 2006; Numan and Stolzenberg, 2009) to hypothesize that pup-related stimuli and hormonal information converge within the medial preoptic area, which projects to the VTA and increases dopamine within AcbSh. In turn, AcbSh reduces its GABAergic influence on the VP to elicit maternal responsiveness. It is inferred that the VPvm, which receives AcbSh projections, is highly involved in maternal behavior.

5.4 Behaviors related to cognition

5.4.1. Sensorimotor Gating—Sensorimotor gating refers to the suppression of sensory, motor, or cognitive events that may interfere with focused attention and sequential information processing. The acoustic startle reflex induced by an unexpected loud sound can be greatly reduced if preceded by a weak auditory warning sound (referred to as prepulse inhibition). Thus, prepulse inhibition (PPI) of an acoustic startle is used as an operational measure of sensorimotor gating and a reduction in PPI is associated with deficits in focus, motivation and cognition.

PPI of the startle reflex is *mediated* at or below the pons, and the reflex *regulated* by ascending dopaminergic projections and descending corticostriatopallidal systems. Accordingly, intra-VP injections of GABA-A antagonists disrupt PPI in rats (Swerdlow et al., 1990; Kodsi and Swerdlow, 1995a,b). Other transmitter systems converge on this descending system at the level of the VP to modulate PPI, e.g., intra-VP injections of the 5-HT_{2A} agonist, DOI, disrupts PPI (Sipes and Geyer, 1997) (**Table 5**).

The AcbSh, VP, and MD play a role in PPI (Swerdlow et al., 1990; Kodsi and Swerdlow, 1995a,b;1997), suggesting the involvement of a serial AcbSh-VPvm-MD pathway. Another pathway, involving the VPvm or VPr neurons that project to the PPTg (Tripathi et al., 2013), may potentially play a role in PPI because lesions of, or muscimol injections into the PPTg reduce PPI (Kodsi and Swerdlow, 1997). STN lesions do not alter PPI (Kodsi and Swerdlow, 1997), and PPI is more sensitive to intra-VP injections of the GABA-A antagonist picrotoxin within more medially-centered sites compared with more laterally-centered sites (Kodsi and Swerdlow, 1995a). Given that the VPdl is the location of STN-projecting VP neurons, the VPdl-STN pathway is unlikely to participate in PPI.

5.4.2 Working memory and associative learning—Task performance involving working memory can be disrupted by manipulations of Acb, VP, mPFC, and orbitofrontal cortex (**Table 5**; Ferry et al., 2000). Lidocaine injections into either the Acb or the VP immediately prior to testing in radial arm maze tasks significantly increases performance errors (injections during training have no effect; Seamans and Phillips, 1994; Floresco et al., 1999). Intra-VP DAMGO or AMPA impairs working memory, which is reduced by MD GABA blockade (Kalivas et al., 2001); therefore, an Acb-VPvm-MD-cortical pathway maybe necessary for optimal performance in working memory tasks. However, it is important to note that intra-VP vehicle injections can disrupt working memory performance (Chrobak and Napier, 2002); therefore, appropriate controls need to be rigorously applied to these studies. VP involvement in cognitive function can also be inferred by studies of structures that input the VP. For example, the STN is involved in mnemonic processes (Baunez et al., 2011), and it will be of great interest for future evaluations to ascertain the role of the STN-VP-STN circuit, and in particular the VPdl-STN pathway, in cognitive function.

Early assessments of cortically evoked electrophysiological events related to reinforcement-mediated learning implicated a role for the VP in associative learning processes. Using scalp electroencephalographic (EEG) recordings of human frontal cortical regions, Walter and colleagues (1964) discovered that a long (1 to 2 sec) descending potential developed as an association was made between a conditioned stimulus (CS+) and a conditioned response or reinforcer. Early studies described this evoked EEG event as a ‘contingent negative variation’ (CNV) (Walter et al., 1964). CNV occurs in the time between the CS+ and the response, develops with learning of an operant task, and declines with extinction (Walter et al., 1964). The development of the CNV is thought to reflect learning and its magnitude provides a reliable means to ascertain the degree of association or the salience of a stimulus that was previously paired with a reinforcer. Pirch and Barnes (1972) described a negative slow (or steady) potential (SP) recorded from *rat* cortex during the 1-2 sec interval between a CS+ and the delivery of a reward. Similar to the human CNV, shifts in rat SP reflects learning of the association between the CS+ and a reward, and the SP also shows extinction upon removal of the reward. These SP characteristics are independent of the CS modality (tone, light or subthreshold brain stimulation) and type of reinforcer (food, rewarding brain stimulations, footshock) (Rucker et al., 1986; Pirch, 1993), and clearly involve dopaminergic transmission (Pirch et al., 1981; Pirch, Napier and Corbus, 1981; Pirch and Corbus, 1983). The SPs correlate with event-related changes in single neuron firing in both the frontal cortex (Pirch and Peterson, 1981; Pirch et al., 1985) as well as in the VP (Rigdon and Pirch, 1986; note: only a caudal portion of VP was tested, which was termed the substantia innominata in this report). Event-related cortical SPs and single unit responses are regulated by cortical cholinergic receptors (Pirch et al., 1992; Hars et al., 1993), and their development is largely dependent upon intact projections from the basal forebrain cholinergic neurons, including those that reside in the VP (Rigdon and Pirch, 1984; Pirch et al., 1985; Rigdon and Pirch, 1986). Moreover, intra-VP microinjection of the GABA-A agonist, muscimol produces a profound suppression of cortical unit responses to conditioned stimuli (Rigdon and Pirch, 1984; Pirch et al., 1991) whereas basal forebrain stimulation (Hars et al., 1993) and microiontophoretic application of acetylcholine onto the cortical neurons (Pirch et al., 1991) enhances conditioned stimulus-evoked responses in the cortex. These historical studies help explain more recent work showing that cholinergic transmission in the frontal cortex is critical for the development of cue detection (see Parikh et al., 2007). The operational requirements for an organism to link cues with important stimuli and to translate significant stimuli into appropriate motor responding are critical for survival. It appears that the VP, including cholinergic corticopetal neurons that reside within this region, are neuroanatomical substrates that influence these functions.

5.5. VP supports brain self-stimulation behavior

Historically, one of the first approaches towards examining brain reward mechanisms involved studies using the intracranial self-stimulation procedure in which animals will respond on a lever to self-deliver an electrical stimulus directly to specific parts of their brains (Olds and Milner, 1954). It has been reported that the entire VP supports self-stimulation at low frequency thresholds (Panagis et al., 1995; Burgdorf et al., 2007) and this behavior induces c-fos-IR in medial prefrontal cortex, Acb, lateral hypothalamus, and VTA (Panagis et al., 1997). Dopamine appears to be involved in VP self-stimulation because systemic cocaine or 7-OH-DPAT (a D_2/D_3 agonist) decreases threshold frequencies, whereas haloperidol, raclopride, and sulpiride (D_2 antagonists) or SCH23390 (a D_1 antagonist) increases threshold frequencies to maintain VP self-stimulation (**Table 5**; Panagis and Spyraki, 1996). Furthermore, intra-VTA muscimol or baclofen increase (Panagis and Kastellakis, 2002) and morphine decrease (Panagis et al., 1998) VP frequency thresholds, suggesting that the VP projection to VTA, which arises predominantly from the VPvm, participates in brain stimulation reward.

AcbSh 6-OHDA-induced lesions have no effect on VP self-stimulation thresholds while VP lesions or intra-VP lidocaine injections decrease medial forebrain bundle self-stimulation (Huston et al., 1987; Waraczynski and Demco, 2006) without affecting the locus of rise or threshold (Johnson and Stellar, 1994a,b; Waraczynski and Demco, 2006). These data indicate that the VP–VTA pathway, which is downstream from the AcbSh, is sufficient to support self-stimulation behavior. Anterior-posterior VP differences exist in mediating self-stimulation behavior. Caudal VP injections of DAMGO increase self-stimulation of the LH while more rostral VP injections decrease hypothalamic self-stimulation (Johnson et al., 1993). However, because the ascending and descending fibers of the medial forebrain bundle pass through the VPvl, actions of locally administered drugs or electrical stimulation could be confused with VP cellular actions.

5.6 Aversion

VP has a role in mediating the effects of aversive stimuli as well as predicting aversive outcomes (**Table 5**): Intra-VP injections of naloxone or the *mu* opioid antagonist CTOP is sufficient for the formation of a conditioned place aversion (Skoubis and Maidment, 2003). In rats that developed anxiety and despair-like behavior, intra-VP glutamate antagonists restore reduced VTA dopamine neuron activity to levels observed in nondepressed rats, perhaps through a BLA-VP-VTA circuit (Chang and Grace, 2014). Complex stereotyped behaviors such as “defensive” forepaw treading are induced by DAMGO or bicuculline injections throughout the VP, even though these drugs can also increase “liking” orofacial reactions and consumption within the posterior regions of VP (Smith et al., 2005). D1 receptor agonists injected in VP enhance inhibitory avoidance learning (Peczely et al. 2014).

The RMTg is critical for aversive processing and this region is linked with the VP through a VPvm – lateral habenula – RMTg pathway (Zahm et al., 1996; Jhou et al., 2009a; Goncalves et al., 2012). In rats and primates, RMTg and lateral habenula neurons decrease firing in response to reward-related cues but increase firing following reward omission (Matsumoto and Hikosaka, 2007; Jhou et al., 2009b; Hong and Hikosaka, 2008). The decreased firing of midbrain dopaminergic neurons that follow unexpected negative events (reward omission), is mediated by the lateral habenula – RMTg – midbrain dopamine serial pathway (Hong et al. 2011). Whether and how the VP plays a role in reward-prediction through its connections with lateral habenula, VTA, and/or RMTg is largely unexplored (Hong and Hikosaka, 2013). Primate VP neurons were not found to exhibit reward-prediction error signals (Tachibana and Hikosaka, 2012). Nevertheless, the circuits of the VPvm suggest complex manipulation of VTA neurons. In one examination (section 6.2.2), a small population of rat VP neurons were observed to exhibit differential firing patterns following cocaine reward versus no cocaine reward, suggesting some neurons may distinguish reward receipt from errors (Root et al., 2013).

6.0. Drugs of abuse; Influences on VP function and behavior

Neuroscience has come to view drug and alcohol addiction as a chronically relapsing disorder with an impaired ability to inhibit drug-seeking behavior (Kalivas, 2009; Koob and Volkow, 2010). This impairment could arise, in part, from alterations in VP function. It is therefore expected that if abused drugs act within the VP, there may be changes in motivated behavior as well as the processing of cue salience and/or mnemonic events. To discuss these possibilities, this section will overview the effects that abused drugs have on VP function as well as the subregionally-specific consequences that these alterations have on behaviors associated with substance use disorders.

6.1. VP consequences of exposure to abused drugs

6.1.1 Cocaine

6.1.1.1 Sensitivity: Individual VP neurons are comparatively more sensitive to intravenously injected cocaine than Acb or VTA neurons (Johnson and Napier, 1996; Henry and White, 1992; White, 1990). Based on this observation, Johnson and Napier (1996) posed that the behavioral consequences of low dose cocaine may largely reflect VP function, a concept that will be further explored in the below discussions. Consistent with this possibility, pharmacological inactivation of the Acb does not alter the number of VP neurons that respond to intravenous cocaine, nor change the capacity of cocaine to inhibit VP firing; however, excitatory VP effects of cocaine were enhanced with Acb inactivation (Johnson and Napier, 1996). This latter outcome may reflect a disinhibitory effect, as cocaine can reduce AcbC to VP GABA transmission (Torregrossa et al., 2008). Thus, while VP neuronal responding to systemic cocaine can be independent of the Acb, the Acb can regulate the magnitude of some VP cocaine-mediated firing patterns. To explore this interpretation, and the VP integration of other inputs, the Napier laboratory evaluated whether cocaine can modulate the effects of glutamate and GABA on VP firing. This was accomplished by using local (microiontophoretic) applications of cocaine in anesthetized rats wherein cocaine ejections that were too low to alter spontaneous firing were sufficient to modulate the excitatory effects of glutamate in 85% of the neurons tested, and the inhibitory effects of GABA in 50% of the neurons tested. These actions of cocaine mirror the ability of microiontophoretically applied dopamine to modulate VP glutamate and GABA (Johnson and Napier, 1997). Thus, the high sensitivity of VP neurons to cocaine likely relates to the ability of cocaine to elevate VP dopamine (overviewed below), and thus activate VP dopamine receptors, as well as to modulate GABA and glutamate transmission at the level of VP neurons.

The sensitivity of VP neurons to cocaine may provide a neurophysiological substrate for maintaining psychostimulant self-administration. Intravenous cocaine alters the firing rate in over 80% of VP neurons tested (Johnson and Napier, 1996). During cocaine self-administration, most VP neurons exhibit a ‘progressive reversal’ slow phasic firing pattern which consists of a post-cocaine change in firing rate followed by a reversal of this change as the drug level decays over time (Root et al., 2012). In the Acb, the slow phasic progressive reversal firing pattern is correlated with the time between cocaine infusions (Peoples and West, 1996), is independent of locomotion (Peoples et al., 1998), and in both the Acb and VP, is highly correlated with cocaine concentrations that wax and wane over several hours of a self-administration binge (Nicola and Deadwyler, 2000; Root et al., 2012). Given that drug level is the prepotent stimulus regulating psychostimulant self-administration (Norman and Tsibulsky, 2006; Pickens and Thompson, 1968; Root et al., 2011), West and colleagues proposed that the slow phasic progressive reversal pattern within the Acb (Peoples and West, 1996) and VP (Root et al., 2012) constitutes a mechanism that transduces fluctuating cocaine levels into neural signals that influence continued drug self-administration.

Significant numbers of VP neurons that project to VTA exhibit c-fos-IR in response to self-administration of cocaine (Geisler et al., 2008), and because the VPvm is the primary VP nucleus projecting to VTA, a VPvm-VTA pathway may be involved in maintaining cocaine self-administration. The region medial to VP, the lateral preoptic area (LPO), is also sensitive to fluctuating self-administered cocaine-levels. In fact, this preoptic area is comparatively more sensitive to fluctuating cocaine-levels during the maintenance phase of cocaine self-administration than VP (Barker et al., 2014). Similar to VP, the LPO receives input from Acb and projects to VTA (Usuda et al., 1998; Kowski et al., 2008), and therefore the LPO likely contributes to maintaining cocaine self-administration behavior (Barker et al., 2014a). Further research will be necessary to determine the unique contributions of VP and LPO towards the maintenance of cocaine self-administration. In both cases, because positive and negative emotional states also correlate with rising and falling self-administered cocaine levels (Barker et al., 2010, 2014b), it will also be interesting to determine if affective state can be discerned from VP or LPO firing patterns during self-administration.

6.1.1.2 Neurochemistry and adaptation: Cocaine dose-dependently increases extracellular dopamine concentrations in VP following non-contingent systemic (Gong et al., 1997a) and local (Gong et al., 1997a, 1998) administration. Extracellular concentrations of dopamine and 5-HT are also increased in VP during cocaine self-administration (Sizemore et al., 2001). The capacity of cocaine to alter VP neurotransmission appears to reflect aspects of motivation, as different changes in dopamine and glutamate turnover were observed following 30 days of cocaine self-administration but not after yoked exposure alone (Smith et al., 2003). Cocaine experience also alters basal glutamate and GABA extracellular concentrations in the VP during abstinence (Wydra et al. 2013). These outcomes may reflect adaptations that are related to the protracted cocaine treatment. Studies by Napier, Chafer and Shippenberg (Napier et al., 2001) of rats taken three days after five once daily injections of 20 mg/kg cocaine indicated a decrease in basal uptake and release with no change in dopamine levels in the VP. These latter studies also revealed that increases in VP dopamine caused by an acute challenge of cocaine are reduced in cocaine-experienced rats. These outcomes add to the emerging evidence (as further discussed below) of the dose, treatment duration and context of the cocaine experience all may influence the maladaptive nature of transmitter turnover within the VP.

Chronic exposure to cocaine results in a complex set of neuronal adaptations within the VP. Basal/spontaneous firing rates (in anesthetized rats) are reduced by >30% three days after five once-daily (non-contingent) injections of 15 mg/kg cocaine (a treatment protocol that induces behavioral sensitization; McDaid et al., 2005). This cocaine treatment protocol also reduces the ability of exogenously applied GABA to inhibit firing and promotes the ability of glutamate to increase firing (McDaid et al., 2005). These cocaine-mediated adaptations likely involve VP dopamine because the behaviorally sensitizing protocol for cocaine treatment enhances the ability of dopamine and the D_1 receptor agonist SKF38393 to alter VP neuronal activity (**Table 6**) as well as the ability of dopamine to modulate amino acid transmission in the VP (Johnson and Napier, 1997). These observations suggest that after the development of cocaine sensitization, VP neurons become hyper-responsive to the rate-altering effects of dopamine and amino acid transmitters contained in VP afferents. Thus, chronic cocaine results in a reduced ability of GABAergic inputs to blunt an enhanced glutamatergic drive, and given that these effects are superimposed on a reduced background firing, the summated consequences would serve to promote glutamatergic and dopaminergic influences on VP function. The role of D_1 receptors in these adaptations may be particularly relevant, as receptors in the D_2 family are not altered by even robust chronic cocaine treatments (20 mg/kg/day for 14 days; Stanwood et al., 2000).

The complexities of adaptations involving VP afferents are also observed after cocaine self-administration (Kupchik et al., 2014). A tonic reduction in GABA transmission is associated with elevated VP enkephalin levels, likely reflecting the reduced ability of VP *mu* receptor activation to presynaptically inhibit GABA release and *mu* receptor dependent long-term depression of GABA transmission is eliminated. Given that many Acb efferents to VP are GABAergic and enkephalinergic, these results suggest that this Acb neuronal subtype is altered by a history of cocaine self-administration.

6.1.2 Amphetamine, methamphetamine, and 3,4-methylenedioxy-methamphetamine (MDMA)—*In vivo* studies illustrate that VP neurons are readily engaged by low doses of amphetamines. VP neurons exhibit dose-related changes in firing to intravenously administered methamphetamine, with an ED_{50} of about 0.6 mg/kg (McDaid et al., 2007; Napier and Istre, 2008). A single 5 mg/kg intraperitoneal injection of amphetamine activates Fos in numerous VP neurons, many of which project to the VTA (Colussi-Mas et al., 2007).

Changes in VP are observed following repeated administration of abused amphetamines. With five, once-daily subcutaneous (non-contingent) injections of 2.5 mg/kg methamphetamine, the maximal excitatory effect (Emax) of acute methamphetamine is enhanced by 150% following three days of abstinence (Napier and Istre, 2008), whereas after 30 days, Emax is reduced to half of that obtained from methamphetamine-naïve rats (McDaid et al., 2007). Moderate doses of MDMA (5 and 10 mg/kg) produce a dose-related increase the number of Fos-immunoreactive neurons in the VP, and the MDMA-induced effect is enhanced two days after five days of repeated injections (Colussi-Mas and Schenk, 2008). We interpret these effects as VP neurons adapting to repeated exposure of amphetamines, the nature of which reflects the dosing protocol and the post-treatment withdrawal time. This interpretation also follows changes in VP signal transduction/gene transcription that are associated with chronic exposure to psychostimulants. For example, protein levels of the activated (phosphorylated) cAMP response element binding protein (pCREB; a constitutively expressed transcriptional regulator) are decreased in the Acb and the VP fourteen days after five once-daily injections of methamphetamine, a treatment/time paradigm that produces motor sensitization (McDaid et al., 2006). This finding is consistent with reports that increased Acb pCREB/CREB is associated with reductions in cocaine-induced motor sensitization (Sakai et al., 2002) and reward-motivated behaviors (Carlezon et al., 1998). Basal ΔFosB (a long-lasting transcription factor) is elevated in the Acb and VP following three days of abstinence from repeated methamphetamine (McDaid et al., 2006), consistent with ability of overexpression of ΔFosB in the Acb to enhance cocaine-induced motor behavior (Kelz et al.,1999). However, only in the VP did ΔFosB levels remain elevated following fourteen days of abstinence, which correlated with persistent methamphetamine-induced motor sensitization (McDaid et al., 2006). Amphetamine-induced CPP also is associated with c-Fos activity in the VP, AcbSh, and AcbC, as well as synaptogenesis in the VP and AcbSh (but not AcbC) (Rademacher et al., 2006).

Amphetamine-induced changes in monoaminergic systems are not widely studied for the VP. Three days after five once-daily injections of 2.5 mg/kg methamphetamine in rats, 5-$HT_{2A/2C}$ receptors are functionally upregulated in the VP (Napier and Istre, 2008). The effects of amphetamines on VP glutamate and GABA systems have only involved indices of receptor trafficking. For instance, a single low dose (1 mg/kg) of methamphetamine does not alter surface expression dynamics of AMPA or mGluR5 receptors in the VP (Herrold et al., 2013), nor is surface expression of mGlu5 or GABA-B receptors changed five days after three every other day treatments of 1 mg/kg methamphetamine, even though methamphetamine-induced CPP was observed (Herrold et al., 2011). However, the portion of mGluR5 receptors trafficked to the cell surface is enhanced fourteen days after three once-daily injection of 1 mg/kg methamphetamine, which is a time frame when methamphetamine induces expression of an mGluR5-dependent motor sensitization (Herrold et al., 2013).

Chronic exposure to amphetamines also alters VP processing of natural rewards and their predictors. VP neurons in animals sensitized to, or under the influence of amphetamine exhibit larger changes in firing rate following reward proximal cues, as well as following natural reward presentation, compared with nonsensitized animals (Tindell et al., 2005).

6.1.3 Alcohol—In alcohol-preferring rats, extracellular dopamine concentrations are increased during anticipation, self-administration, and following self-administration of ethanol, but not during similar periods for water or sucrose (Melendez et al., 2004). The enhanced dopamine concentrations likely reflects activity of the VTA because VTA dopamine neurons projecting to the VP are stimulated by local administration of ethanol, which is mediated at least in part by 5-HT_3 receptor subtypes (Ding et al., 2011). The VP input may arise from more caudal parts of the VTA as injection of dopamine receptor antagonists into VP disrupts intracranial ethanol self-administration within the posterior VTA. Inhibiting VP D_2 receptors significantly increases ethanol intake in alcohol-preferring rats (Melendez et al., 2005), suggesting that activating D_2 receptors in the VP limits ethanol intake.

VP GABA and opioids are capable of bidirectionally controlling ethanol consumption. GABA-A or GABA-B receptor agonists decrease ethanol intake whereas the GABA-A antagonist bicuculline increases ethanol consumption (Kemppainen et al., 2012a). Of the GABA-A receptors within the VP, the GABA-A1 isoform clearly plays a role in regulating ethanol self-administration (Harvey et al., 2002; June et al., 2003). Intra-VP injection of the *mu* opioid agonists DAMGO or morphine dose-dependently decreases ethanol intake and conversely, blocking *mu* receptors with CTOP increases ethanol intake (Kemppainen et al., 2012b). Simultaneous VP administration of DAMGO and bicuculline blocks induced ethanol intake (Kemppainen et al., 2012a).

6.1.4 Opioids—Repeated VP injections of *mu* opioid agonists DAMGO or morphine are sufficient to induce behavioral sensitization (Zarrindast et al., 2007; Mickiewicz et al., 2009; Rokosik et al., 2013), revealing that activation of *mu* opioid receptors is sufficient for the induction of the behavior. Showing that these receptors are also necessary, behavioral sensitization induced by repeated systemic injections of morphine is blocked by intra-VP injections of the *mu* opioid antagonist CTOP (Johnson and Napier, 2000; Mickiewicz et al., 2008). Moreover, VP ionotropic glutamatergic receptors are necessary for the maintenance of behavioral sensitization previously induced by systemic injections of morphine, as maintenance is blocked by VP injections of the glutamate antagonists, CNQX and AP-5 (Dallimore et al., 2006). Glutamatergic adaptations to chronic exposure to opiates include an increase in VP mGlu5 receptor surface expression (Herrold et al., 2013). VP GABA is another critical contributor to the behavioral effects of chronic opioids. Self-administration of heroin decreases extracellular GABA concentrations in the VP (Caillé and Parsons 2004), and elevated extracellular VP GABA concentrations decrease heroin self-administration (Xi and Stein, 2000).

6.1.5 Stimulant interactions with opioids at the level of the VP—As many abused drugs alter the function of VP, part of the maladaptations that occur with chronic exposure to one abused drug may influence the function of another. For example, opioid receptor expression is increased within VP as a consequence of chronic cocaine exposure (Hammer, 1989) and the capacity of morphine to alter VP neuronal activity is enhanced in cocaine-sensitized rats (McDaid et al., 2005). Likewise, in post-mortem cocaine users, VP dynorphin concentration is increased by over 300% from controls (Frankel et al., 2008).

6.2 Self-administration

6.2.1 Circuits—VP is part of several circuits that are necessary for drug self-administration (**Table 7**; **Figure 7**). In addition to the VP, regions included in these these circuits are the ventral tegmental area, medial prefrontal cortex, AcbC and AcbSh, VP, BLA, and MD (McGregor and Roberts, 1993, 1995; Weissenborn et al., 1997, 1998; Fabbricatore et al., 2010; Di Ciano 2008; Bari and Pierce, 2005; Di Ciano and Everitt 2004; You et al., 2007; Xi and Stein, 2002; Roberts and Koob, 1982; Kantak et al., 2002; Yun and Fields, 2003; Carelli et al., 2003; Roberts et al., 1980; Pettit et al., 1984; Schenk et al., 1991; Sun and Rebec, 2005; Hubner and Koob, 1990; Li et al. 2009; Goeders and Smith, 1983). The VPvm is positioned to affect most of the above brain regions but VPdl is also highly likely to play key roles in drug self-administration.

VPdl and VPvl are positioned to affect the nigrostriatal system (**Figure 7**). Dopaminergic antagonism of the substantia nigra (SN) (Quinlan et al., 2004) or dorsolateral striatum (Vanderschuren et al., 2005; Belin and Everitt, 2008) reduces cocaine self-administration suggesting the dopaminergic projection SN to dorsolateral striatum is involved in this behavior. Given that the VPvl projects to SNc, this VP subregion may play a role in modulating the nigrostriatal involvement in cocaine self-administration. STN lesions alter cocaine self-administration behavior, including cocaine breakpoints (Baunez et al., 2005; Uslaner et al., 2009; Rouaud et al., 2010). Both the AcbC and VPdl project to STN, suggesting the AcbC-STN and VPdl-STN pathways may also manipulate nigrostriatal involvement in cocaine self-administration.

6.2.2. Associations between VP neuronal activity and drug-motivated behaviors

6.2.2.1 Behavior-related firing patterns: Subsets of VP neurons exhibit “rapid phasic” changes in firing rate surrounding cocaine-reinforced responses (Root et al., 2010), supporting a VP involvement in drug-seeking behavior. Root and colleagues (2013) extended their initial investigation of VP firing patterns by investigating 1) what behaviors VP neurons are sensitive to during cocaine self-administration and 2) whether differences exist in the changes in firing rate between neurons of the VPdl and VPvm subregions, as delineated by substance P-IR, calbindin d28k-IR, and neurotensin-IR. A number of critical insights were made into VP subregional function.

Of responsive VP neurons, changes in firing rate occurred when animals were approaching to obtain cocaine, responding to acquire cocaine, retreating away after responding, or any combination of these behaviors (Root et al., 2013; **Figure 8**). Similar VP firing patterns were observed between the initial investigation using a lever-press response requirement, and a subsequent investigation using a vertical head movement response requirement, suggesting VP neurons acquire responsivity to drug-seeking behaviors, despite different motor demands to acquire cocaine. Ventral striatopallidal processing has been hypothesized to involve the “initiation” of actions (Mogenson et al., 1980) and if so, firing patterns might be expected to precede the onset of approaching to obtain cocaine. However, it was identified that VP firing patterns were coincident with approach, response, and retreat behaviors (**Figure 8A,B**), and did not occur preceding the onset of approach. Moreover, VP behavioral firing patterns during cocaine self-administration differed according to the particular subregion in which the VP neuron was recorded from. Root and colleagues (2013) interpreted these results as neurons within discrete VP subregions playing different roles in the process of self-administering cocaine.

6.2.2.2 Differential roles of VP subregions: VPdl neurons exhibit significantly greater changes in firing rate than VPvm neurons during the drug-seeking approach as well as during the drug-taking response. When single VPdl neurons change in firing rate during the approach, these changes were highly likely to continue in the same direction (increase or decrease from baseline), with similar or greater magnitude through the response (**Figure 8C-F**). The stronger, sustained firing rate changes of VPdl neurons during approach and response implicate VPdl in the processing of drug-seeking and drug-taking as a singular behavior. A significant population of VPdl neurons continues to change its firing rate through the entire sequence of acquiring cocaine, approach-response-retreat (**Figure 8G**). In other words, VPdl sends a signal related to pursuing cocaine and the reaction to obtain cocaine.

The pursue and react signals of VPdl neurons are similar to proposed function of AcbC neurons in biasing an organism to “go to it” (the reward) (Floresco, 2014). VPdl neurons exhibit a greater change in firing rate during the approach and response for cocaine than VPvm neurons, and likewise, AcbC neurons exhibit a greater change in firing rate than medial AcbSh neurons during the same behaviors (Ghitza et al., 2004; Hollander and Carelli, 2005; Fabbricatore et al., 2010). Furthermore, during the response, AcbC neurons are significantly more excited than AcbSh neurons (Ghitza et al., 2004) and VPdl neurons are significantly more inhibited than VPvm neurons (Root et al., 2013), suggesting that excited AcbC neurons inhibit VPdl neurons during the response for cocaine (**Figure 7**). Inhibition of VPdl neurons is likely to disinhibit the VPdl targets STN and SNr during drug-taking movements. Putative GABA neurons recorded in the medial SNr, a termination site of VPdl (Zahm 1989; Zahm et al., 1996), exhibit robust changes in firing rate during responses (Fan et al., 2012). Taken together, the AcbC-VPdl circuit is an important regulator of drug seeking and taking behaviors, possibly through the SNr (**Figure 7**; further discussed in Section 6.3.2).

VPvm neurons are typically heterogeneous with respect to behavioral firing patterns and firing direction (increase or decrease from baseline). VPvm neurons have a significantly weaker approach-response firing change relationship than VPdl neurons (**Figure 8C**). However, VPvm exhibits some behavior-related firing patterns significantly more often than VPdl. These firing patterns occur during retreat alone and response-retreat (**Figure 8E**). Firing patterns involving the retreat may reflect processing of the outcome of responding, which likely is a function of the part of VP that receives inputs from AcbSh (e.g., the VPvm; Leung and Balleine, 2013). An outcome-processing component of the VPvm may reflect the proposed function of AcbSh neurons in biasing an organism to “stay on task” (Floresco, 2014).

The heterogeneous firing patterns of VPvm neurons implicates VPvm in facilitating its targets (e.g., mesocortical structures) with information related to the sequence of individual behaviors (approach, response, retreat), and consequences of actions (retreat, response-retreat) involved in predicting the attainment of cocaine. This is supported by the finding that approach or response-related firing patterns within the mPFC typically occur *after* approach or response-related firing patterns occur within the Acb (Chang et al., 2002). Our results together with those of Chang and colleagues suggest that mPFC behavioral firing patterns are facilitated by VPvm-MD-mPFC or VPvm-VTA-mPFC circuits (**Figure 7**). This may facilitate prefrontal processing of response-outcome relationships in order to guide future behavior. In conclusion, the VPvm and VPdl subregions appear to process distinct aspects of cocaine self-administration. Processing within both VP subregions is likely necessary to produce coherent self-administration behavior, with the VPvm signaling the conditions involved in attaining cocaine and the VPdl involved in the actions that obtain cocaine.

6.3. Drug-seeking behaviors

6.3.1 Cue reactivity—VP participates in the conditioning of stimulus-drug associations. CPP is formed following intra-VP dopamine, cocaine, or amphetamine injections (Gong et al., 1996; though see Ikemoto 2003). Several transmitters are important for this process. Cocaine-induced CPP can be attenuated by VP *mu* opioid receptor antagonism, which creates conditioned place aversion (Skoubis and Maidment, 2003), or by 6-OHDA-induced lesions of VP (Gong et al., 1997b). Further, morphine-induced CPP can be blocked by intra-VP injections of the AMPA and NMDA glutamate receptor antagonists CNQX and AP-5 (Dallimore et al., 2006). Dopamine within the Acb and VP are also involved in psychostimulant-induced CPP, and dopamine concentrations within both regions correlate with CPP to cocaine conditioned place preference (Sellings and Clarke, 2003; Gong et al., 1997b).

Drug-induced CPP also results in plasticity within VP. Repeated pairings of amphetamine and a unique context which produced CPP in rats results in increases in VP synaptophysin (a marker for synaptogenesis) as well as increases in tyrosine kinase B receptor protein (a receptor for BDNF, a neurotrophic factor that mediates synaptic plasticity) (Rademacher et al., 2006). These outcomes were not obtained when an association was not made between amphetamine treatments and a particular context (referred to as unpaired controls). As the amphetamine treatments were the same for these two conditions, it appears that ‘learning’ was the unique factor that contributed to VP synaptic plasticity.

6.3.2 Reinstatement—The VP is part of several circuits necessary for reinstatement of extinguished drug-seeking behavior (**Figure 9**). Injections of cocaine or high doses of morphine into VP alone are sufficient to reinstate extinguished drug-seeking responses (Tang et al., 2005). Reinstatement of extinguished seeking behavior is disrupted by intra-VP microinjections triggered by the following stimuli: conditioned reinforcers (commonly referred as “cue-induced”; Rodgers et al., 2008; Torregrossa and Kalivas, 2008), heroin (Rodgers et al., 2008), cocaine (McFarland et al., 2001; Torregrossa and Kalivas, 2008; Li et al., 2009; Tang et al., 2005), alcohol (Perry and McNally, 2013), footshock (McFarland et al., 2004), context (Perry and McNally, 2013), and food (McFarland and Kalivas, 2001) (**Figure 9**). Similar to self-administration behavior, cocaine-induced reinstatement decreases VP extracellular concentrations of GABA, which are blocked (along with reinstatement) by intra-VP injections of *mu* opioid receptor agonists (Tang et al., 2005) or mGluR7 agonists (Li et al., 2009).

The AcbC-VPdl circuit plays a role in drug-seeking behavior. AcbC is required for most reinstatement protocols and is most closely linked with dorsomedial PFC and dorsal hippocampal systems, both of which also have critical roles in reinstatement (**Figure 9**). Given that the VPdl projects to the SNr, which is also important for reinstatement (Rodgers et al., 2008), as is the SNr target, the dorsolateral striatum (Fuchs et al., 2006; See et al., 2007; Rodgers et al., 2008; Bossert et al., 2009), the VPdl likely has a role in reinstatement behaviors. AcbC neurons projecting to the VP exhibit elevated fos-IR during reinstatement (Perry and McNally, 2013). During the cocaine-seeking response, AcbC neurons exhibit elevated firing rates (Ghitza et al., 2004; Fabbricatore et al., 2010), which decrease VPdl firing rates during the same response behavior (Root et al., 2013). Preventing VPdl neurons from decreasing their firing rates during the response through optogenetic inhibition of AcbC-VPdl terminals blocks cocaine-plus-cue-primed reinstatement (Stefanik et al., 2013). Optical inhibition of the VPdl-AcbC and AcbC-SN pathways had no effect on this type of reinstatement, demonstrate the necessity of the AcbC-VPdl pathway for drug-seeking behavior.

The AcbSh-VPvm circuit is also likely to play a role in drug-seeking behavior. AcbSh pathways involving the ventromedial PFC and ventral hippocampal systems are involved in several reinstatement types (**Figure 9**). Given that the AcbSh discriminates cocaine-related cues from neutral cues during reinstatement (Ghitza et al., 2003), VPvm may play a role in cued reinstatement, but has not been investigated. Intra-VP injection of the neurotensin agonist NT8-13 potentiates cocaine-induced reinstatement and attenuates cue-reinforced reinstatement (Torregrossa and Kalivas, 2008). Because neurotensin-IR partially defines VPvm, these data raise the possibility that VPvm is involved in at least cocaine-induced reinstatement.

It has recently been established that the VP-VTA pathway is an important circuit involved in reinstatement. Of VP neurons that project to VTA (e.g., from the VPvm), significantly more exhibit c-fos-IR following conditioned reinforcer reinstatement than under extinction conditions alone, following neutral cue exposure, or following novel cue exposure (Mahler and Aston-Jones, 2012). Furthermore, the percent of fos-immunoreactive VP neurons projecting to VTA predicts the number of cocaine-seeking lever presses during reinstatement. These data are consistent with the notion that VPvm facilitates information related to the events or conditions that predict cocaine self-infusions (section 6.2.2).

Differential projection targets of VPvm neurons have the potential to control different drug-seeking behaviors. Alterations of VTA neurochemistry decrease most reinstatement methods (McFarland and Kalivas, 2001, 2004; Sun et al., 2005; Di Ciano and Everitt, 2004; Wang et al., 2005, 2009; You et al., 2007; Schmidt et al., 2009; Mahler et al., 2012; Lu et al., 2012; **Figure 9**). Disruption of the VP-VTA pathway arising from the anterior half of VP, but not from the posterior half of VP, blocks conditioned reinforcer reinstatement (Mahler et al. 2014). In addition, disruption of the VP-VTA pathway arising from the posterior half of VP, but not from the anterior half of VP, blocks cocaine-induced reinstatement (Mahler et al.

2014). While MD baclofen/muscimol injections have no effect on cocaine or footshock induced reinstatement (McFarland and Kalivas, 2001; McFarland et al., 2004), MD and VP lesions are reported to reduce sucrose-mediated CPP (McAlonan et al., 1993).

6.4 Beyond mice and rats

6.4.1 Prairie voles and zebra finches—While not covered in the present review, VP has a long evolutionary history (Smeets et al., 2000; O'Connell and Hofmann, 2011, 2012; Ganz et al., 2012). Similar to rats, subregional differences exist in VP function of other species. Research into the underlying neural mechanisms for monogamy using *Microtus ochrogaster* voles has revealed the VP as a critical nucleus for monogamous pair bonding. In this model, viral upregulation of vasopressin V1a receptors within and surrounding VP enhances pair bonding (Pitkow et al., 2001). Furthermore, VP V1a receptor antagonism decreases partner contact time compared with stranger contact time (partner preference) (Lim and Young, 2004). Critically, mRNA expression of the V1a receptor is localized to the VPvm (Lim et al., 2004), indicating that the circuits of the VPvm selectively influence pair bonding.

Research into the underlying neural mechanisms for zebra finch song learning have revealed that single VP neurons decrease firing rates most robustly in response to the bird's own unique song (Gale and Perkel, 2010). Such decreases may disinhibit VTA/SN neurons (Gale and Perkel, 2010). Future research is needed to identify the subregional VP contributions towards birdsong processing.

6.4.2 The role of the VP in human normal behaviors and brain disorders—As preclinical characterization of the VP is emerging, the role of this region in emotional processing, motivated behaviors, and the psychiatric consequence of its dysregulation in humans is gaining attention (for review, see Napier and Mickiewicz, 2010). Several clinical reports point to VP involvement in disorders of motivation and impulsivity. Functional magnetic resonance imaging (fMRI) during forced choice tasks that require controlling desire for immediate rewards show reductions in task-induced activation of the VP in male participants (Diekhof et al., 2012). Single-photon emission computed tomography of Parkinson disease patients with pathological gambling show enhanced resting state activity (regional cerebral blood flow) in the VP of these individuals compared to non-gambling patients (Cilia et al., 2008). fMRI can be used to assess rapid responses of the brain to “unseen” reward cues, or cues that are recognized outside of our awareness. Presentation of unseen cues for natural and drug-related rewards (Childress et al., 2008), or monetary rewards (Pessiglione et al., 2007), results in rapid activation of the VP prior to conscious recognition. Similar responses also predict the positive affect evoked by the same stimuli when presented in a visible manner (Childress et al., 2008). These findings are substantiated by fMRI reports of visually perceived foods showing increased VP activity that correlats with the degree of food ‘pleasantness’ (Rudenga et al., 2010; Simmons et al., 2014). Underscoring the role of the VP in dysregulated food reward processes is the positive correlation of positron emission tomography (PET) for $5HT_4$ receptor density in this region with body mass index indicative of obesity in humans (Haahr et al., 2012). PET for *mu* opioid receptors indicate that increases in negative affect ratings by healthy human volunteers, which are associated with sustained sadness (Zubieta et al., 2003), or sustained muscle pain (Zubieta et al., 2002), correlate with deactivation of these receptors in the VP. Underscoring the involvement of the VP in substance use disorders are PET observations that dopamine D_3 receptors are upregulated in human methamphetamine polydrug users, which is in stark contrast to other forebrain regions wherein D_2 receptors are down-regulated (Boileau et al., 2012). Suggesting VP involvement in cocaine addiction, an endogenous opioid, dynorphin, is strikingly upregulated (i.e., by 346%) in the VP of *post mortem* brains from human cocaine abusers (Frankel et al., 2008). In summary, the VP is not yet widely studied in humans and caution is needed in interpreting human imaging studies as the VP is often not clearly resolved (Zaborszky et al., 2015b). Nonetheless, current reports of the human brain largely concur with the conclusions drawn from research in laboratory animal models, and are consistent with predictions based on the anatomical connections of the VP. The role of this region as an integrator of sensory, emotional and cognitive information with appropriate motoric responses is becoming clear, and the association of pallidal dysfunction in human brain disorders is also becoming increasingly apparent.

7.0 Concluding remarks – differential information flow across VP subregions and neuronal phenotypes

The VP is necessary for a variety of behaviors. Some are adaptive, such as those involving seeking and consuming food or ensuring the health and safety of offspring. Other behaviors are pathological, such as the self-administration of abused drugs. In this review, we put forth the notion that VP regulates these diverse behaviors via unique channels of information processing from GABAergic neurons belonging to individual subregions and from nonGABAergic neuronal phenotypes.

The VPdl, which receives projections from the AcbC and targets the STN and SNr, is intimately connected with the extrapyramidal motor system. Though untested for other behaviors, VPdl is necessary for the reinstatement of drug-seeking behavior (Stefanik et al., 2013). Evidence suggests that VPdl is involved in processing various reward-motivated behaviors. VPdl neurons exhibit significantly larger changes in firing rate than VPvm neurons during approaches toward, and responses on, a cocaine-reinforced device (Root et al., 2013). Further, VPdl approach-related changes in firing rate largely continue through the completion of the response (Root et al., 2013), suggesting VPdl signals are related to the pursuit and attainment of rewards, similar to a “go to it” function of the AcbC (Floresco, 2014). Taken together, the VPdl subregion and its projections to STN and SNr constitute one mechanism by which various motivated behaviors may be mediated.

The VPvm receives projections from the AcbSh and targets the MD, VTA, LH, and lateral habenula. The broad targets of this subregion suggest that the VPvm is involved in a variety of situations that involve cognition, reward prediction, and feeding. VPvm neurons exhibit heterogeneous firing patterns including approach-only, response-only, and approach-response, and exhibit significantly more retreat-only and response-retreat patterns than do VPdl neurons (Root et al., 2013). These data suggest that VPvm neurons have a role in processing the sequence of behaviors (Root et al., 2013) or conditions (Mahler and Aston-Jones, 2012; Leung and Balleine, 2013; Mahler et al. 2014) that predict reward, similar to a "stay on task" function of the AcbSh (Floresco, 2014). Such processing may enable higher order structures (e.g., MD and mPFC) to regulate complex situations such as reversal learning (Ferry et al., 2000). The VPvm also regulates food consumption, likely through its LH and/or VTA projections. Taken together, the VPvm subregion and its diverse targets constitute another mechanism by which various cognitive or feeding-related behaviors may be processed.

The less understood "finger-like" VPr subregion appears to be more VPvm-like than VPdl-like. The VPr receives inputs from the olfactory tubercle rather than a substantial Acb input (Zahm and Heimer, 1987; Tripathi et al., 2010), but has some similar targets to VPvm, such as MD, LHb, and rostral sublenticular extended amygdala (Tripathi et al., 2013). VPr neurons also collateralize within basal forebrain areas that are populated with cholinergic neurons. The collateralization patterns of VPr neurons suggest that this subregion might exhibit differential function from other VP subregions. Identification of the postsynaptic basal forebrain neuronal phenotypes (i.e., cholinergic, glutamatergic, GABAergic) that VPr neurons synapse onto will provide further insight into VPr function.

The nonGABAergic subpopulations of VP neurons also appear to be more VPvm-like than VPdl-like. Similar to VPvm GABAergic neurons, glutamatergic neurons expressing VGluT2 mRNA project to at least the VTA (Geisler et al., 2007) and therefore may influence reward-related circuits. Though it remains unclear how cholinergic neurons are integrated into the VP circuit, these neurons likely to play a role in ventral striatopallidocortical processing by their receipt of accumbal projections (Zaborszky and Cullinan, 1992), establishment of local synapses in VP (Záborszky et al., 1986), and their targeting of mPFC neurons (Hur and Zaborszky, 2005), which also is the target of MD neurons receiving GABAergic VPvm input. Moreover, cholinergic neurons, including the subpopulation that co-expresses markers of glutamate transmission, provide a significant input to the amygdala (Carlsen et al., 1985; Záborszky et al., 1986; Poulin et al., 2006). Some cholinergic neurons of the VP also express vesicular GABA transporter and Gad2 (Saunders et al., 2015a,b), thus diverse subpopulations of cholinergic neurons provide additional neurochemical channels of information processing within VP circuits. Further subregional-based heterogeneity likely exists in pathways arising from discrete ventral striatopallidal cell types (e.g., D_1, D_2, or D_3 receptor-expressing Acb neurons) and from the various types of VP neurons.

The underscoring of VP subregions and neuronal phenotypes in this review is not unlike the emphasis made by Heimer and colleagues (1997) when they discussed the importance of the AcbSh/AcbC divide, as well as VP/extended amygdala divide, towards opening "new and promising avenues for discussions of the neural basis of neuropsychiatric disorders and drug abuse". Each VP subregion and neuronal phenotype likely processes distinct roles in facilitating motivated behaviors via unique modulation of their respective systems. At the behavioral output level, each unique channel of information processing integrates towards a coherent goal-directed behavior. For instance, the initial processing of the appropriate conditions in which to approach a reward may be carried out through the VPvm while the physical acts of approach and response involve the VPdl.

Finally, given the VP's role in behavior related to food or drug self-administration, responsiveness to drug cues in human subjects, and adaptations from chronic exposure to drugs of abuse, VP is a likely candidate for therapeutic intervention. Further research into the functionality of VP subregions, neuronal phenotypes, and neurotransmitter signaling capacities will undoubtedly advance neuroscientific insights into the neural bases of behavior, cognition, and psychiatric disorders.

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Abbreviation List

BLA	basolateral amygdala
BM	basal nucleus of Meynert
BNST	bed nucleus of the stria terminalis
ChAT	choline acetyltransferase
DLS	dorsolateral striatum
dHipp	dorsal hippocampus
dPFC	dorsal prefrontal cortex
DR	dorsal raphe
EPN	entopeduncular nucleus
GABA	γ-amino butyric acid
GAD	glutamic acid decarboxylase
GP	globus pallidus
GPi	internal globus pallidus/entopeduncular nucleus
HDB	horizontal diagonal band
Lat	lateral
LH	lateral hypothalamus
LHb	lateral habenula
LHbM	medial part of lateral habenula
LHbL	lateral part of lateral habenula
LPO	lateral preoptic area

IPAC	interstitial nucleus of the anterior commissure
IR	immunoreactivity
Med	medial
MD	mediodorsal thalamus
mPFC	medial prefrontal cortex
MPO	medial preoptic nucleus
Acb	nucleus accumbens
AcbSh	nucleus accumbens shell
AcbC	nucleus accumbens core
NTS	nucleus tractus solitarius
OT	olfactory tubercle
PPTg	peduncopontine tegmental nucleus
PPTg-MEA	pedunculopontine tegmental nucleus – mesencephalic extrapyramidal area
RMTg	mesopontine rostromedial tegmental nucleus
RRF	retrorubral field
RTN	reticular thalamic nucleus
SLEAR	rostral sublenticular extended amygdala
SIB	basal part of substantia innominata
SN	substantia nigra
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
STN	subthalamic nucleus
TH	tyrosine hydroxylase
VGluT	vesicular glutamate transporter
vHipp	ventral hippocampus
VP	ventral pallidum
VPdl	dorsolateral ventral pallidum
VPvm	ventromedial ventral pallidum
VPr	rostral VP
VPvl	ventrolateral VP
vPFC	ventral prefrontal cortex
VL/VMT	ventrolateral/ventromedial thalamus

VTA	ventral tegmental area

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Highlights

VP contains several GABAergic subregions with distinct neuronal circuits

Additional circuits arise from nonGABAergic (e.g., glutamatergic) neuronal phenotypes

Dorsolateral VP neurons are sensitive to and necessary for drug-seeking responses

Ventromedial VP neurons discriminate conditions of reward acquisition and consumption

VP is an information integrator capable of dysregulation induced by drugs of abuse

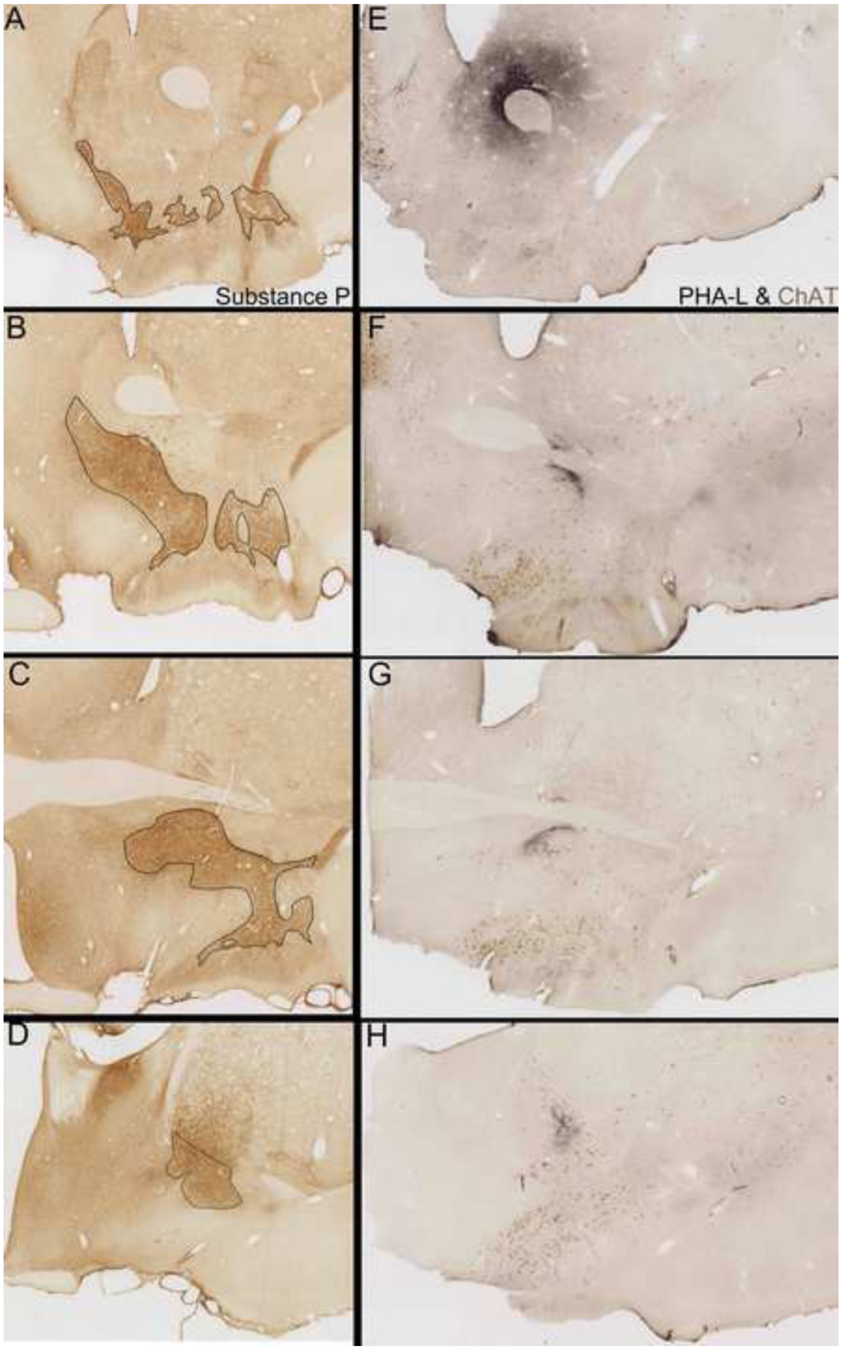

Figure 1. Delineation of the ventral pallidum and topographic input from nucleus accumbens core to the dorsolateral ventral pallidum subregion

A-D. Four anteroposterior planes of the VP, defined by the presence of substance P-IR (black outline). **A.** Plane of the "finger-like" rostral VP subregion. **B-D.** Planes of the VP that contain the ventromedial, dorsolateral, and ventrolateral VP subregions (shown in Figure 2). In the caudal extreme of the VP **(D),** substance P-IR is also observed in the more dorsally located globus pallidus (**D**). **E-H.** Four anteroposterior planes showing labeling of the anterograde tracer phaseolus vulgaris leucoagglutinin (black label) at the injection site within the AcbC (**E**) and efferent fibers within the dorsolateral VP (**F-H**). Note labeled cells at the injection site are concentrated in the heavily stained area, slight enhancement of background labeling due to local edema. Labeling in panels G-H are from a slightly medially-shifted AcbC injection compared to labeling from case in panels E-F. Brown labeling indicates neurons immunolabeled for choline acetyl transferase (ChAT; a marker for cholinergic elements). Material from Dr. Zaborszky.

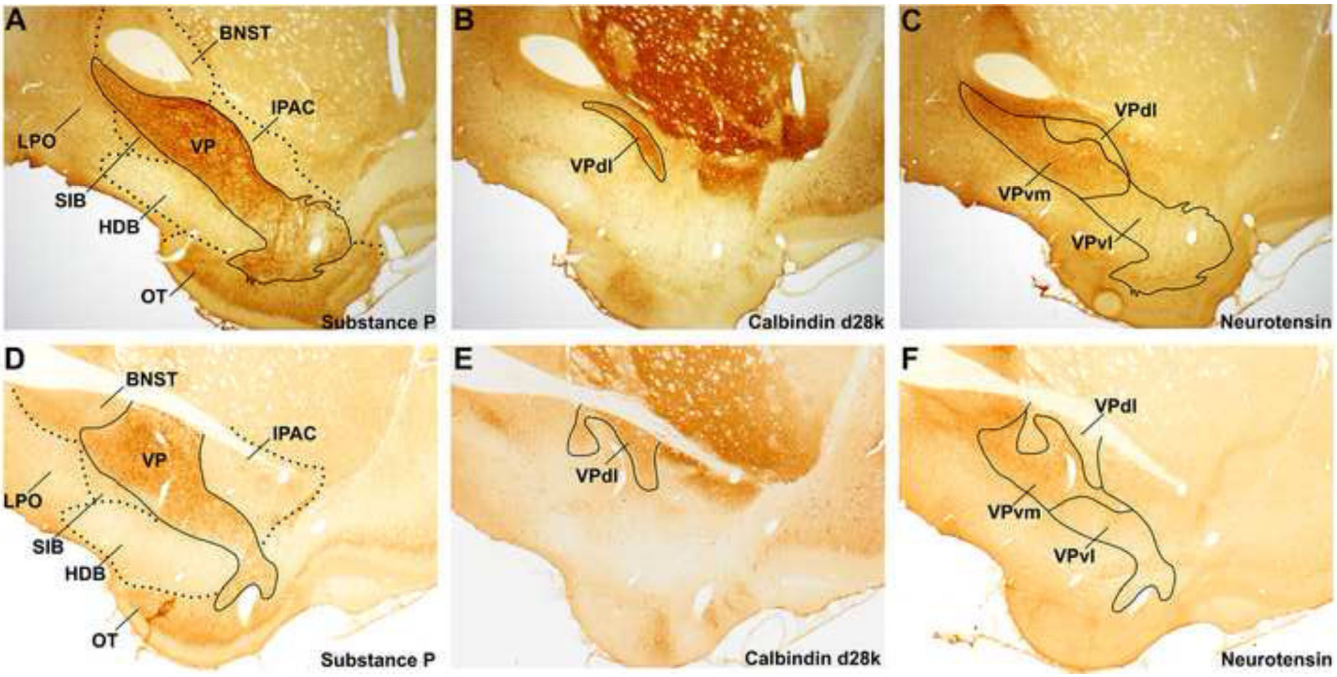

Figure 2. Subregions of the ventral pallidum

A,D. Two anteroposterior levels of the VP, defined by the presence of substance P-IR, at approximately +0.36 mm (**A**) and −0.12 mm (**D**). **B-C.** Sections proximal to tissue in panel D showing calbindin d28k-IR (**B**) and neurotensin-IR (**C**). **E-F.** Sections proximal to tissue in panel D showing calbindin d28k-IR (**E**) and neurotensin-IR (**F**). The VPdl subregion exhibits fibers with calbindin-d28k-IR but not neurotensin-IR. The VPvm subregion exhibits fibers with neurotensin-IR but not calbindin-d28k-IR, and the VPr and VPvl subregions do not express calbindin-d28k-IR or neurotensin-IR. This compartmentation of VP is observed across the anteroposterior extent of VP, except in the VPr (Zahm and Heimer, 1988, 1990; Zahm 1989; Zahm et al., 1996; Riedel et al., 2002; Tripathi et al., 2010, 2013). All sections are 30 μm thick. Neighboring locations to the VP are demarcated by dotted lines. Material from Dr. Root (Morales laboratory, NIDA).

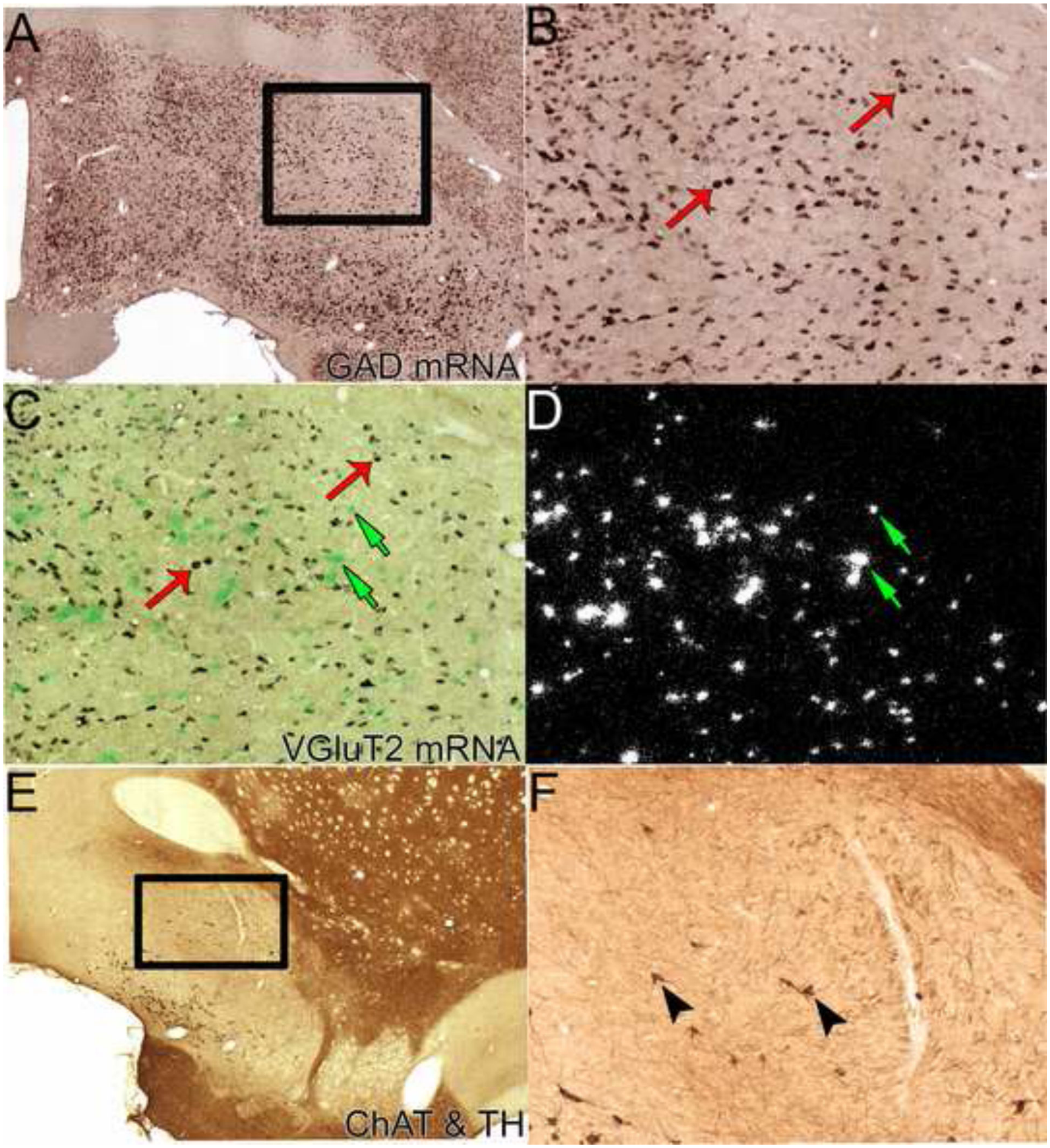

Figure 3. Neuronal phenotypes of the ventral pallidum

A-B. GABAergic neurons. Double *in situ* hybridization; the purple labeled neurons display digoxigenin-labeling for GAD 65 and GAD 67 mRNAs. Box in **A** showing VP regions displayed in B, C, and D. **B.** Higher resolution photograph of GAD mRNA neurons. Note abundance of GABAergic neurons, two examples shown by red thin arrows. **C-D.** Glutamatergic neurons. The same section as B further processed with radioactive *in situ* hybridization for VGluT2 mRNA under brightfield (C) and darkfield (D) illumination. Clusters of green grains (C) or white grains (D) indicate VGluT2 mRNA neurons. Note abundance of glutamatergic neurons, uniquely localized within VPvm. Examples of VGluT2-expressing neurons indicated by green small arrows. **E-F.** Immunohistochemistry for tyrosine hydroxylase (TH; a marker for noradrenergic/dopaminergic elements) and choline acetyl transferase (ChAT; a marker for cholinergic elements). Boxed in region in the low power photomicrograph (E) is the region shown in the high power photomicrograph (F). The VP is delineated by fewer TH-fibers than neighboring structures (i.e., bed nucleus of the stria terminalis, interstitial nucleus of the anterior commissure, striatum, and tubercle). ChAT-labeled soma (brown diaminobenzadine reaction); two examples of cholinergic neurons are indicated by black arrow heads. Material from Dr. Root (Morales laboratory, NIDA).

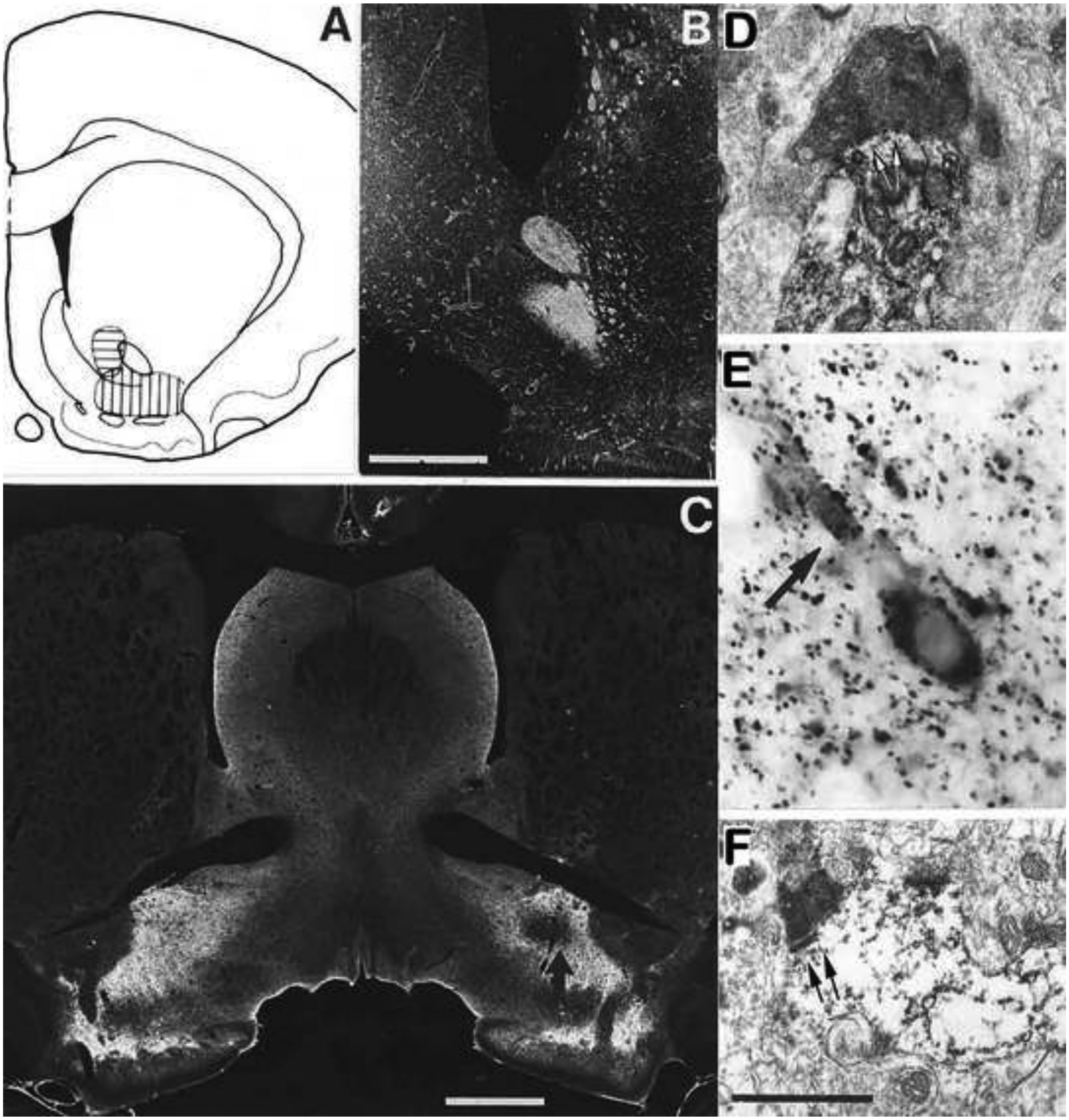

Figure 4. Accumbens neurons establish inhibitory synapses onto VP GABA neurons
A-C. Accumbal to ventral pallidal projections determined by lesion studies. **A**. Electrolytic lesion locations in the AcbC (horizontal hatching) and AcbSh (vertical hatching). **B**. Degenerating terminals in VP after AcbC lesion using a silver-impregnation method (Gallyas et al., 1980). **C**. Loss of GAD-IR (arrow) in VP after lesion of the AcbSh. **D-F**. Electron microscopy evidence of a GABAergic AcbSh and AcbC projection to GABAergic VP neurons. **D**. A large degenerating bouton establishing a symmetric synapse with a GAD-positive dendrite in the VP after lesion of the AcbC. **E**. A GABAergic cell and dendrite

ensheathed by GAD-expressing terminals in the VP. **F**. Small degenerating bouton contacting a GAD-expressing dendrite after lesion of the AcbSh. Arrows in D and F point to the postsynaptic membrane. Scale bars in B,C: 1 mm, F: 1 μm (also refers to D). Material from Dr. Zaborszky.

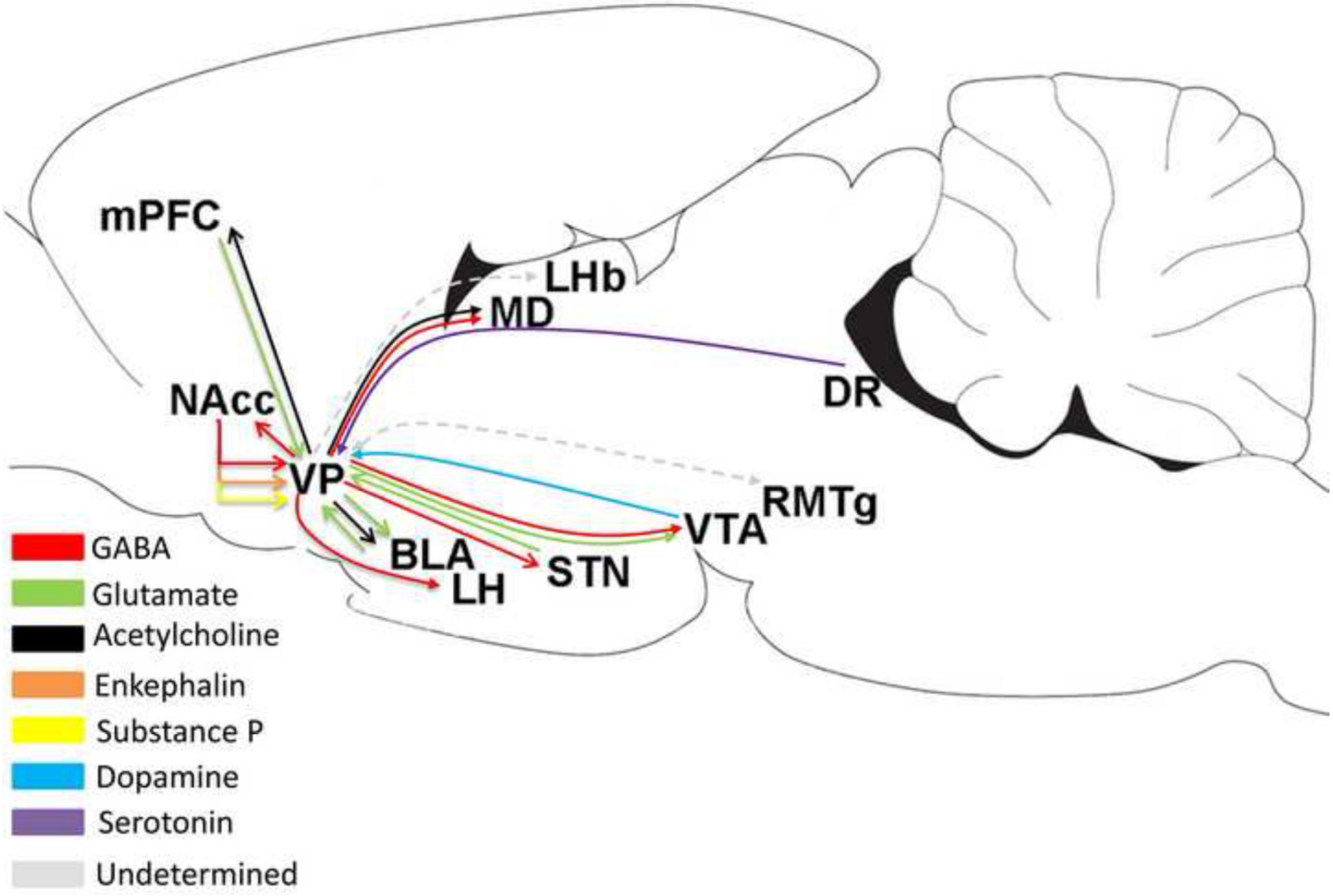

Figure 5. General overview of afferents and efferents of the ventral pallidum

Nonsubregional illustration of the major transmitter phenotype and associated brain structures of the projections. Supporting literature includes: VP/mPFC (medial prefrontal cortex) - Carlsen et al. 1985; Hur and Zaborszky, 2005. VP/Acb Haber and Nauta, 1983; Zahm et al. 1985; Churchill et al. 1990; Kalivas et al. 1993; Groenewegen and Russchen 1984; Chrobak and Napier, 1993; Napier et al. 1995. VP/BLA - Fuller et al. 1987; Carlsen et al. 1985; Poulin et al. 2006; Maslowski-Cobuzzi and Napier, 1994; Mitrovic and Napier, 1998. VP/STN - Bevan et al. 1997; Ricardo et al. 1980; Turner et al., 2001, 2008. VP/LH - Bevan et al. 1997. VP/DR - Semba et al. 1988. VP/VTA – Maslowski-Cobuzzi and Napier, 1994; Mitrovic and Napier, 2002; Klitenick et al. 1992; Geisler et al. 2005, 2007; Kalivas et al. 1993. VP/RMTg - Jhou et al. 2009; Taylor et al. 2014. VP/LHb - Groenwegen et al. 1993. VP/RTN - Young et al. 1984; O'Donnell et al. 1997. VP/MD - Young et al. 1984; Mariotti et al. 2001; MD/mPFC Pirot et al. 1994. The VP projection to LHb and RMTg projection to VP have not explicitly tested a GABAergic phenotype. Sagital outline modified from Paxinos and Watson (2007).

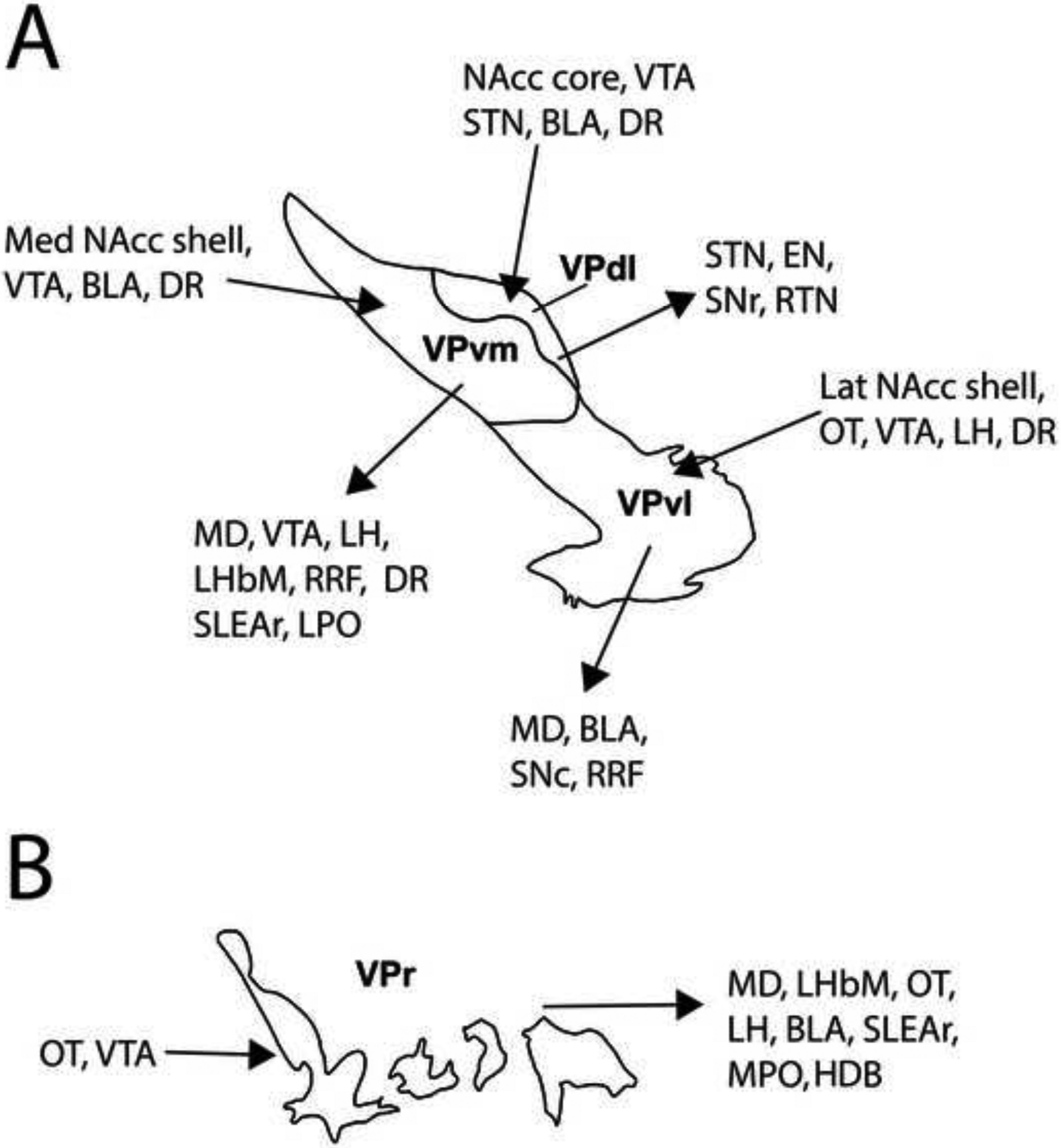

Figure 6. Subregional afferent and efferent connections of the ventral pallidum

A. Known afferent and efferent projections of the VPvm, VPdl, and VPvl subregions. Subregions are illustrated to represent projections from any anteroposterior location within these VP subregions. Anatomical studies have also demonstrated that the BLA projects to, and receives projections from, cholinergic neurons that reside in all VP subregions (Gritti et al., 1993; Poulin et al., 2006; Mascagni and McDonald, 2009; Záborszky et al., 1986, 1999, 2012), but electrophysiological studies consistent with monosynaptic afferents suggest a wider influence on VP neuronal populations (Maslowski-Cobuzzi and Napier, 1994;

Mitrovic and Napier, 1998). Glutamatergic neuron distribution for VP subregions has yet to be validated, but appear to be located largely within the VPvm, and thus far have been shown to project to the VTA (Geisler et al. 2007). VTA and DR appear to project to all VP subregions (Maslowski-Cobuzzi and Napier, 1994; Mitrovic and Napier, 2002; Klitenick et al. 1992; Semba et al. 1988). **B**. Known afferent and efferent projections of the VPr subregion.

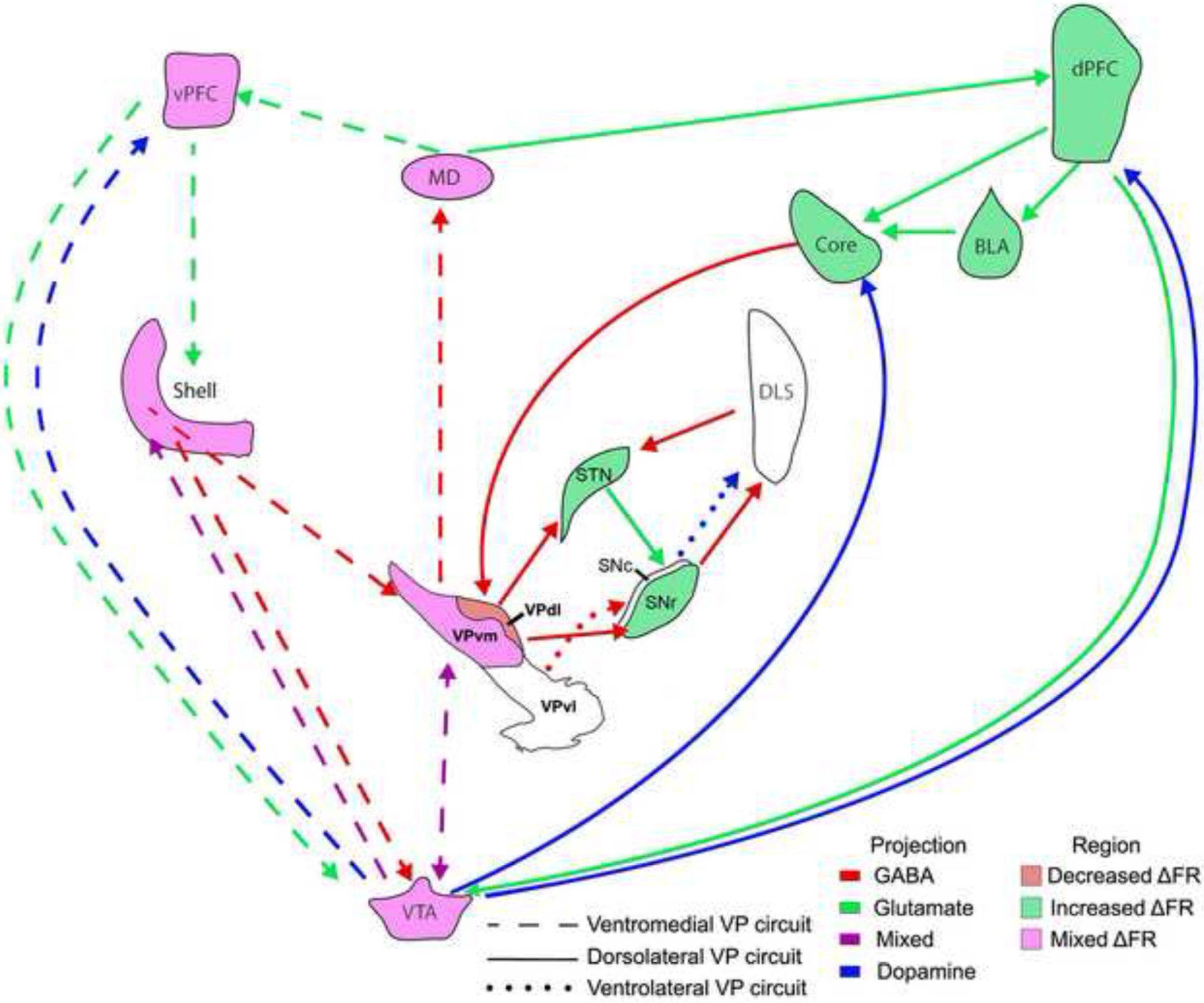

Figure 7. Proposed changes in firing rate during responses for drugs of abuse involving the VP subregions

Neurons of the AcbC exhibit increased firing rates during responses for cocaine (Ghitza et al. 2004), which are likely the result of dPFC and BLA activation during the same behavior (Chang et al., 1997, 2000; Carelli et al., 2003). Activation of AcbC leads to decreased firing rates of VPdl neurons during the response (Root et al., 2013) and likely disinhibits its target structures SNr and STN (Lardeux et al., 2013; Fan et al., 2012). While AcbSh neurons are less sensitive to the response compared with AcbC neurons, AcbSh neurons exhibiting changes in firing rate during the response are heterogeneous (Ghitza et al., 2004). Such heterogeneity is found within the VPvm subregion (Root et al., 2013) and is likely to continue within its target regions VTA and MD. The involvement of VPvl and its circuits (SNc and DLS; dotted lines with arrows) is unclear (white color). Dashed lines with arrows represent circuits involving VPvm. Solid lines with arrows represent circuits involving VPdl. Purple shaded structure indicates heterogeneous (increased or decreased) change in firing rate during cocaine self-administering responses. Red shaded structure and green shaded structure indicates decreased and increases change in firing rate during cocaine self-administering responses. The illustrated subregions are proposed to represent subregions throughout the anteroposterior extent of the VP.

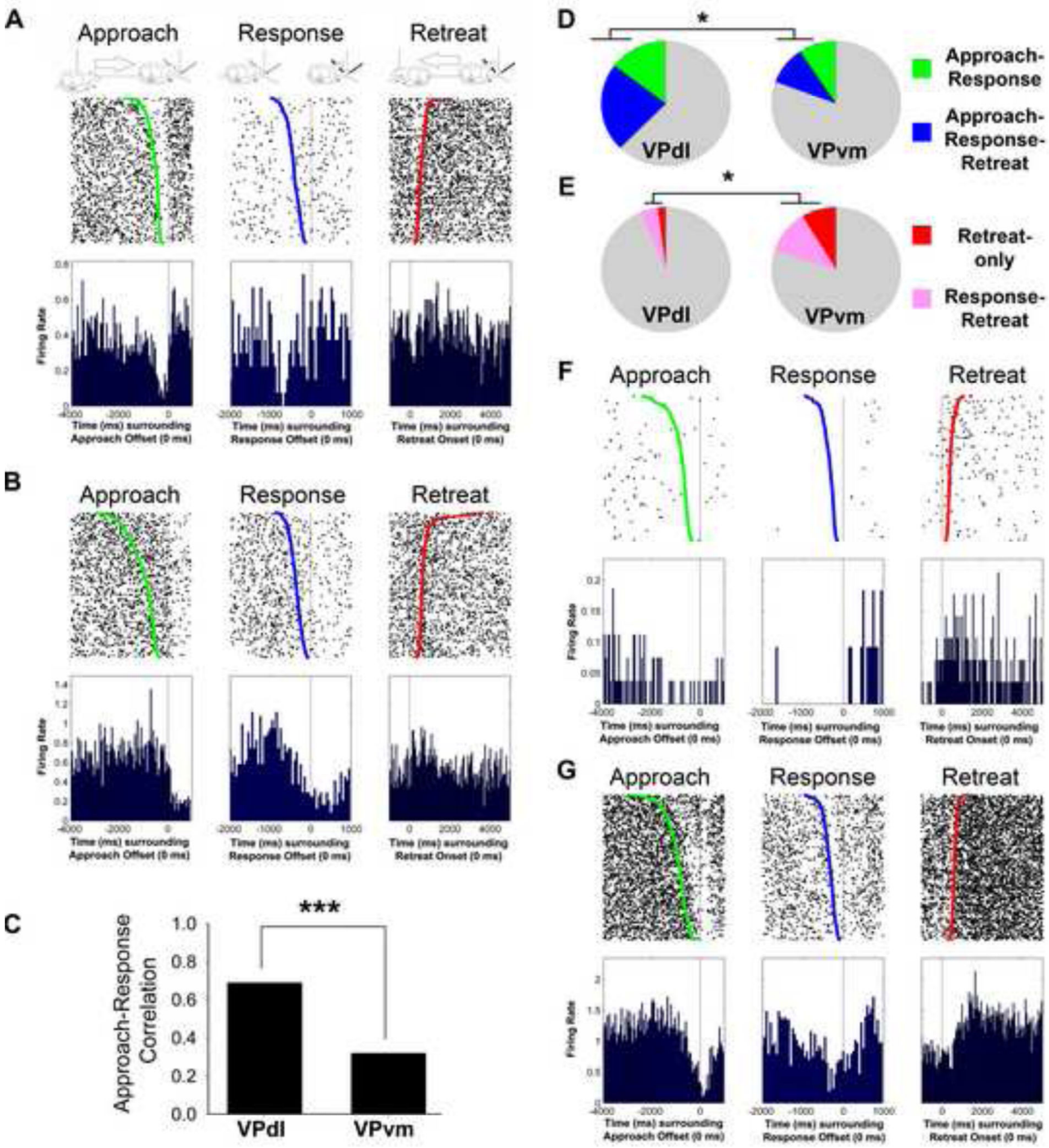

Figure 8. VP subregions are differentially associated with drug-seeking behaviors during cocaine self-administration

A. Top shows illustration of behaviors used to analyze changes in firing rate recorded from single VP neurons during discrete behaviors involved in self-administering cocaine. Approach occurred when the animal initially moved towards a set of photocells used as a response device (left), response occurred when the animal emitted a learned long distance vertical head movement (middle), and retreat occurred when the animal moved away from the photocells; right). Bottom shows an example approach-related firing pattern of a VPvm neuron. For A, B, F, and G, green dot is the onset of the approach and time zero is the offset of approach (left), blue dot is the onset of response and time zero is offset of response (middle), and red dot is offset of retreat while time zero is onset of retreat (right). **B**. An example response-related firing pattern of a VPvm neuron. **C**. VPdl neurons exhibit a significantly greater correlation between directional changes in firing rate during approach and response compared to VPvm neurons. Directional change in firing rate refers to change from baseline according to a B/(A+B) formula, where 'B' is firing rate during movement (e.g., approach or response), and 'A' is firing rare during baseline. **D**. Neurons classified as approach-response and approach-response-retreat were observed significantly more often within VPdl compared to VPvm, $\chi^2(1) = 4.03$, $p = 0.04$. **E**. Neurons classified as retreat-only and response-retreat were observed significantly more often within VPvm compared to VPdl, $\chi^2(1) = 5.96$, $p = 0.01$. **F**. Example approach-response firing pattern of VPdl neuron. **G**. Example approach-response-retreat firing pattern of VPdl neuron. * $p < 0.05$; *** $p < 0.001$. Data from Dr. Root while in the West laboratory (Rutgers), published in Root et al., 2013.

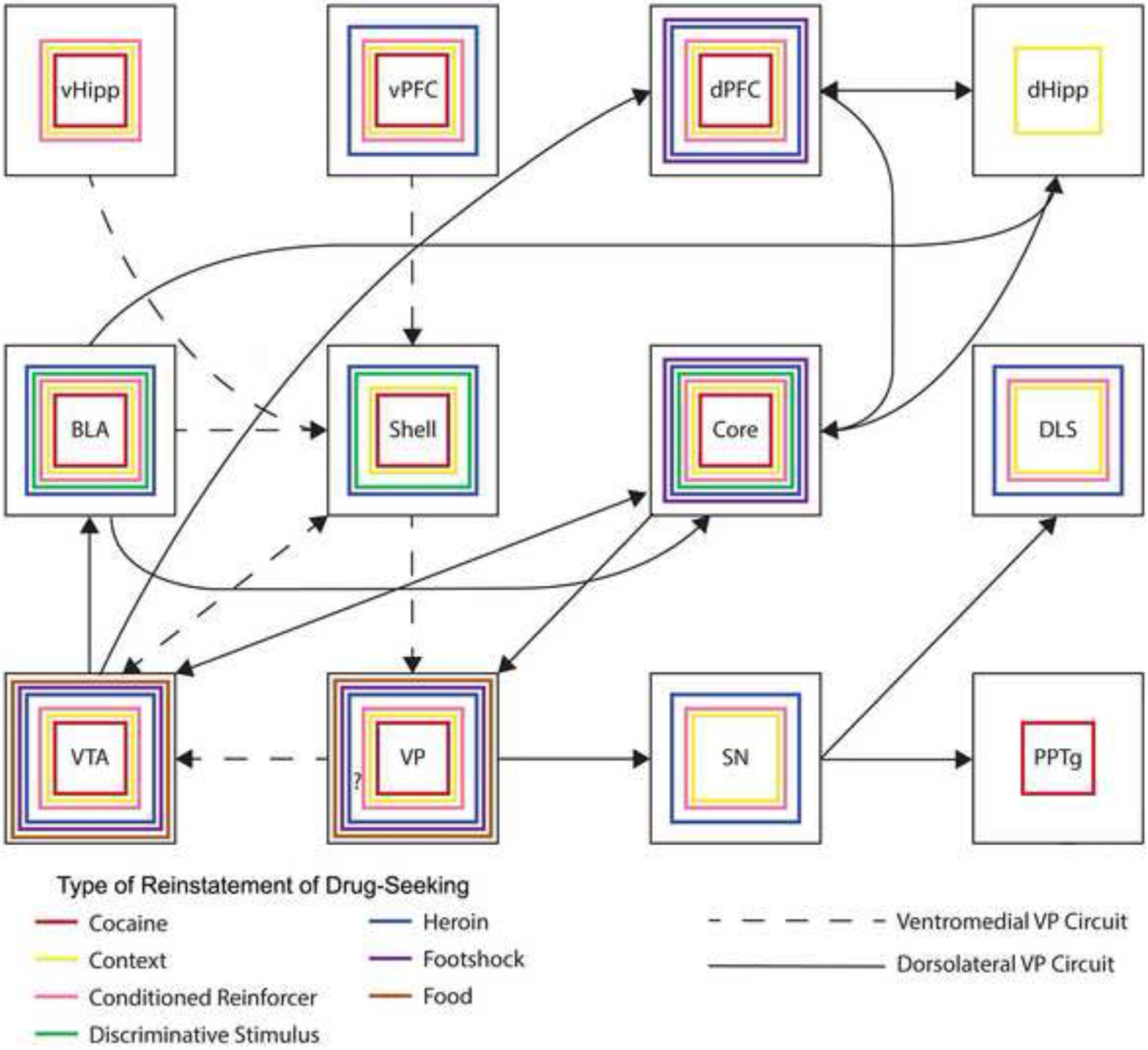

Figure 9. Proposed reinstatement circuits involving the VP subregions

Theoretical schema of brain regions and circuits that involve VP subregions and their participation in different types of reinstatement of drug-seeking behavior. Presence of colored squares indicates region is necessary for the type of reinstatement. Question mark in VP indicates that a test has not yet been performed. Absence of colored squares in all other regions indicates either test not yet performed or region not involved. Dashed lines represent circuits involving VPvm. Solid lines represent circuits involving VPdl. Supporting literature includes the following: Ventral hippocampus (vHipp) - Lasseter et al. 2010; Sun and Rebec 2003; vPFC – Peters et al., 2008; Rodgers et al. 2008; Bossert et al. 2011; LaLumiere et al., 2012; Dorsal prefrontal cortex (dPFC) - McFarland and Kalivas 2001, 2004; Rodgers et al. 2008; Fuchs et al. 2005; Capriles et al. 2003; Dorsal hippocampus (dHipp) - Fuchs et al.

2005; dPFC/dHipp - Fuchs et al. 2007; BLA - Kantak et al. 2002; Feltenstein and See 2007; Alleweireldt et al. 2006; Fuchs et al. 2005; You and Fields, 2003; Ledford et al. 2003; McLaughlin and See, 2003; Hayes et al. 2003; Fuchs and See 2002; Kruzich and See 2001; Grimm and See, 2000; Stefanik and Kalivas, 2013. BLA/dHipp - Fuchs et al. 2007; AcbSh – Peters et al., 2008; Rodgers et al. 2008; Bossert et al. 2007; BLA/AcbC – Stefanik and Kalivas, 2013; dPFC – Stefanik and Kalivas, 2013; BLA/AcbC – Stefanik and Kalivas, 2013; dPFC/AcbC – based on Kalivas and McFarland, 2001; vPFC/AcbSh – Peters et al., 2008; Bossert et al. 2012; LaLumiere et al., 2012; AcbC - Rodgers et al. 2008; McFarland and Kalivas 2001, 2004; Bossert et al. 2007; Xie et al., 2012; Fuchs et al., 2008; AcbC/VPdl – Stefanik et al., 2013; DLS - Fuchs et al. 2006; See et al. 2007; Rodgers et al. 2008; Bossert et al. 2009; SN/DLS – based on Bossert et al., 2009; VTA - McFarland and Kalivas 2001, 2004; Sun et al. 2005; Di Ciano and Everitt 2004; Wang et al. 2009; You et al. 2007; Schmidt et al. 2009; VP/VTA - Mahler et al. 2014; VP - Tang et al. 2005; Rodgers et al. 2008; McFarland and Kalivas 2001, 2004; Li et al. 2009; Torregrossa and Kalivas 2008; Lu et al. 2012; Mahler et al. 2012; Perry and McNally, 2013; VTA/dPFC – based on McFarland and Kalivas, 2001; McFarland et al., 2004; Capriles et al., 2003; SN - Sun et al. 2007; Rodgers et al. 2008; PPTg - Schmidt et al. 2009; VTA/AcbSh - LaLumiere et al., 2012; Bossert et al., 2007; VTA/BLA - LaLumiere et al., 2012; VTA/AcbC – based on Bossert et al., 2007.

Table 1

Effects of intra-VP injections of opioids on hemicholinium binding in VP cholinergic terminal regions.

Treatment (nmoles/0.5µl/side)	**Frontal Cortex**	**Amygdala**
Vehicle	12.7±1.2	111.9±8.4
DAMGO (0.03)	13.4±2.2	88.8±8.7
DAMGO (1.0)	11.1±0.9	83.2±14.2
DAMGO (33)	8.5±0.9*	68.3±5.4*
CTOP (0.01) + DAMGO (33)	8.8±0.6*	107.8±20.2
U50488H (10)	10.4±2.1	89.4±23.3
U50488H (33)	10.3±1.9	65.0±10.0*
nBNT (0.1) + U50488H (33)	9.9±0.9	132.3±19.3
DPDPE (10)	12.1±1.3	68.3±5.4*
Naltrindole10mg/kg,ip + DPDPE (10)	9.3±1.6	105.5±16.9

Bilateral intra-VP injections were accomplished in awake male Sprague-Dawley rats *via* injectors inserted into chronically embedded cannula following published methods (e.g., see Napier, 1992). Injections were infused as 0.1µl/min. The rats were killed 30 min after infusion, brain regions were harvested and fast frozen, and hemicholinium binding was conducted by Dr. Linda Gorman, as previously published (Muma et al., 2001). Data are in fmoles hemicholinium/mg protein. Sample size varied from 6-12. When given alone, the tested antagonists did not alter binding (data not shown), but were effective in blocking the agonist-induced decreases, with the exception of DAMGO effects on the cortex.

*p=0.05 vs. respective vehicle controls. DAMGO, *mu* receptor agonist; CTOP *mu* receptor antagonist; U50488H, *kappa* agonist; nBNT (norbinaltorphamine) *kappa* antagonist; DPDPE, *delta* agonist; Nalttrindole), *delta* antagonist. Intra-VP antagonists were given immediately before intra-VP agonists, with the excpetion of naltrindol, which was administered intraperitoneally, 30 min prior to intra-VP DPDPE. Data from Dr. Napier.

Table 2

VP manipulations and motoric effects.

Reference	VP Manipulation	System	Effects	Task	Result
Kitamura et al., 2001	Muscimol	GABA	GABA-A Agonist	Contraversive pivoting induced by AcbSh SKF 38393/quinpi role	Blocked
Kitamura et al., 2001	Bicuculline	GABA	GABA-A Antagonist	Contraversive pivoting induced by AcbSh SKF 38393/quinpi role	Blocked
Kitamura et al., 2001	Muscimol	GABA	GABA-A Agonist	Contraversive turning	Increase
Napier 1992	DADL	Opioid	Multiple	Contraversive turning	Increase
Napier 1992	DAMGO	Opioid	Mu agonist	Contraversive turning	Increase
Hoffman et al., 1991	DAMGO	Opioid	Mu agonist	Contraversive turning	Increase
Hoffman et al., 1991	DPDPE	Opioid	Delta agonist	Contraversive turning	Increase
Hoffman et al., 1991	U50,488H	Opioid	Kappa agonist	Contraversive turning	No effect
Napier 1992	DAMGO + SCH 23390	Opioid + Dopamine	Mu agonist + D2 Antagonist	Contraversive turning	Attenuated
Napier 1992	DAMGO + Sulpiride	Opioid + Dopamine	Mu agonist + D2 Antagonist	Contraversive turning	Attenuated
Kitamura et al., 2001	Bicuculline	GABA	GABA-A Antagonist	Contraversive turning induced by AcbSh carbachol	Attenuated
Kitamura et al., 2001	Muscimol	GABA	GABA-A Agonist	Contraversive turning induced by AcbSh carbachol	Blocked
Gong et al., 1996	Cocaine	DA	Multiple	Locomotion	Decrease
Gong et al., 1996	Amphetamine	DA	Multiple	Locomotion	Increase
Gong et al., 1996	Dopamine	DA	Multiple	Locomotion	Increase
Alesdatter and Kalivas 1993	SCH 23390	Dopamine	D1 antagonist	Locomotion	Decrease
Alesdatter and Kalivas 1993	Raclopride	Dopamine	D2 antagonist	Locomotion	No effect
Austin and Kalivas 1991	Haloperidol	Dopamine	D2 Antagonist	Locomotion	No effect
Austin and Kalivas 1991	Fluphenazine	Dopamine	D1/D2 antagonist	Locomotion	No effect
Fletcher et al., 1998	Amphetamine	Dopamine	Multiple	Locomotion	Increase
Gong et al., 1999	SKF 38393	Dopamine	D1 Agonist	Locomotion	Mixed
Gong et al., 1999	Quinpirole	Dopamine	D2 Agonist	Locomotion	Decrease
Hooks and Kalivas 1994	Dopamine	Dopamine	Dopamine	Locomotion	Increase
Klitenick et al., 1992	Dopamine	Dopamine	Multiple	Locomotion	Increase
Johnson et al., 1996	Dopamine + VTA baclofen	Dopamine	Multiple	Locomotion	No effect

Reference	VP Manipulation	System	Effects	Task	Result
Austin and Kalivas 1991	Haloperidol+picrotoxin	Dopamine + GABA	D2 Antagonist + GABA-A Antagonist	Locomotion	Attenuated
Austin and Kalivas 1991	Fluphenazine+picrotoxin	Dopamine + GABA	D1/D2 antagonist + GABAA Antagonist	Locomotion	Attenuated
Alesdatter and Kalivas 1993	Fluphenazine+DA MGO	Dopamine + Opioid	D1/D2 antagonist + Mu agonist	Locomotion	Attenuated
Alesdatter and Kalivas 1993	SCH 23390+DAMGO	Dopamine + Opioid	D1 antagonist + Mu agonist	Locomotion	Attenuated
Alesdatter and Kalivas 1993	Raclopride+DAMGO	Dopamine + Opioid	D2 antagonist + Mu agonist	Locomotion	No effect
Austin and Kalivas 1991	DAMGO+haloperidol	Dopamine + Opioid	D2 antagonist + Mu agonist	Locomotion	Attenuated
Austin and Kalivas 1991	Fluphenazine+DAMGO	Dopamine + Opioid	D1/D2 antagonist + Mu agonist	Locomotion	Attenuated
Austin and Kalivas 1989	Picrotoxin	GABA	GABA-A Antagonist	Locomotion	Increase
Austin and Kalivas 1989	Bicuculline	GABA	GABA-A Antagonist	Locomotion	Increase
Austin and Kalivas 1989	Phaclofen	GABA	GABA-B Antagonist	Locomotion	No effect
Austin and Kalivas 1989	Muscimol	GABA	GABA-A Agonist	Locomotion	Decrease
Austin and Kalivas 1989	Muscimol+Picrotoxin	GABA	GABA-A Agonist + GABA-A Antagonist	Locomotion	Blocked
Austin and Kalivas 1990	Bicuculline	GABA	GABA-A Antagonist	Locomotion	Increase
Austin and Kalivas 1990	Picrotoxin	GABA	GABA-A Antagonist	Locomotion	Increase
Austin and Kalivas 1990	Phaclofen	GABA	GABA-B Antagonist	Locomotion	No effect
Austin and Kalivas 1991	Picrotoxin	GABA	GABA-A Antagonist	Locomotion	Increase
Churchill et al., 1998	Muscimol	GABA	GABA-A Agonist	Locomotion	Increase
Churchill et al., 1998	Muscimol + Acb DAMGO	GABA	GABA-A Agonist	Locomotion	Blocked
Churchill et al., 1998	Muscimol + Acb DA	GABA	GABA-A Agonist	Locomotion	Blocked
Fletcher et al., 1998	Picrotoxin	GABA	GABA-A Antagonist	Locomotion	Increase
Gong et al., 1997	Picrotoxin	GABA	GABA-A Antagonist	Locomotion	Increase
Kalivas et al., 1991	Picrotoxin	GABA	GABA-A Antagonist	Locomotion	Increase
Klitenick et al., 1992	Muscimol	GABA	GABA-A Agonist	Locomotion	Increase
Lawrence et al., 2003	Picrotoxin	GABA	GABA-A Antagonist	Locomotion	Increase
Patel and Slater 1988	Picrotoxin	GABA	GABA-A Antagonist	Locomotion	Increase
Patel and Slater 1988	Bicuculline	GABA	GABA-A Antagonist	Locomotion	Increase

Reference	VP Manipulation	System	Effects	Task	Result
Smith et al., 2005	Bicuculline	GABA	GABA-A Antagonist	Locomotion	Increase
Swerdlow and Koob 1987	Picrotoxin	GABA	GABA-A Antagonist	Locomotion	Increase
Swerdlow and Koob 1987	Picrotoxin + mediodorsal thalamus lesion	GABA	GABA-A Antagonist	Locomotion	Blocked
Patel and Slater 1988	Muscimol + Acb ADTN (DA analog)	GABA	GABA-A Agonist	Locomotion	Decrease
Patel and Slater 1988	Baclofen + Acb ADTN (DA analog)	GABA	GABA-B Agonist	Locomotion	Decrease
Patel and Slater 1988	Isoguvacine + Acb ADTN (DA analog)	GABA	GABA-A Agonist	Locomotion	Decrease
Patel and Slater 1988	Picrotoxin + Acb ADTN (DA analog)	GABA	GABA-A Antagonist	Locomotion	No effect
Patel and Slater 1988	Bicuculline + Acb ADTN (DA analog)	GABA	GABA-A Antagonist	Locomotion	No effect
Wallace and Uretsky 1991	Muscimol + Acb AMPA	GABA	GABA-A Agonist	Locomotion	Blocked
Wallace and Uretsky 1991	Muscimol + Acb amphetamine	GABA	GABA-A Agonist	Locomotion	Blocked
Wallace and Uretsky 1991	Muscimol + Acb kainic acid	GABA	GABA-A Agonist	Locomotion	Blocked
Wallace and Uretsky 1991	Muscimol + Acb NMDA	GABA	GABA-A Agonist	Locomotion	Blocked
Wallace and Uretsky 1991	Muscimol + Acb picrotoxin	GABA	GABA-A Agonist	Locomotion	Blocked
Klitenick et al., 1992	Muscimol+Dopamine	GABA + Dopamine	GABA-A Agonist + multiple	Locomotion	Increase
Wallace and Uretsky 1991	Picrotoxin + DNQX	GABA + Glutamate	GABA-A Antagonist + AMPA antagnoist	Locomotion	Attenuated
Austin and Kalivas 1989	Muscimol+DAMGO	GABA + Opioid	GABA-A Agonist + Mu agonist	Locomotion	Blocked
Churchill and Kalivas 1999	AMPA	Glutamate	AMPA	Locomotion	Increase
Churchill and Kalivas 1999	AMPA + mediodorsal thalamus procaine	Glutamate	AMPA	Locomotion	No effect
Churchill and Kalivas 1999	AMPA + midbrain extrapyramidal region procaine	Glutamate	AMPA	Locomotion	Blocked
Churchill et al., 1998	AMPA	Glutamate	AMPA	Locomotion	Increase
Churchill et al., 1998	AMPA + VTA Baclofen	Glutamate	AMPA	Locomotion	Blocked
Gong et al., 1997	AMPA	Glutamate	AMPA	Locomotion	Increase
Hooks and Kalivas 1994	AMPA	Glutamate	AMPA agonist	Locomotion	Increase
Li et al., 2009	AMN082	Glutamate	R7 agonist	Locomotion	No effect
Wallace and Uretsky 1991	AMPA	Glutamate	AMPA agonist	Locomotion	Increase
Wallace and Uretsky 1991	kainate	Glutamate	AMPA agonist	Locomotion	Increase

Reference	VP Manipulation	System	Effects	Task	Result
Wallace and Uretsky 1991	NMDA	Glutamate	NMDA agonist	Locomotion	Increase
Wallace and Uretsky 1991	DNQX + Acb amphetamine	Glutamate	AMPA Antagonist	Locomotion	No effect
Wallace and Uretsky 1991	DNQX + Acb AMPA	Glutamate	AMPA Antagonist	Locomotion	No effect
Wallace and Uretsky 1991	GAMS + Acb amphetamine	Glutamate	Antagonist	Locomotion	No effect
Wallace and Uretsky 1991	GAMS + Acb AMPA	Glutamate	Antagonist	Locomotion	No effect
Wallace and Uretsky 1991	DAA + Acb amphetamine	Glutamate	NMDA antagonist	Locomotion	No effect
Wallace and Uretsky 1991	DAA + Acb AMPA	Glutamate	NMDA antagonist	Locomotion	No effect
Johnson et al., 1996	AMPA + VTA Baclofen	Glutamate	AMPA agonist	Locomotion	Blocked
Wallace and Uretsky 1991	AMPA + muscimol	Glutamate + GABA	AMPA agonist + GABA agonist	Locomotion	Blocked
De Leonibus et al., 2001	Lesion	NA	NA	Locomotion	Increase
Johnson et al., 1996	Lesion	NA	NA	Locomotion	Decrease
De Leonibus et al., 2001	Lesion + Acb MK801	NA	NA	Locomotion	Blocked
Johnson et al., 1996	DAMGO + VTA baclofen	Opiod	Mu agonist	Locomotion	Blocked
Kemppainen et al., 2012	DAMGO	Opioid	Mu agonist	Locomotion	Increase
Alesdatter and Kalivas 1993	DAMGO	Opioid	Mu agonist	Locomotion	Increase
Austin and Kalivas 1989	DAMGO	Opioid	Mu agonist	Locomotion	Increase
Austin and Kalivas 1989	DPEN	Opioid	Delta agonist	Locomotion	Increase
Austin and Kalivas 1989	Naloxone	Opioid	Multiple	Locomotion	No effect
Austin and Kalivas 1990	DAMGO	Opioid	Mu agonist	Locomotion	Increase
Austin and Kalivas 1990	DPDPE	Opioid	Delta agonist	Locomotion	Increase
Austin and Kalivas 1991	DAMGO	Opioid	Mu agonist	Locomotion	Increase
Churchill and Kalivas 1999	DAMGO	Opioid	Mu agonist	Locomotion	Increase
Churchill and Kalivas 1999	DAMGO with Mediodorsal thalams procaine	Opioid	Mu agonist	Locomotion	Blocked
Churchill and Kalivas 1999	DAMGO + midbrain extrapyramidal region procaine	Opioid	Mu agonist	Locomotion	Blocked
Churchill et al., 1998	DAMGO	Opioid	Mu agonist	Locomotion	Increase

Reference	VP Manipulation	System	Effects	Task	Result
Churchill et al., 1998	DAMGO + VTA Baclofen	Opioid	Mu agonist	Locomotion	Blocked
Hoffman et al., 1991	DAMGO	Opioid	Mu agonist	Locomotion	Increase
Hoffman et al., 1991	DPDPE	Opioid	Delta agonist	Locomotion	No effect
Hoffman et al., 1991	U50,488H	Opioid	Kappa agonist	Locomotion	No effect
Kalivas et al., 2001	AMPA	Glutamate	AMPA receptor Agonist	Locomotion	Increase
Kalivas et al., 2001	VP AMPA & MD GABA-B saclofen	Glutamate	AMPA receptor Agonist	Locomotion	No effect
Kalivas et al., 2001	DAMGO	Opioid	Mu agonist	Locomotion	Increase
Kalivas et al., 2001	VP DAMGO & MD GABA-B saclofen	Opioid	Mu agonist	Locomotion	Blocked
Kalivas et al., 1991	DAMGO	Opioid	Mu agonist	Locomotion	Increase
Skoubis and Maidment 2003	Naloxone	Opioid	Multiple	Locomotion	Decrease
Skoubis and Maidment 2003	CTOP	Opioid	Mu agonist	Locomotion	Increase
Smith et al., 2005	DAMGO	Opioid	Mu agonist	Locomotion	Increase
Austin and Kalivas 1990	DAMGO+muscimol	Opioid + GABA	Mu agonist + GABA-A Agonist	Locomotion	Attenuated
Gong et al., 1996	Procaine	Sodium	Antagonist	Locomotion	Decrease
Napier et al., 1995	DiMeC7	Substance P	Agonist	Locomotion	Increase
Gong et al., 1997	6-OHDA	DA/NE	NA	Locomotion induced by cocaine	Decrease
McFarland and Kalivas 2001	Fluphenazine	Dopamine	D1/D2 antagonist	Locomotion induced by cocaine	Decrease
McFarland and Kalivas 2001	Baclofen/Muscimol	GABA	GABA-A/B Agonist	Locomotion induced by cocaine	No effect
Skoubis and Maidment 2003	Naloxone	Opioid	Multiple	Locomotion induced by cocaine	No effect
Tang et al., 2005	CTAP	Opioid	Mu Antag	Locomotion induced by cocaine	No effect
Kretschmer 2000	Lesion	NA	NA	Locomotion induced by dizocilpine	No effect
Hooks and Kalivas 1995	Muscimol	GABA	GABA-A Agonist	Locomotion induced by novelty	Decrease
Hooks and Kalivas 1994	DAMGO	Opioid	Mu agonist	Locomotion induced by novelty	Increase
Uchida et al., 2005	Shell SKF82958/quinpirole + VP muscimol	Dopamine	Multiple	Repetitive jaw movements	Blocked
Uchida et al., 2005	Shell SKF82958/quinpirole + VP bicuculline	Dopamine	Multiple	Repetitive jaw movements	Blocked
Uchida et al., 2005	Bicuculline	GABA	GABA-A Antagonist	Repetitive jaw movements	No effect

Reference	VP Manipulation	System	Effects	Task	Result
Kretschmer 2000	Lesion	NA	NA	Stereotyped sniffing induced by dizocilpine	No effect
Shimura et al., 2006	Bicuculline	GABA	GABA-A Antagonist	Rearing	Increase
Shimura et al., 2006	Muscimol	GABA	GABA-A Agonist	Rearing	Decrease
Shimura et al., 2006	Bicuculline	GABA	GABA-A Antagonist	Horizontal Movements	Increase
Shimura et al., 2006	Muscimol	GABA	GABA-A Agonist	Horizontal Movements	Decrease

Manipulation refers to an intra-VP injection or VP lesion, unless stated otherwise.

Table 3

Intra-VP injections of dopamine and dopamine agonists produced oral dyskinesia that is comparable to that seen with intraperitoneal amphetamine.

Treatment (intra-VP, μg/0.5μl/side)	**Dyskinesia Score**
Vehicle	9±2.0
Amphetamine 1mg/kg ip	24±5.8**
Dopamine (10)	49±11.4**
Quinpirole (13.5)#	19±3.5**
SKF82958 (21.7)#	34±9.8**
SCH23390 0.1mg/kg ip + SKF82958 (21.7)#	7±3.3
SCH23390 (0.1) + SKF82958 (21.7)#	16±4.4

An oral dyskinesia count was assigned if the animal engaged in any one of the following: chewing, teeth-grinding, licking/tongue protrusions or yawing. The oral behaviors were quantified for one min, every five min, for a total of 13 assessment periods. Intra-VP injections are described in Table 1 legend. Intraperitoneal (ip) amphetamine served as the positive control.

[*] P<0.05

[#] equal molar to 10 μg dopamine. ANOVA with *post doc* Dunnets

[**] P<0.001, *vs*. intra-VP Vehicle. Quinpirole, D2 receptor family agonist; SKF82958, D1 receptor family agonist; SCH23390, D1 receptor family antagonist. SCH23390 ip was given 30 min prior to intra-VP SKF82958 injection. Intra-VP SCH23390 immediately preceded intra-VP SKF82958. Data from Dr. Napier.

Table 4

VP manipulations and consummatory effects.

Reference	VP Manipulation	System	Effects	Task	Result
Inui et al., 2007	Bicuculline	GABA	GABA-A Antagonist	Consumption	Increase
Stratford et al., 1999	Bicuculline	GABA	GABA-A Antagonist	Consumption	Increase
Stratford and Wirtshafter, 2012	Lesion	NA	NA	Consumption induced by shell muscimol	Attenuated
Stratford and Wirtshafter, 2013	Bicuculline	GABA	GABA-A Antagonist	Consumption	Increase
Stratford and Wirtshafter, 2013	Bicuculline	GABA	GABA-A Antagonist	Consumption after LH lesion	Attenuated
Covelo et al. 2014	Bicuculline	GABA	GABA-A Antagonist	Consumption of fat	Increase
Taha et al., 2009	Muscimol	GABA	GABA-A Agonist	Consumption	Decrease
Smith et al., 2005	Bicuculline	GABA	GABA-A Antagonist	Consumption	Increase
McAlonen et al., 1993	Lesion	NA	NA	Consumption	No effect
Smith et al., 2005	DAMGO	Opioid	Mu agonist	Consumption	Mixed
Smith et al., 2007	DAMGO	Opioid	Mu agonist	Consumption	Increase
Harvey et al., 2002	3-PBC	GABA	A1 Mixed	Saccharin Consumption	Decrease
Shimura et al., 2006	Muscimol	GABA	A Agonist	Consumption of Preferred saccharin	Decrease
Shimura et al., 2006	Bicuculline	GABA	GABA-A Antagonist	Consumption of Preferred saccharin	Increase
Shimura et al., 2006	CNQX	Glutamate	AMPA Antagonist	Consumption of Preferred saccharin	Decrease
Shimura et al., 2006	DAMGO	Opioid	Mu agonist	Consumption of Preferred saccharin	Mixed
Shimura et al., 2006	SCH-23390	Dopamine	D2 Antagonist	Consumption of Preferred saccharin	Decrease
Shimura et al., 2006	Sulpiride	Dopamine	D2 agonist	Consumption of Preferred saccharin	No effect
Shimura et al., 2006	Muscimol	GABA	GABA-A Agonist	Consumption of Nonpreferred quinine	Decrease
Shimura et al., 2006	Bicuculline	GABA	GABA-A Antagonist	Consumption of Nonpreferred quinine	Decrease
Shimura et al., 2006	CNQX	Glutamate	AMPA Antagonist	Consumption of Nonpreferred quinine	No effect
Shimura et al., 2006	DAMGO	Opioid	Mu agonist	Consumption of Nonpreferred quinine	Decrease
Shimura et al., 2006	SCH-23390	Dopamine	D2 Antagonist	Consumption of Nonpreferred quinine	No effect
Shimura et al., 2006	Sulpiride	Dopamine	D2 agonist	Consumption of Nonpreferred quinine	No effect
Shimura et al., 2006	Muscimol	GABA	GABA-A Agonist	Consumption of Water	Decrease
Shimura et al., 2006	Bicuculline	GABA	GABA-A Antagonist	Consumption of Water	No effect
Shimura et al., 2006	CNQX	Glutamate	AMPA Antagonist	Consumption of Water	No effect
Shimura et al., 2006	DAMGO	Opioid	Mu agonist	Consumption of Water	Decrease
Shimura et al., 2006	SCH-23390	Dopamine	D2 Antagonist	Consumption of Water	No effect

Reference	VP Manipulation	System	Effects	Task	Result
Shimura et al., 2006	Sulpiride	Dopamine	D2 agonist	Consumption of Water	No effect
Farrar et al., 2008	Muscimol	GABA	GABA-A Agonist	Consumption during food self-administration	Mixed
Farrar et al., 2008	Muscimol	GABA	GABA-A Agonist	Consumption of preferred substance	Mixed
Taha et al., 2009	Muscimol	GABA	GABA-A Agonist	Consumption induced by Acb DAMGO	Blocked
Taha et al., 2009	Lesion	NA	NA	Consumption induced by Acb DAMGO	No effect
Smith et al., 2007	VP Naloxone & Acb DAMGO	Opioid	Antagonist	Consumption induced by Acb DAMGO	No effect
Smith et al., 2007	VP DAMGO & Acb naloxone	Opioid	Mu agonist	Consumption induced by VP DAMGO	Decrease
Johnson et al., 1996b	Lesion	NA	NA	Responses during food self-administration	Decrease
Fletcher et al., 1998	Amphetamine	Dopamine	Multiple	Responses during food self-administration with conditioned reinforcer	Increase
Fletcher et al., 1998	Picrotoxin	GABA	GABA-A Antagonist	Food self-administration with conditioned reinforcer	Decrease
Smith et al., 2005	Bicuculline	GABA	GABA-A Antagonist	Food carrying	Increase
Smith et al., 2005	DAMGO	Opioid	Mu agonist	Food carrying	No effect
Inui et al., 2007	Bicuculline	GABA	GABA-A Antagonist	Hedonic taste reactivity	Increase
Smith et al., 2005	Bicuculline	GABA	GABA-A Antagonist	Hedonic taste reactivity	No effect
Smith et al., 2005	DAMGO	Opioid	Mu agonist	Hedonic taste reactivity	Mixed
Smith et al., 2007	DAMGO	Opioid	Mu agonist	Hedonic taste reactivity	Increase
Shimura et al., 2006	Muscimol	GABA	GABA-A Agonist	Hedonic taste reactivity	Decrease
Shimura et al., 2006	Bicuculline	GABA	GABA-A Antagonist	Hedonic taste reactivity	No effect
Shimura et al., 2006	CNQX	Glutamate	AMPA Antagonist	Hedonic taste reactivity	No effect
Shimura et al., 2006	DAMGO	Opioid	Mu agonist	Hedonic taste reactivity	No effect
Shimura et al., 2006	SCH-23390	Dopamine	D2 Antagonist	Hedonic taste reactivity	No effect
Inui et al., 2007	Bicuculline	GABA	GABA-A Antagonist	Aversive taste reactivity	Decrease
Shimura et al., 2006	Muscimol	GABA	GABA-A Antagonist	Aversive taste reactivity	Increase
Shimura et al., 2006	Bicuculline	GABA	GABA-A Antagonist	Aversive taste reactivity	No effect
Shimura et al., 2006	CNQX	Glutamate	AMPA Antagonist	Aversive taste reactivity	No effect
Shimura et al., 2006	DAMGO	Opioid	Mu agonist	Aversive taste reactivity	No effect
Shimura et al., 2006	SCH-23390	Dopamine	D2 Antagonist	Aversive taste reactivity	No effect
Smith et al., 2007	VP Naloxone & Acb DAMGO	Opioid	Antagonist	Taste reactivity induced by Acb DAMGO	Blocked
Smith et al., 2007	VP DAMGO & Acb naloxone	Opioid	Antagonist	Taste reactivity induced by VP DAMGO	Blocked
Inui et al., 2007	Bicuculline	GABA	GABA-A Antagonist	Taste aversion	Blocked

Manipulation refers to an intra-VP injections or VP lesion, unless stated otherwise.

Table 5

VP manipulations and cognitive, maternal, rewarding (selfstimulation), and aversive effects.

Reference	VP Manipulation	System	Effects	Task	Result
Numan et al., 2005a	SCH 23390	Dopamine	D1 Antagonist	Maternal Behavior (Pup retrieval)	No effect
Numan et al., 2005b	Muscimol	GABA	GABA-A Agonist	Maternal Behavior (Pup retrieval + Nursing duration)	Decrease
Numan et al., 2005b	VP muscimol (contralateral) + MPOA lesion (ipsilateral)	GABA	GABA-A Agonist	Maternal Behavior (Pup retrieval + Nursing duration)	Decrease
Swerdlow et al., 1990	Picrotoxin	GABA	GABA-A Antagonist	Pre-pulse inhibition	Decrease
Swerdlow et al., 1990	VP Muscimol + Acb DA	GABA	GABA-A Agonist	Disruption of Pre-pulse inhibition by Acb DA	Blocked
Kodsi and Swerdlow 1995a	Medial VP Picrotoxin	GABA	GABA-A Antagonist	Pre-pulse inhibition	Decrease
Kodsi and Swerdlow 1995a	Central and lateral VP Picrotoxin	GABA	GABA-A Antagonist	Pre-pulse inhibition	No effect
Kodsi and Swerdlow 1995a	2-OH-saclofen	GABA	GABA-B Antagonist	Pre-pulse inhibition	No effect
Kodsi and Swedlow 1995b	Picrotoxin	GABA	GABA-A Antagonist	Pre-pulse inhibition	Decrease
Swerdlow et al., 1990	Picrotoxin	GABA	Antagonist	Pre-pulse inhibition	Decrease
Kretschmer and Koch 1998	Lesion	NA	NA	Pre-pulse inhibition	No effect
Sipes and Geyer 1997	DOI	Serotonin	5-HT2A agonist	Pre-pulse inhibition	Decrease
Sipes and Geyer 1997	MDL 100,907	Serotonin	5-HT2A antagonist	Pre-pulse inhibition	Increase
Ferry et al., 2000	Lesion	NA	NA	Reversal learning	Decrease
Zhang et al., 2005	Muscimol	GABA	GABA-A Agonist	Working memory task performance (lever)	Decrease
Zhang et al., 2005	AMPA	Glutamate	AMPA agonist	Working memory task performance (lever)	Decrease
Zhang et al., 2005	Lesion	NA	NA	Working memory task performance (lever)	Decrease
Zhang et al., 2005	DAMGO	Opioid	Mu Agonist	Working memory task performance (lever)	Decrease
Kalivas et al., 2001	AMPA	Glutamate	AMPA agonist	Working memory task performance (maze)	Decrease
Kalivas et al., 2001	DAMGO	Opioid	Mu Agonist	Working memory task performance (maze)	Decrease
Kalivas et al., 2001	VP DAMGO & MD GABA GABA-B saclofen	Opioid	Mu Agonist	Working memory task performance (maze) impairment	Blocked
Chrobak and Napier 2002	Saline or aCSF	NA	NA	Working memory task performance (maze)	Decrease
Floresco et al., 1999	Lidocaine	Sodium	Antagonist	Working memory task performance (maze)	Decrease
Huston et al., 1987	Lesion	NA	NA	Brain Stimulation Reward	Decrease

Reference	VP Manipulation	System	Effects	Task	Result
Johnson and Stellar 1994b	Lesion	NA	NA	Brain Stimulation Reward	No effect
Johnson et al., 1993	DAMGO	Opioid	Mu agonist	Brain Stimulation Reward	Mixed
Johnson and Stellar 1994a	DPDPE	Opioid	Delta agonist	Brain Stimulation Reward	Decrease
Waraczynski and Demco 2006	Lidocaine	Sodium	Antagonist	Threshold of self-stimulation of Medial Forebrain Bundle	No effect
Ollman et al., 2014	Neurotensin	Neurotensin	Agonist	Conditioned place preference	Established
Panagis and Spyraki 1996	VP self-stimulation	Dopamine	Multiple	Threshold of self-stimulation and Systemic cocaine	Decrease
Panagis and Spyraki 1996	VP self-stimulation	Dopamine	D3 agonist	Threshold of self-stimulation and Systemic 7-OH-DPAT	Decrease
Panagis and Spyraki 1996	VP self-stimulation	Dopamine	D2 Antagonist	Threshold of self-stimulation and Systemic haloperidol	Increase
Panagis and Spyraki 1996	VP self-stimulation	Dopamine	D1 Antagonist	Threshold of self-stimulation and Systemic SCH 23390	Increase
Panagis and Spyraki 1996	VP self-stimulation	Dopamine	D1 Antagonist	Threshold of self-stimulation and Systemic raclopride	Increase
Panagis and Spyraki 1996	VP self-stimulation	Dopamine	D2 Antagonist	Threshold of self-stimulation and Systemic Sulpiride	Increase
Panagis and Kastellakis 2002	VP self-stimulation	GABA	GABA-A Agonist	Threshold of self-stimulation and VTA muscimol	Increase
Panagis and Kastellakis 2002	VP self-stimulation	GABA	GABA-B Agonist	Threshold of self-stimulation and VTA baclofen	Increase
Panagis and Kastellakis 2002	VP self-stimulation	Glutamate	NMDA agonist	Threshold of self-stimulation and VTA NMDA	No effect
Panagis and Kastellakis 2002	VP self-stimulation	Glutamate	AMPA agonist	Threshold of self-stimulation and VTA AMPA	No effect
Panagis et al., 1998	VP self-stimulation	Opioid	Multiple	Threshold of self-stimulation and VTA morphine	Decrease
Smith et al., 2005	Bicuculline	GABA	GABA-A Antagonist	Digging	Increase
Smith et al., 2005	DAMGO	Opioid	Mu agonist	Digging	No effect
Mingote et al., 2008	Muscimol	GABA	GABA-A Agonist	Effort task impairment induced by Acb Adenosine A2A agonist	Blocked
Smith et al., 2005	Bicuculline	GABA	GABA-A Antagonist	Forepaw “defensive” treading	Increase
Smith et al., 2005	DAMGO	Opioid	Mu agonist	Forepaw “defensive” treading	Increase
Lawrence et al., 2003	Picrotoxin	GABA	GABA-A Antagonist	Latent Inhibition	No effect
Lawrence et al., 2003	Muscimol	GABA	GABA-A Agonist	Latent Inhibition	No effect

Manipulation refers to an intra-VP injection or VP lesion, unless stated otherwise.

Table 6

Comparisons of ejection current-response relationships for microiontophoretically applied dopamine and D1 agonists on VP neuronal firing between cocaine naïve and cocaine exposed rats.

		Cocaine Naïve			**Cocaine Exposed**		
Iontophoresed treatment	**Response Category**	**Threshold[2] (nA)**	**Ecur$_{50}$ (nA)**	**Emax (% BL)[3]**	**Threshold[2] (nA)**	**Ecur$_{50}$ (nA)**	**Emax (% BL)[3]**
Dopamine	Increase	26±4	36±4	+93±17	10±3[*]	29±5	+101±18
Dopamine	Decrease	32±4	38±4	-58±5	15±4[*]	39±7	-73±4[*]
D1 Agonists[1]	Decrease	33±9	44±10	-41±4	13±3[*]	36±7	-86±4[*]

[1] Both SKF38393 and SKF82958 were tested. The data did not differ for the two agonists and were pooled.

[2] Threshold, the nA of current that produced a change in firing of 20% from baseline.

[3] BL, pretreatment baseline firing, standardized as 100%. Protocols follow those used in McDaid et al., 2005. In brief, cocaine was given once daily as 15mg/kg (intraperitoneal) for five days. Three days later (a time when this treatment paradigm is sufficient to evoke sensitized motor responding to an acute cocaine challenge), the rats were prepared for *in vivo* electrophysiological evaluations of individual VP neurons. Microiontophoresis was used to locally apply dopamine and the D1 agonists, SKF38392 and SKF82958. Recordings conducted by Dr. Pat Johnson. Chronic exposure to cocaine decreased the threshold for both the firing rate increases and decreases to DA, and responding to the D1 agonists. Repeated cocaine administration also increased the magnitude of the rate decreases induced by DA and the D1 agonists (Emax). Potency (indicated by the iontophoretic current that produced 50% of the Emax, designated as Ecur$_{50}$) for DA or the D1 agonists was not changed by chronic cocaine.

[*] p<0.05, compared to cocaine naïve. Data from Dr. Napier.

Table 7

VP manipulations and effects related to drugs of abuse.

Reference	VP Manipulation	System	Effects	Task	Result
Dallimore et al., 2006	CNQX and AP-5	Glutamate	Multiple	Behavioral sensitization with morphine	Blocked
Kalivas et al., 1991	DAMGO	Opioid	Mu agonist	Behavioral sensitization with morphine	Expressed
Rokosik et al., 2013	DAMGO	Opioid	Mu agonist	Behavioral sensitization with morphine	Expressed
Johnson and Napier 2000	CTOP	Opioid	Mu	Behavioral sensitization with morphine	Blocked
Mickiewicz et al., 2008	CTOP	Opioid	Mu	Behavioral sensitization with morphine	Blocked
Mickiewicz et al., 2009	Morphine	Opioid	Multiple	Behavioral sensitization with morphine	Expressed
Zarrindast et al., 2007	Morphine	Opioid	Multiple	Behavioral sensitization with morphine	Expressed
Chen et al., 2001	MK801	Glutamate	NMDA antagonist	Behavioral sensitization with amphetamine	Blocked
Skoubis and Maidment 2003	Naloxone	Opioid	Multiple antagonist	Conditioned Place Aversion	Formed
Skoubis and Maidment 2003	CTOP	Opioid	Mu antagonist	Conditioned Place Aversion	Formed
Gong et al., 1996	Cocaine	DA	Multiple	Conditioned Place Preference	Formed
Gong et al., 1996	Amphetamine	DA	Multiple	Conditioned Place Preference	Formed
Ikemoto 2003	Cocaine	Dopamine	Multiple	Conditioned Place Preference	No effect
Gong et al., 1997	Picrotoxin	GABA	Antagonist	Conditioned Place Preference	No effect
Gong et al., 1997	AMPA	Glutamate	AMPA	Conditioned Place Preference	No effect
Gong et al., 1996	Procaine	Sodium	Antagonist	Conditioned Place Preference	No effect
Gong et al., 1997	6-OHDA	DA/NE	NA	Conditioned place preference (cocaine)	Decrease
Skoubis and Maidment 2003	Naloxone	Opioid	Multiple	Conditioned place preference (cocaine)	Attenuated
Dallimore et al., 2006	CNQX and AP-5	Glutamate	Multiple	Conditioned place preference (morphine)	Blocked
McAlonen et al., 1993	Lesion	NA	NA	Conditioned place preference (sucrose)	Attenuated
Ikemoto 2003	Cocaine	Dopamine	Multiple	Intracranial self-adminsitration	No effect
Torregrossa and Kalivas 2008	NT8-13	Neurotensin	Agonist	Reinstatement of cocaine-seeking maintained by conditioned reinforcer	Attenuated
McFarland and Kalivas 2001	Fluphenazine	Dopamine	D1/D2 antagonist	Reinstatement of cocaine-seeking triggered by cocaine	No effect
McFarland and Kalivas 2001	Baclofen/Muscimol	GABA	GABA-A/B Agonist	Reinstatement of cocaine-seeking triggered by cocaine	Decrease

Reference	**VP Manipulation**	**System**	**Effects**	**Task**	**Result**
Tang et al., 2005	Cocaine	Multiple	Multiple	Reinstatement of cocaine-seeking triggered by cocaine	Increase
Tang et al., 2005	Cocaine+Morphine	Multiple	Multiple	Reinstatement of cocaine-seeking triggered by cocaine	Mixed
Torregrossa and Kalivas 2008	NT8-13	Neurotensin	Agonist	Reinstatement of cocaine-seeking triggered by cocaine	Increase
Torregrossa and Kalivas 2008	SR142948	Neurotensin	Antagonist	Reinstatement of cocaine-seeking triggered by cocaine	No effect
Tang et al., 2005	CTAP	Opioid	Mu Antag	Reinstatement of cocaine-seeking triggered by cocaine	Decrease
Tang et al., 2005	Morphine	Opioid	Multiple	Reinstatement of cocaine-seeking triggered by cocaine	Increase
Li et al., 2009	AMN082	Glutamate	mGluR7 Agonist	Reinstatement of cocaine-seeking triggered by cocaine	Decrease
Stefanik et al. 2013	Optogenetic inhibition of Core projection to VPdl	GABA	NA	Reinstatement of cocaine-seeking triggered by cocaine+cues	Decrease
McFarland et al., 2004	Baclofen/Muscimol	GABA	GABA-A/B Agonist	Reinstatement of cocaine-seeking triggered by footshock	Decrease
Tang et al., 2005	CTAP	Opioid	Mu Antagonist	Reinstatement of cocaine-seeking triggered by morphine	Blocked
Tang et al., 2005	CTAP	Opioid	Mu Antagonist	Reinstatement of cocaine-seeking triggered by morphine	Blocked
Perry and McNally, 2013	CTAP	Opioid	Mu Antagonist	Reinstatement of alcohol-seeking triggered by context	Blocked
Perry and McNally, 2013	CTAP	Opioid	Mu Antagonist	Reinstatement of alcohol-seeking triggered by alcohol	Blocked
McFarland and Kalivas 2001	Baclofen/Muscimol	GABA	GABA-A/B Agonist	Reinstatement of food-seeking triggered by food	Decrease
McFarland and Kalivas 2001	Unilateral VP Baclofen/ Muscimol & Contralateral mPFC baclofen/muscimol	GABA	GABA-A/B Agonist	Reinstatement of cocaine-seeking triggered by cocaine	Decrease
Tang et al., 2005	CTAP	Opioid	Mu Antagonist	Reinstatement of food-seeking triggered by food	No effect
Rogers et al., 2008	Baclofen/Muscimol	GABA	GABA-A/B Agonist	Reinstatement of heroin-seeking maintained by conditioned reinforcer	Blocked
Rodgers et al., 2008	Baclofen/Muscimol	GABA	GABA-A/B Agonist	Reinstatement of heroin-seeking maintained by conditioned reinforcer	Blocked
Rogers et al., 2008	Baclofen/Muscimol	GABA	GABA-A/B Agonist	Reinstatement of heroin-seeking triggered by heroin	Blocked
Rodgers et al., 2008	Baclofen/Muscimol	GABA	GABA-A/B Agonist	Reinstatement of heroin-seeking triggered by heroin	Blocked
Li et al., 2009	AMN082	Glutamate	R7 agonist	Self-administration of cocaine	Decrease
Robledo and Koob 1993	Lesion	NA	NA	Self-administration of cocaine	Decrease
Robledo and Koob 1993	Lesion	NA	NA	Cocaine self-administration breaking point (progressive ratio)	No effect
Torregrossa and Kalivas 2008	NT8-13	Neurotensin	Agonist	Self-administration of cocaine	No effect

Reference	**VP Manipulation**	**System**	**Effects**	**Task**	**Result**
Torregrossa and Kalivas 2008	SR142948	Neurotensin	Antagonist	Self-administration of cocaine	No effect
Li et al., 2009	AMN082	Glutamate	R7 Agonist	Self-administration of cocaine breakpoint	Decrease
Robledo and Koob 1993	Lesion	NA	NA	Self-administration of cocaine breakpoint	No effect
Torregrossa and Kalivas 2008	NT8-13	Neurotensin	Agonist	Self-administration of cocaine extinction	No effect
Torregrossa and Kalivas 2008	SR142948	Neurotensin	Antagonist	Self-administration of cocaine extinction	No effect
Harvey et al., 2002	3-PBC	GABA	GABA-A1 Mixed	Self-administration of cocaine ethanol	Decrease
June et al., 2003	BCCt	GABA	GABA-A1 Mixed	Self-administration of ethanol	Decrease
Harvey et al., 2002	3-PBC	GABA	GABA-A1 Mixed	Self-administration of saccharine	Increase
Melendez et al. 2005	Sulpiride	Dopamine	D2 antagonist	Ethanol intake	Increase
Kemppainen et al., 2012a	Muscimol	GABA	GABA-A Agonist	Ethanol intake	Decrease
Kemppainen et al., 2012a	Bicuculline	GABA	GABA-A Antagonist	Ethanol intake	Increase
Kemppainen et al., 2012a	Bicuculline + DAMGO	GABA + Opioid	Multiple	Ethanol intake	Blocked
Kemppainen et al., 2012a	Baclofen	GABA	GABA-B Agonist	Ethanol intake	Decrease
Kemppainen et al., 2012a	Saclofen	GABA	GABA-B Antagonist	Ethanol intake	No effect
Kemppainen et al., 2012b	DAMGO	Opioid	Mu agonist	Ethanol intake	Decrease
Kemppainen et al., 2012b	Morphine	Opioid	Agonist	Ethanol intake	Decrease
Kemppainen et al., 2012b	CTOP	Opioid	Mu antagonist	Ethanol intake	Increase

Manipulation refers to an intra-VP injection or VP lesion, unless stated otherwise.