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An update on the connections of the ventral mesencephalic dopaminergic complex

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Abstract

This review covers the intrinsic organization and afferent and efferent connections of the midbrain dopaminergic complex, comprising the substantia nigra, ventral tegmental area and retrorubral field, which house, respectively, the A9, A10 and A8 groups of nigrostriatal, mesolimbic and mesocortical dopaminergic neurons. In addition, A10dc (dorsal, caudal) and A10rv (rostroventral) extensions into, respectively, the ventrolateral periaqueductal gray and supramammillary nucleus are discussed. Associated intrinsic and extrinsic connections of the midbrain dopaminergic complex that utilize gamma-aminobutyric acid (GABA), glutamate and neuropeptides and various co-expressed combinations of these compounds are considered in conjunction with the dopamine-containing systems. A framework is provided for understanding the organization of masssive afferent systems descending and ascending to the midbrain dopaminergic complex from the telencephalon and brainstem, respectively. Within the context of this framework, the basal ganglia direct and indirect output pathways are treated in some detail. Findings from rodent brain are briefly compared with those from primates, including human. Recent literature is emphasized, including traditional experimental neuroanatomical and modern gene transfer and optogenetic studies. An attempt was made to provide sufficient background and cite a representative sampling of earlier primary papers and reviews so that people new to the field may find this to be a relatively comprehensive treatment of the subject.

Keywords

substantia nigra; compacta; reticulata; ventral tegmental area; retrorubral field; periaqueductal gray

Introduction

The vertebrate mesencephalic ventral tegmentum houses a collection of dopamine (DA)-expressing neurons that influences neural systems subserving important adaptive functions

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such as arousal and locomotion (Kelly et al., 1975), control of intended movements (Mink, 1996), reinforcement (Yokel and Wise, 1975), learning (Schultz et al., 1997; Wise, 2004; Matsumoto and Hikosaka, 2009; Matsumoto and Takada, 2013) and state of mind, as in, e.g., wanting and willingness to exert effort (Berridge and Robinson, 1998; Salamone and Correa, 2012). Changes in patterns of DA neuron activity and metabolism caused by drugs of abuse, such as psychostimulants and opioids, contribute to drug addiction (Wise and Koob, 2014; Zahm, 2010). Degeneration of DA-expressing neurons underlies the deficits in movement initiation and posture experienced by Parkinson's disease patients (Lang and Lozano, 1998a; b). Dysregulation of DA neurons underlies the positive symptoms of schizophrenia (Moore et al., 1999; Goto and Grace, 2007; Lau et al., 2013). In view of the broad spectrum of brain functions in which the DAergic (DA) ventral mesencephalic tegmentum has a role and its clinicopathologic significance, it is critically important to understand its interconnections, both intrinsic and with other parts of the brain. This review thus is presented as an update on recent progress mainly with regard to connectivity. A broader perspective on the structure and function of the midbrain ventral tegmentum can be acquired by reference to many outstanding prior reviews devoted to various aspects of the topic (e.g., Moore and Bloom, 1978; Lindvall and Björklund, 1983; Björklund and Lindvall, 1984; Oades and Halliday, 1987; Graybiel et al., 1990; van Domburg and ten Donkelaar, 1991; Langer et al., 1991; Gerfen, 1992; Parent et al., 1995; Fallon and Loughlin, 1995; Heimer et al., 1985; 1995; Haber and Fudge, 1997; Joel and Weiner, 2000; Haber, 2003; Bentivoglio and Morelli, 2005; Marinelli et al., 2006; Björklund and Dunnett, 2007; Fields et al., 2007; Ikemoto, 2007; Prensa et al., 2009; Haber and Knutson, 2010; Sesack and Grace, 2010; Schultz, 2010; Morikawa and Paladini, 2011; Hong, 2013; Roeper, 2013; Ikemoto and Bonci, 2014; Lammel et al., 2014).

Intrinsic organization and connections

A9, A10 and A8 groups of catecholamine-fluorescing cells occupying the ventral tegmental area (VTA), substantia nigra pars compacta (SNc), and retrobrubral field (RRF), respectively, were discovered by the great Swedish histochemists (Dahlström and Fuxe, 1964; Anden et al., 1964, 1965; 1966a; 1966b; Ungerstedt et al., 1971), who verified the DA nature of these cell groups (reviewed in Björklund and Lindvall, 1984; see also Björklund and Dunnett, 2007) and also showed that they give rise to a *mesolimbic* pathway to the limbic forebrain and orbitofrontal cortex and a *nigrostriatal* pathway to the striatum. We previously have referred to them collectively as the 'ventral mesencephalic dopaminergic complex' (Zahm et al., 2011b), which herein will be shortened to, 'midbrain DA complex'. It should be clear that the A8–10 taxonomy refers explicitly to DA neurons, whereas the VTA, SNc, RRF are brainstem structures that also contain locally and distantly projecting neurons that utilize as transmitters, either co-expressed with DA or separately, gamma-aminobutyric acid (GABA), glutamate (GLU), various neuropeptides and possibly as yet unknown compounds.

A9, A10 and A8 comprise a single constellation of DA neurons that approximates the shape of an ellipsoid anchored in the VTA by A10 (Fig. 1). A9, more rostrally (Fig. 1A–E), and then A8 (Fig. 1D and E) extend lateralward from A10 beneath and above the medial lemniscus, through the SNc and RRF, respectively, to meet again in the ventrolateral

tegmentum. A8 extends caudomedialward beyond the caudal limits of A9 and A10, ultimately to arch toward the periaqueductal gray (PAG). Rostroventral (rv), rostrodorsal, caudal (c) and dorsocaudal (dc) extensions of A10 into, respectively, supramammillary nucleus, medial habenula, dorsal midline of the caudal VTA and the rostral ventrolateral (vl) quadrant of the PAG (Fig. 1F) were designated later by Hökfelt et al. (1984b). A10rv and A10dc provide rich innervations of he lateral septum and extended amygdala, respectively, to be described in more detail below. Where they intermingle, neurons of A8 are morphologically indistinguishable from those in A9 or A10, as are A9 and A10 neurons at any imaginary boundary between the VTA and SNc (Fig. 1A–E). Nonetheless, A8, A9 and A10 are structurally and functionally differentiated and this is reflected in the relatively distinct, albeit broadly overlapping, topographies and functions of their ascending projections (Fallon et al., 1978; Fallon and Moore, 1978; Swanson, 1982; Lindvall and Björkland, 1983; Fallon and Loughlin, 1985; 1995; Deutch et al., 1988; Fallon, 1988).

The VTA is a paramedian sector of the reticular formation at the ventral surface of the midbrain (Fig. 1A–E) that has within it a number of cell groups that have been categorized as nuclei (Taber, 1961; Berman, 1968; Phillipson, 1979a; Oades and Halliday, 1987; van Domburg and ten Donkelaar, 1991). These, which were reviewed in some detail by Ikemoto (2007), comprise a ventromedial, cell-dense nucleus paranigralis, a more lateral and dorsal nucleus parabrachialis pigmentosus and some midline structures, including a nucleus interfascicularis (Phillipson, 1979a) and a of couple linear nuclei - rostral and, depending on the account, either caudal (Phillipson, 1979a) or central (Swanson, 1982; Ikemoto, 2007), the latter of which extends in the midline from the main body of the VTA to the PAG and houses the A10c group of Hökfelt et al. (1984b). Neurons of the VTA are said to comprise a heterogeneous mixture of DA (~65%), GABAergic (GABA, ~30%) and GLUergic (GLU, ~5%) neurons (Nagai et al. 1983; Mugnaini and Oertel, 1985; Kosaka et al. 1987; Steffensen et al. 1998; Carr and Sesack, 2000a; Kawano et al., 2006; Margolis et al. 2006; 2012; Nair-Roberts et al. 2008; Steffensen et al., 2008; Dobi et al. 2010; Yamaguchi et al. 2011) of which none is distributed in a manner that correlates systematically with the aforementioned nuclear organization. Most VTA DA neurons occupy regions taken up by the paranigral and parabrachialis pigmentus nuclei, consistent with the greater proportional size of those VTA subnuclei (Dahlstorm and Fuxe, 1964; Swanson, 1982; Olson and Nestler, 2007), but significant numbers also are centered in the midline, particularly within the central linear nucleus and interfascicularis, where, despite its smaller size, the density of DA neurons is said to be greatest (Ikemoto, 2007). DA neurons are sparse in the rostral linear nucleus and a caudal part of the VTA which extends into the paramedian mesopontine tegmentum (Perrotti et al., 2005; Ikemoto, 2007; Olson and Nestler, 2007). In contrast, GABA neurons are scattered throughout the VTA, but are densest in a rostral, dorsolateral cluster identified by Olson and Nestler (2007) and the aforementioned DA neuron-sparse caudal region, where ovoid aggregates of GABA neurons flank the interpeduncular nucleus on both sides of the midline (see Fig. 2E–H in Jhou et al., 2009b). Perrotti et al. (2005) and others (Ikemoto, 2007; Kaufling et al., 2009; Bourdy and Barrot, 2012) have designated this region as the ‘tail’ of the ventral tegmental area (tVTA), but others regarded it as a structure distinct from the VTA (e.g., Jhou, 2005; Geisler et al., 2008) and it was recently given a name, rostromedial tegmental nucleus (RMTg, Jhou et al., 2009a; b; Lavezzi and Zahm, 2011), to

formalize the distinction. Presently, both names are used in the literature. It should be noted, however, that the cell-dense structure identified as the ventral tegmental tail (their VTT) in Figure 8 of the review by Ikemoto (2007) does not represent what subsequently was identified as the RMTg (compare with Fig. 1 in Jhou et al., 2009b, and Fig. 2 in Lavezzi and Zahm, 2011; see also Jhou et al., 2009a; Kaufling et al., 2009; Barrot and Thome, 2011; Bourdy and Barrot, 2012).

The VTA also contains GLU neurons, said to be relatively few and most numerous rostromedially (Yamaguchi et al., 2007; Nair-Roberts et al., 2008). However, numerous recent multidisciplinary studies have provided evidence for abundant functionally significant release of GLU and/or GABA from the axons of DA neurons, irrespective of the relative strength of the corresponding neuroanatomical evidence for co-localization (Joyce and Rayport, 2000; Chuhma et al., 2004; 2009; Hnasko et al., 2010; 2012; Stuber et al., 2010; Alsiö et al., 2011; Fortin et al., 2012; Tritsch et al., 2012; Stamatakis et al., 2013). Moreover, in the case of GLU, in vivo co-expression is reported to peak early and decline as rats mature (Mendez et al., 2008). Consequently, the true extent of overlap of DA, GLU and GABA expression in the midbrain DA complex is presently uncertain. In contrast to GABA and GLU, which only recently have been shown persuasively to co-express with DA, co-expression of the neuropeptides cholecystokinin (CCK) and neurotensin (NT) in midbrain DA neurons has been recognized for decades (Hökfelt et al., 1980a; b; 1984a; Kalivas and Miller, 1984; Kalivas 1985; Seroogy et al., 1987, 1988, 1989; Studler et al., 1988; Crawley, 1991; Tan et al., 1999; Geisler et al., 2006).

The SNc, PAGvl, RRF and SN pars lateralis (SNl), which occupies the interval between the lateralmost border of the SNr and ventromedial border of the inferior colliculus (Fig. 1B–D), also comprise combinations of DA, GABA and GLU neurons (Moriizumi et al., 1992, Rogriguez and Gonzalez-Hernandez, 1999; Nair-Roberts et al., 2008; Geisler et al., 2007; Omelchenko and Sesack, 2010; Yamaguchi et al., 2013). The SNc and RRF are reported to contain approximately 29% and 58% GABA neurons, respectively, but apparently few GLU neurons (Nair-Roberts et al., 2008). However, Yamaguchi et al. (2013) have reported, based on a double-labeling protocol, that approximately 15% of SNc neurons expressed VGLUT2 and 85% expressed tyrosine hydroxylase (TH, the rate limiting enzyme in catecholamine synthesis, characteristically indicates DA phenotype in the midbrain DA complex). In the RRF, approximately 36% of total TH and VGLUT2 neurons expressed VGLUT2, with the numbers increasing in a rostralcaudal gradient, and 63% expressed TH. Interestingly, these data leave little room for significant co-expression of GLU and DA in the SNc and RRF. The PAG also contains GLU (Geisler et al., 2007) and GABA projection neurons (Omelchenko and Sesack, 2010).

The heterogeneous composition of the midbrain DA complex is also reflected in the distribution within subpopulations of DA neurons of different calcium buffering enzymes. Calbindin-D 28kD is expressed in the VTA, preferentially in neurons projecting to the accumbens (Acb) core (Tan et al., 1999; Barrot et al., 2000), RRF and a dorsal tier of the SNc (Gerfen et al., 1985). Another calcium binding protein, calretinin (Rogers, 1992; Isaacs and Jacobowitz, 1994), is expressed by about equivalent numbers of Acb core- and Acb

shell-projecting DA neurons (Tan et al., 1999) and occupies mainly the ventral tier of the SNc (Haber et al., 1995; Krzywkowski et al., 1995).

Intrinsic connections

Following injections of the anterograde tracer *Phaseolus vulgaris*-leucoagglutinin (PHA-L) into various parts of the VTA, Ferreira et al. (2008) showed that [1] the rostral VTA projects weakly to the caudal, [2] the caudal VTA projects substantially to the rostral, [3] the caudal pole of the VTA heavily and in widespread fashion innervates the VTA, SNc and RRF, [4] the medial supramammillary nucleus innervates the ventro- and caudomedial VTA and [5] the ventrolateral VTA (within subnucleus paranigralis) projects to the interfascicular nucleus. They noted ([5] being the exception) that anterograde labeling most typically tends to spread from medial injections to more lateral VTA terminal fields, consistent with a tendency for medial to lateral flow of information in the midbrain DA complex (see below). Their remarkable injections into the caudal pole of the VTA produced robust labeling throughout the midbrain DA complex, especially in the SNc, where they saw TH immunoreactive neurons and dendrites richly entwined by PHA-L labeled axons and abundantly contacted by labeled axonal varicosities. The caudal injections of Ferreira et al. (2008) foreshadow papers that were to appear in a couple years announcing discovery of the RMTg (Jhou et al., 2009a;b; Kaufling et al., 2009).

In addition, the RRF projects to the VTA, SNc, and PAGvl (Deutch et al., 1988; Arts et al. 1996; Zahm et al., 2011b). The PAGvl has intra-PAG associational connections and GABA (Kirouac et al., 2004) inputs from the VTA (Vianna and Brandao, 2003; Zahm et al., 2011b), GLU outputs to the VTA (Geisler et al., 2007), GABA outputs to the VTA contacting DA and GABA neurons (Omelchenko and Sesack, 2010), and outputs to the RRF of undetermined phenotype (Zahm et al., 2011b).

Interconnectivity of VTA neurons is thought to originate mainly from non-DA VTA neurons because, following VTA tracer injections, few anterogradely labeled axon terminals or retrogradely labeled VTA neurons have TH immunoreactivity (Bayer and Pickel, 1990; Ferreira et al., 2008; Jhou et al., 2009b). Where axons labeled anterogradely following PHA-L injections into the VTA do exhibit synapses (Omelchenko and Sesack, 2009), the membrane appositions typically are symmetric (signifying inhibitory) and involve VTA neurons expressing TH. Many such synaptic profiles are co-labeled with glutamate decarboxylase (GAD, GABA synthesizing enzyme) immunoreactivity. Recent gene transfer and optogenetic studies indicate that VTA DA neurons are mainly inhibited following optogenetic stimulation of VTA GABA neurons (van Zessen et al., 2012; Cohen et al., 2012; Tan et al., 2012; Padgett et al., 2012). However, the extent in these studies to which the illumination may have involved the RMTg is problematic, so that the relative roles played by VTA GABA neurons versus RMTg inputs in regulating the activity of VTA and SNc neurons remains to be worked out (Hong et al., 2011). The few asymmetric (presumably excitatory) contacts observed by Omelchenko and Sesack (2009) fit with evidence provided by Dobi et al. (2010) that GLU neurons establish synaptic contacts with both TH-positive and TH-negative neurons in the VTA. Taken together, these results indicate that GABA and GLU VTA neurons (but few DA neurons) project to DA and non-DA VTA neurons and so

represent a potentially strong and nuanced modulatory influence over DA released both locally and from the ascending DA projections. The actions of intrinsic circuitry may not be uniform throughout the midbrain DA complex, however, in that Ferreira et al. (2008) observed following PHA-L injections into the VTA that close contacts of anterogradely labeled axons with DA neurons were significantly fewer in the VTA as compared to the SNc and RRF. Insofar as Olmelchenko and Sesack (2009) have confirmed that such close contacts commonly are synaptic, intrinsic connectivity may subserve a net synaptically-mediated transfer of information from the VTA to the SNc.

Somatodendritic DA release and sensitivity to circulating hormones and peptides

DA neurons in both the SNc and VTA may also influence the local environment through somatodendritic DA release (Kalivas et al., 1989; Geffen et al. 1976; Rice et al. 1994; 1997; 2011). Whereas local DA release in the SNc appears to be exclusively somatodendritic, somatodendritic release of DA in the VTA is supplemented by DA released from the axons of DA neurons residing in the VTA and SNc, although, as noted above, the local DA innervation is much subordinate to local non-DA innervation (Bayer and Pickel 1990; Ferriera et al., 2008; Jhou et al., 2009b). Somatodendritic release of DA within the SNc and VTA likely activates D1 receptors residing on the terminals of VTA afferents, which might indirectly (via local GABA neurons) facilitate the activity of DA neurons (e.g., Bocklisch et al., 2013). In conditions of repeated exposure to psychostimulant drugs this effect may contribute to the initiation of behavioral sensitization to DA (Pierce et al., 1996; Bocklisch et al., 2013). Alternatively, local release of DA acts on DA D2 autoreceptors (Sesack et al., 1994; Yung et al., 1995), which act to inhibit both local somatodendritic DA release and release of DA from axon terminals in the mesencepalon and forebrain (Lacey et al., 1987; Kalivas and Duffy, 1991; Cragg and Greenfield, 1997). Indeed, intra-VTA infusions of DA D2 agonists are utilized by research neuroscientists as a means to suppress the activity of DA neurons (e.g., Liu et al., 2008).

Much evidence indicates that the sensitivity with which neurons in the midbrain DA complex respond to physiological stimuli is dependent on concentrations of circulating hormones (e.g., Deroche et al., 1995; Rougé-Pont et al., 1995) and peptides (e.g., Abizaid et al., 2006; Fulton et al., 2006; Hommel et al., 2006). These important effects may be mediated at least in part via afferent connections (e.g., Leinninger et al., 2009), but are commonly due to the direct actions of neuroactive compounds on DA neurons and local circuit, e.g., GABA, neurons. This is a large and important field of inquiry that, however, will not be considered further in this review of neuroanatomical connectivity.

Gap junctions

DA and GABA neurons in the VTA and SNc have gap junctions early (Vandecastelle et al., 2005) and later (Grace and Bunney, 1983; Stobbs et al., 2004; Allison et al., 2006) in development. The firing rate of DA neurons in the SNc is reported to be modulated by conduction of currents through gap junctions (Grace and Bunney, 1983; Vandecastelle et al., 2005). VTA GABA neurons are interconnected by connexin 36-expressing gap junctions, through which conduction is enhanced by corticotegmental input and dopamine (Allison et al., 2006). Gap junctional interconnection of VTA GABA neurons may affect addictive

behaviors, such as, e.g., cocaine and alcohol consumption (Stobbs et al., 2004; Steffensen et al., 2011), by disseminating disinhibitory influences among coupled VTA dopamine neurons.

Afferent Connections

VTA

Inputs to the VTA arise in manifold structures in the cortex, basal forebrain, hypothalamus and brainstem (Nauta and Domesick, 1978; Phillipson, 1979b; Oades and Halliday, 1987; Wallace et al., 1989; 1992; Carr and Sesack, 1999; 2000b; Zahm et al., 2001; Fadel and Deutch, 2002; Philpot et al., 2005; Omelchenko and Sesack, 2005; 2006; 2007; 2009; 2010; Ikemoto, 2007; Balcita-Pedicino and Sesack, 2007; Balcita-Pedicino et al., 2011; Ferreira et al., 2008; Omelchenko et al., 2009; Watabe-Uchida et al., 2012) reported to comprise mainly a highly interconnected network (Geisler and Zahm, 2005; 2006; Geisler et al., 2007; Yetnikoff et al., 2013). Table 1, modified after Table 1 in Geisler and Zahm (2005), lists structures in which retrograde label was found following injections of tracer into the VTA, with those that provide robust input bolded. An initial impression conveyed by such a long list of such diverse structures is that the organization of VTA afferents must be rather diffuse. Certainly, the general pattern of retrograde labeling also contributes to this impression, inasmuch as the scatter of labeled neurons is conspicuous in its indifference to neuroanatomical boundaries. That is, mapped VTA-projecting neurons are as numerous between as within different brain structures (see, e.g., Figs. 3 and 8 in Geisler and Zahm, 2005, Figs. 3 and 4 in Zahm et al., 2011b, and 4 in Yetnikoff et al., 2013) and the structures themselves are often mutually coalescent, i.e., separated by ill-defined transition zones rather than discrete boundaries (see Discussion in Zahm et al., 2013).

The massive, convergent complex of VTA afferents essentially comprises three categories of neurons organized into three interconnected tiers. The most proximal of these comprises so-called ‘isodendritic’ neurons strung along the medial forebrain bundle (mfb) in the ventral pallidal-preoptic-hypothalamic continuum and brainstem. Isodendritic morphology was described by Ramon-Moliner and Nauta (1966) in reference to neurons in the so-called isodendritic core with very long, sparsely branched, sparsely to modestly innervated dendrites -consistent with function of a broadly integrative nature. First tier isodendritic VTA inputs (Geisler and Zahm, 2005) likely comprise an interconnected network that relays descending and ascending (see below) influences not only to the VTA, but to multiple forebrain, hypothalamic and brainstem effectors of somatomotor, autonomic and neuroendocrine function (Swanson and Mogenson, 1981). Most tier 1 neurons happen to lie squarely in the path of a second tier of VTA afferents, axons of which descend mainly within the mfb from densely packed medium size, densely spiny neurons (MdSNs) in the Acb, olfactory tubercle and lateral septum and, to a lesser extent, ventromedial caudate-putamen (CPu) and extended amygdala (EA). We use here the abbreviation MdSN in place of the more common MSN because the latter abbreviation has a traditional strong association with the caudate nucleus and putamen exclusively, whereas we would emphasize the broader distribution of MdSNs throughout an extensive, essentially continuous tier of subcortical GABA structures listed in the preceding sentence. MdSNs in these deep telencephalic

structures have varyingly dense direct projections to the VTA and also provide input to tier 1 isodendritic afferents (Zahm, 1989; Loopuijt and Zahm, 2006), more densely to those in rostral parts of the basal forebrain, culminating in very dense projections from the Acb and olfactory tubercle to 'pallidal' neurons in the ventral pallidum (Heimer, 1972; Heimer et al., 1991; Groenewegen and Russchen, 1984). Ventral pallidal neurons project densely to the VTA (Zahm, 1989; Zahm and Heimer, 1990; Groenewegen et al., 1993) and we lump them here with the isodendritic category, although, according to Ramon-Moliner and Nauta (1966), they are not strictly isodendritic due to their dense striatopallidal input.

A number of papers have revealed a significant amount of specificity in connections conforming to the general organizational framework described above. For example, one subpopulation of Acb neurons expresses mainly D1 DA receptors and projects to ventral pallidum and the VTA (Robertson and Jian, 1995, Lu et al., 1998), where it is reported to target mainly GABA neurons (Xia et al., 2011; Bocklisch et al., 2013). Another expresses D2 receptors and projects to the ventral pallidum (Robertson et al., 1992), which, in turn, projects to the mediodorsal thalamic nucleus (Young et al., 1984). Such compartmentation of Acb connections may be a phylogenetic ancestor of the more complete 'balkanization' of CPu outputs that has substantial implications for afferent regulation of DA neurons (see below).

MdSN-containing, VTA-projecting structures, in turn, are massively innervated by a third tier of neurons, these located in the basal and cortical amygdala, subiculum of the hippocampus, and orbitofrontal cortex [i.e., Heimer and Van Hoesen's (2006) cortical limbic lobe], which also have long descending projections to the vicinity of, and that likely are in contact with, first tier isodendritic VTA-projecting neurons. Moderate output from the orbitofrontal cortex even reaches the VTA itself (Sesack et al., 1989), including DA neurons (Carr and Sesack, 1999; 2000b; Sesack and Carr, 2002), although projections to the VTA from cortical and cortical-like structures otherwise is not the rule; i.e., cortex projects to the ventral midbrain mainly via relays in tiers 2 and 1 (for 'cortical-like,' see Heimer and Van Hoesen, 2006, and references therein). This aside, Carr and Sesack's (2000b) elegant electron microscopic tract tracing study indicated that afferents originating in the medial (m) prefrontal cortex (PfC) project preferentially to [1] VTA DA neurons that project reciprocally to the PfC and [2] VTA GABA neurons that project to the Acb, but [3] not to VTA DA neurons that project to the Acb.

Much evidence indicates that tier 3 cortical and cortical-like outputs are exclusively GLU, whereas the outputs of tier 2 deep telencephalic nuclei are prominently GABA (Alheid and Heimer, 1988; Swanson, 2000; Fremeau et al., 2001; 2004; Geisler et al., 2007). In contrast, both GABA and GLU are represented among the important tier 1 VTA inputs, although, with few exceptions (e.g., see Jhou et al., 2009a; b), little is presently known about in which neurons specifically.

More is known about the distributions and functions of tier 1 peptidergic inputs to the VTA, e.g., the capacity of inputs to the VTA from orexinergic (Aston-Jones et al., 2009; Cason et al. 2010; Cason and Aston-Jones, 2013) and neurotensinergic (Rompre et al., 1992; St-Gelais et al., 2004; Reynolds et al., 2006; Geisler et al., 2006; Kortleven et al., 2012;

Kempadoo et al., 2013) neurons in the lateral hypothalmo-preoptic-ventral pallidum continuum to facilitate DA-mediated locomotor and reward behaviors. Interestingly in this regard, Balcita-Pedicino and Sesack (2007), using electron microscopy, detected orexinergic axon terminals and synaptic contacts in the VTA that seemed to these authors inordinately few, in view of the robust functional orexigenic effects that had been reported (refs in preceding sentence). In general, the extent to which VTA neurons of various transmitter phenotypes are preferentially targeted anatomically and physiologically by subsets of neurons in all of the tiers remains to be resolved. Indeed, much detail remains to be learned about the configurations of connections within and between the various structures providing descending projections to the VTA.

VTA descending afferents in general are topographically organized, such that projections to more lateral parts of the VTA tend to come from more lateral parts of the forebrain and brainstem (Phillipson, 1979b; Geisler and Zahm, 2005; Geisler et al., 2007; Ikemoto, 2007). Mediolateral topography is particularly well represented in the ventral striatopallidal-VTA projections, which exhibit, in addition, a rostrocaudal and inverted dorsoventral topography, such that rostral parts of the Acb and ventral pallidum project to more rostral parts of the VTA (Heimer et al., 1991; Zahm and Heimer, 1993; Groenewegen et al., 1993), whereas neurons positioned more dorsally in the Acb project ventrally within the VTA (Deniau et al., 1996; Zahm et al., 2013), consistent with the well known inverted dorsoventral topography that characterizes striatal projections to the SN (Heimer et al., 1985; 1995; Deniau et al., 1996). Although abundant evidence exists that projections conveying functionally diverse information to the midbrain converge in several striatopallidal structures (Bevan et al., 1996; Smith et al., 1998), Deniau, Thierry and colleagues have argued equivalently forcefully that functional segregation is maintained in parallel basal ganglia circuits descending through the midbrain DA complex (Deniau et al., 1996; Deniau and Thierry, 1997; Maurice et al., 1998; Maurin et al., 1999). Within the midbrain DA complex, the generous spread and extensive overlap of afferents from manifold sources (Geisler and Zahm, 2005) and relatively meager evidence of connectional specificity suggests that VTA function must include a broadly integrative component.

Ascending projections to the VTA arise in numerous brainstem structures, including the superior colliculus (deep layer), RMTg, PAG, deep mesencephalic nucleus, dorsal raphe, pedunculopontine (PPTg) and laterodorsal tegmental (LDTg) nuclei, median raphe, parabrachial nucleus, cuneiform nucleus, oral and caudal pontine reticular nuclei and the nucleus of the solitary tract (Vertes, 1991; Oakman et al., 1995; Charara et al., 1996; Zahm et al., 2001; Geisler and Zahm, 2005; Geisler et al., 2006; Geisler et al., 2007; Mejias-Aponte et al., 2009; Omelchenko and Sesack, 2010; Miller et al., 2011). Neurons in a majority of the structures that give rise to ascending inputs to the VTA resemble basal forebrain tier 1 isodendritic afferents both morphologically and in that they are situated along the mfb and get descending input from forebrain tier 2 VTA afferents. Afferents that ascend to the midbrain DA complex from the brainstem, like the descending afferents, are broadly topographically organized and equivalently indifferent to imagined hard line boundaries between structures (Zahm et al., 2001; Geisler and Zahm, 2005; 2006; Geisler et al., 2007; Yetnikoff et al., 2013).

The LDTg and, to a lesser extent, PPTg, long regarded with particular interest as a source of ascending cholinergic inputs to VTA (Oakman et al., 1995; Winn et al., 1997; Mena-Segovia et al., 2008), are now recognized to also provide robust GABA and GLU afferents (Charara et al., 1996; Parent et al., 1999; Geisler et al., 2007; Wang and Morales, 2009). LDTg afferents are thought permissive to burst activity of VTA and SNc DA neurons (Lodge and Grace, 2006a), whereas the PPTg (Floresco et al., 2003), together with subiculum projections relayed through ventral striatopallidum, regulates the population activity and rate of bursting of VTA neurons (Floresco et al., 2003; Lodge and Grace, 2006b; Chen and Lodge, 2013). Apropos of this influence on burst firing, Lammel et al. (2012) determined that LDTg inputs to the VTA have synaptic contacts principally with neurons that project to the lateral Acb shell and subserve reward function. They contrasted these with projections thought to be related to aversive responding, e.g., from the lateral habenula (LHb) mainly to DA neurons projecting to the medial prefrontal cortex. Ascending projections from the PPTg and LDTg to the midbrain DA complex also are reported to be involved in non-DA reward mediated by opiates (Bechara et al., 1992; Ting-A-Kee et al., 2013) and concomitant behaviors that are dependent upon stimulation of M5 muscarinic receptors in the VTA and RMTg (Wasserman et al., 2013).

The dorsal raphe nucleus, which provides serotonin afferents to the VTA (Azmitia, 1978; Herve et al., 1987), now is known to also contain GABA (Charara and Parent, 1998) and GLU (Fremeau et al., 2002: Gras et al., 2002; Commons, 2009; Hioki et al., 2010) neurons of which the latter at least are a major source of input to the VTA (Geisler et al., 2007). A couple recent studies agree that optogenetic stimulation of dorsal raphe projections to the VTA produce a GLU mediated, rewarding activation of VTA neurons, but disagree about a rewarding vs aversive role of dorsal raphe-VTA serotonin (McDevitt et al., 2013; Wang and Morales., 2013).

RRF and PAGvl

The arrangement of inputs to the RRF and PAGvl much resembles that of the VTA, comprising sequential, interconnected isodendritic (tier 1), MdSN (tier 2) and cortical and cortical-like (tier 3) afferents (Zahm et al., 2011b). The list of brain structures that exhibit numerous retrogradely labeled neurons following injections of tracer into the RRF and PAGvl is even longer than observed after injections into the VTA, owing mainly to the addition of abundant, prominent projections from the central division (c) of the extended amygdala (EAc) (Zahm et al., 2011b), which includes the central amygdaloid nucleus (CeA), lateral part of the bed nucleus of stria terminalis (BST), dorsal part of the interstitial nucleus of the posterior limb of the anterior commissure and intervening parts of the sublenticular forebrain (Alheid and Heimer, 1988; de Olmos and Heimer, 1999; Shammah-Lagnado et al., 1999). Robust RRF-PAGvl inputs also arise in the hypothalamic paraventricular nucleus, lateral hypothalamus, parasubthalamic nucleus, parabrachial nucleus and nucleus of the tractus solitarius, of which all are structures with which the EAc is most extensively interconnected (Goto and Swanson, 2004; Mejias-Aponte et al., 2009; Geerling et al., 2010; Zahm et al., 2011b). Thus, the RRF and PAGvl together represent a sector of the midbrain DA complex serving prominently as a node receiving inputs from EAc.

Several investigators (Krettek and Price, 1978; Shinonaga et al., 1992; Zahm et al., 1999; Shammah-Lagnado et al., 2001; Gastard et al., 2002; Zahm et al., 2011b) have reported that deposits of anterogradely transported compounds in EAc structures, including the CeA and dorsolateral (dl) part of the BST produce labeled fibers in the VTA that largely lack the varicose “beaded” appearance of axon terminals with synaptic specializations. Such labeled fibers pass through the VTA and medial SNc, showing little evidence of synaptic differentiation until, as noted above, they reach a site in the lateral part of the SNc and suprajacent RRF, where the projection ramifies extensively and exhibits numerous varicosities. This region was emphasized by Gonzales and Chesselet (1990) as the main nigral recipient of a robust, functionally significant (Han et al., 1997; Lee et al., 2005; El-Amamy and Holland, 2007) projection from the CeA. Price and Amaral (1981), evaluating tritiated amino acid injections placed in the monkey CeA also illustrated little anterograde labeling in the VTA and a strong projection to the lateral SNc and RRF. Contrary evidence, i.e., that the CeA and BST project strongly to the VTA also has been provided (Fudge and Haber, 2000; 2001), but has been questioned on the basis of technical issues (Zahm, 2006; Heimer et al., 2008). Georges and Aston-Jones (2001; 2002; see also Dumont and Williams, 2004), however, demonstrated a short-latency excitation of the VTA following electrical andd chemical stimulation at a single, focal site in the BSTvl. Although the anatomy appears consistent with few direct projections from the EAc to the VTA, great numbers of VTA-projecting neurons form a densely packed column centered on the medial forebrain bundle that invades numerous forebrain structures, including the lateral and medial hypothalamus, sublenticular region, lateral and medial preoptic regions, diagonal band, septal nuclei, ventral pallidum and ventral parts of the BST (Geisler and Zahm, 2005). Many of the neurons in this column are thought to be GLU, i.e., excitatory, whereas the output from the MdSN-containing BST is mainly GABA (McDonald et al., 1989; Takayama and Miura, 1991; Sun and Cassell, 1993; Korotkova et al., 2004; Geisler et al., 2007). It is thus reasonable to suspect that excitatory responses in the VTA elicited by stimulation of the BSTvl are due to the activation of GLU neurons in the transition area between the BST and mfb. However, in the mean time, a number of groups have weighed in on a BST-VTA connection using modern chemico- and optogenetic methods (e.g., Kudo et al., 2012; Jennings et al., 2013; Kim et al., 2013) with the result of further complicating the issues of neural connectivity. Thus, there may be additional complexity in these relationships and, however they are resolved in future studies, it seems worth emphasizing that a comprehensive understanding of brain systems interactions cannot be realized in the absence of agreement, or logical basis for disagreement, among the various ways of looking at the problems.

SNc

The SNc contains a dense accumulation of A9 group DA neurons (Fig 1A–E) and extends lateralward from the VTA within the dorsalmost part of the substantia nigra reticulata (SNr) as a flat, wing-like mass (Fig. 1A and B), comprising a loosely organized dorsal tier of DA neurons with more or less horizontally oriented dendrites and a ventral cell-dense tier, from which vertically oriented dendrites of DA neurons descend far into the SNr (Gerfen, 1984). Modest to dense aggregations of A9 DA neurons also are scattered throughout the SNr, particularly in the rodent (Fig. 1C and D). Bolam and colleagues have reported that the

density of GABA synapses as a proportion of total synapses is significantly greater for DA neurons and dendrites occupying the SNr beneath the ventral tier of DA neurons (Henny et al., 2012), which is consistent with the observed innervation of DA neurons by SNr GABA output neurons (Tepper et al., 1995) and which supports the notion that input to A9 DA neurons must in some way reflect that to the SNr. Consistent with its role as a basal ganglia output nucleus, the SNr and, presumably, SNc, get much afferent input from the CPu and intrinsic basal ganglia circuitry (Heimer et al., 1985; 1995), which has a fundamental organization similar to that of the descending afferents of the VTA. That is, SNr tier 1 input (Fig. 2) comes mainly from the globus pallidus (GP), entopeduncular nucleus (EPN, medial segment of the GP in primates) and subthalamic nucleus (STN), all comprising neurons with very long, sparely ramifying, mainly aspiny dendrites. Due to the dense striatopallidal and pallido-STN input to such neurons, however, they are not regarded as isodendritic (Ramon-Moliner and Nauta, 1966). The main second tier innervation of the SNr comprises MdSNs in the CPu, which, in turn, are recipient to a third tier of afferent innervation - a massive input from the neocortex (Künzle and Akert, 1977; Künzle, 1978; McGeorge and Faull, 1989). The mediolateral and dorsoventral topographies of these dorsal striatonigral projections are, respectively, preserved and inverted (Deniau et al., 1996).

As noted in a preceding section, a ‘balkanization’ (i.e., compartmentation) of inputs to the SNr and SNc from the CPu (dorsal striatum) is more differentiated than is that of the inputs to the VTA from ventral striatum. That is, cortico-striatonigral/striatopallidal-thalamocortical mechanisms in the classical basal ganglia have been thought to depend substantially on the interactions of distinct functionally opposed *direct* and *indirect* pathways (Albin et al., 1989; Gerfen, 1992; Smith et al., 1998; Gerfen and Surmeier, 2011) from the striatum to GABAergic basal ganglia output nuclei, i.e., the SNr, EPN and ventral pallidum. The direct pathway originates with a subset of GABAergic MdSNs (about half of striatal MdSNs) that co-expresses the peptides substance P and dynorphin and projects directly to the output nuclei, which, in turn, project to the cortex, via thalamus, and to brainstem motor nuclei (*dir* in Fig. 2A). Excitation of the direct pathway is thought to disinhibit its thalamocortical and brainstem targets, producing behavioral arousal, by inhibiting GABA projection neurons in the output nuclei. The indirect pathway originates with the other about half of striatal MdSNs, which co-express GABA and the neuropeptides leu- and/or met-enkephalin and project, via a relay in the GABA GP, to the STN, a GLU structure that projects to the output nuclei. Excitation of the indirect pathway results in disinhibition of the GLU projection from the STN to the output nuclei, which activates them, such that they, in turn, inhibit their thalamocortical and brainstem targets *(indir* in Fig. 2A), consistent with behavioral suppression. Modern optogenetic and chemicogenetic functional-anatomical studies have provided results consistent with the afore-mentioned theoretical functional roles of the direct and indirect pathways, showing that the direct pathway facilitates and indirect pathway interferes with acquisition and retention of reward-based learning (Hikida et al., 2010; Kravitz et al., 2012; Ferguson et al 2013), behavioral sensitization (Ferguson et al., 2011), movement and movement initiation (Kravitz et al., 2010; Tai et al., 2012; Agnoli et al., 2013; Farrell et al., 2013; Sano et al., 2013; Freeze et al., 2013), risk-based decision making (Stopper et al., 2013) and cocaine self-administration (Bock et al., 2013).

Excitation of the direct and indirect pathways is usually attributed to the cortical inputs, but may also (or instead) reflect activity in thalamostriatal projections from the midline-intralaminar thalamic nuclei (Pasupathy and Miller, 2005). Indeed, the midline-intralaminar thalamus has been much neglected as a potentially important source of input to MdSNs (Fig. 2B), insofar as it transmits informational content derived from the brainstem reticular formation (Ramon-Moliner, 1975; Groenewegen and Berendse, 1994; van der Werf et al., 2002; Geisler, 2009), presumably including interoceptive and nociceptive signaling (Peschanski and Besson, 1984; Bernard et al., 1996; Craig, 1996; Gariau and Bernard, 2002; Willis et al, 2004). In any event, a recent retrograde labeling investigation using a modified rabies virus showed that the overall patterns of afferent innervation of the two pathways differ (Wall et al., 2013).

Discovery of the direct and indirect pathways owed to differential visualization within them of peptides, immediate early genes and reporters of metabolic activity following administration of DA receptor subtype specific ligands (Trugman and Wooten, 1987; Albin et al., 1989; Mitchell et al., 1989; Robertson et al., 1990; Engber et al., 1990). MdSNs that give rise to the direct pathway express mainly DA D1 receptors, which mediate facilitatory responses to the binding of DA (Fig. 2A, green arrow), whereas those that give rise to the indirect pathway express DA D2 receptors that mediate DA-elicited inhibitory responses (Fig. 2A, yellow arrow). Consequently, increased striatal DA concentration should enhance behavioral activation associated with direct pathway-mediated inhibition and attenuate behavioral suppression associated with indirect pathway-mediated excitation of GABA neurons in the output nuclei. But, might not the direct pathway also suppress, and the indirect pathway also enhance, the activity of DA neurons in the SNc and SNr? Were this to occur, paradoxical behavioral correlates should ensue. What actually happens, of course, depends completely on how the axonal terminations of the direct and indirect pathways are distributed in the SNc and SNr relative to GABA and DA projection neurons, and, as it turns out, various data are discordant on this point. Whereas several functional studies indicate that the direct pathway acts preferentially on GABA neurons in the VTA and SNr (Grace and Bunney, 1979; 1985; Chuhma et al., 2011; Xia et al., 2011; Bocklisch et al., 2013) and negligibly affects the activity of nigrostriatal DA neurons, the available ultrastructural evidence shows, in contrast, that striatonigral (Smith et al., 1987; Nitsch and Riesenberg, 1988; Anderson et al., 1991; Pickel et al., 1993; Groenewegen et al., 1994) and pallidonigral (Hattori et al., 1975; Smith and Bolam, 1990) projections have abundant synaptic contacts with both DA and non-DA neurons. In addition, a recent chemicogenetic study designed to selectively demonstrate the afferents specifically of DA neurons in the VTA and SNc revealed that they receive modest to robust inputs from virtually all structures that project to the SNr (Watabe-Uchida et al., 2012). Of particular relevance to the present topic, this study showed particularly strong direct projections to DA neurons from MdSNs in the caudate-putamen, which is incongruous with the above-cited functional studies.

Thus, however well it has served as a heuristic framework, the theory of direct and indirect cortico-basal ganglia-thalamocortical pathways falls short of comprehensively modelling basal ganglia control of the activity of its DA and non-DA outputs, not only due to the aforementioned issues of connection specificity, but also because it neglects important connectivity (Fig. 2B). For example, Watabe-Uchida et al. (2012) also observed that SNc

DA neurons are contacted by a strong projection from the EPN, which is a connection incongruous with the theory of direct and indirect pathways. Nor does the theory account for the so-called hyper direct projection *(hyperdir* in Fig. 2B) from the cortex to the STN (Nambu et al., 2002; Nambu, 2009; Jahfari et al., 2011; Nougaret et al., 2013) or a robust projection from one output nucleus, the EPN, to the other, the SNr. Possible preferential activation of the direct or indirect pathways by midline-intralaminar thalamic inputs is also not considered in the theory (Groenewegen and Berendse, 1994; van der Werf et al., 2002). Presumably, any of these connections could exert profound modulation on through-conduction of signals in the basal ganglia. Moreover, any theory concerned with this circuitry must take into account the effects of neruopeptides such as dynorphin, substance P, enkephalins and neurotensin, which co-exist with GABA in various subpopulations of MdSNs and tier 1 neurons (e.g., Deutch et al., 1985; Kalivas, 1985; Kelley and Cador, 1988; Steiner and Gerfen, 1998; Zahm et al., 1998; Geisler and Zahm, 2006; Reynolds et al. 2006).

None of this is meant to imply that the overall pattern of inputs to the SNc is not distinct from that to the SNr. Indeed, the ventral tier of the SNc is preferentially innervated by MdSNs in the CPu patch compartment, to which the ventral tier, in turn, preferentially projects (Gerfen, 1984; Jimenez-Castellanos and Graybiel, 1989a; b). In addition, abundant reports describe a lateralward spread through the SNc of numerous afferents that traverse the mfb, including ones originating in the Acb (Nauta and Domesick, 1978; Nauta et al., 1978; Nauta and Domesick, 1984; Zahm and Heimer, 1990; 1993; Heimer et al., 1991), ventral pallidum (Groenewegen et al., 1993), lateral hypothalamus (van der Kooy et al., 1984), paraventricular hypothalamic nucleus (Geerling et al., 2010); EAc (Krettek and Price, 1978; Gonzales and Chesselet,1990; Rosen et al., 1991; Zahm et al., 1999; Dong et al., 2001; Gastard et al., 2002) and parabrachial nucleus (Coizet et al., 2012). In this regard, Nauta and Domesick (1984) pointed out that “the limbic striatum’ seems enabled by its striatonigral efferents to modulate not only the source of its own dopamine innervation but also that of a large additional striatal region,” which they maintained is consistent with Mogenson’s ‘motivation to action’ conceptualization of the Acb-subpallidal-VTA axis (Mogenson et al., 1980). Haber and colleagues later picked up on this theme in describing a lateralward ‘spiraling’ of striato-nigro-striatal connectivity (Haber et al., 2000), which has generated interest in the drug abuse field. The ‘spirals’ are viewed as a presumptive substrate for a process by which early, rewarding, medially-mediated phases of drug self-administration later progress to a state thought to be more habitual, consistent with the role of lateral parts of the striatum in the formation and maintenance of motor habits (Everitt and Robbins, 2005; Balleine and O’Doherty, 2010, Belin-Rauschent et al., 2012).

Additional important SNc inputs

The RMTg provides a very robust GABA projection to the entire midbrain DA complex, including the SNc (Jhou et al. 2009a; b; Balcita-Pedicino et al., 2011). Activation of the RMTg has a strong suppressive effect on mesotelencephalic DA neurotransmission (Jhou et al., 2009a; Hong et al., 2011; Matsui and Williams, 2011) and thus is thought to have fundamental implications for neuropsychiatry and therapy (Barrot and Thome, 2011; Lavezzi and Zahm, 2011). The RMTg receives a very dense GLU input from the LHb, which is a presumptive integrator of negative hedonic information conveyed in afferent

projections to the LHb from the basal forebrain, particularly the ventral pallidum (Haber et al., 1993; Tachibana and Hikosaka, 2012) and a site extending from the internal medullary lamina through the GPi and into the underlying sublenticular region that Hong and Hikosaka (2008; 2013) have called the GP border region (GPb). Contrary to expectations, projections from GPb to the LHb are excitatory (Shabel et al., 2012; Hong and Hikosaka; 2013). In addition, the lateral preoptic area has prominent neuroanatomical relationships with the RMTg, involving both direct projections (Zahm et al., 2011a) and a projection that relays in the LHb (Kowski et al., 2008). Thus, the RMTg is a final common site of through-conduction from widespread parts of brain for negative hedonic information to access DA neurons throughout the midbrain DA complex.

Redgrave and colleagues have promoted a projection to the SNc preferentially from the deep layers of the superior colliculus (Comoli et al., 2003; Coizet et al., 2003; McHaffie et al., 2006; Redgrave et al., 2008), which, consonant with its role in conveying short latency visual information, they suggest subserves the critical mental property of agency, i.e., an individual's awareness of its own role in causation.

Presynaptic stimulation of DA release in forebrain structures

Afferents of DA neurons of the midbrain DA complex need not terminate within the complex itself, but rather may target the terminals of DA axons, particularly in forebrain structures. Howland et al. (2002) have demonstrated that DA is released into the Acb and PfC upon stimulation of GLU projections from the basal amygdala to those structures. Reverse microdialysis of DNQX, an antagonist of the AMPA-kainate GLU receptor, into the Acb or PfC, but not the VTA, blocked the effect, which thus is interpreted as a paracrine-like axo-axonal interaction, insofar as projections from the basal amygdala to the Acb and PfC do not have axo-axonic synapses with DA axon terminals. This mechanism of releasing DA in forebrain may have extraordinary behavioral significance, particularly in the primate, and especially human, brain, wherein mesocortical and mesothalamic DA projections are much more pervasive than in the rat (Lewis and Sesack, 1997; Lewis et al., 1998; Bentivoglio and Morelli, 2005).

Efferent connections

The VTA and SNc are widely regarded as having distinct efferent projections and, insofar as, respectively, about 60% and 80% of neurons comprising them are DA, the difference in part reflects the existence of distinct DA mesolimbic (A10) and nigrostriatal (A9) projection systems. This taxonomy, however, severely under-emphasizes extensive overlap of the terminal fields of VTA and SNc neurons (Beckstead et al., 1979; Nauta and Domesick, 1984; Lynd-Balta and Haber, 1994a; b; c; Bentivoglio and Morelli, 2005; Björklund and Dunnett, 2007). Indeed, nearly every telencephalic region that receives DA innervation has a medial aspect innervated by the VTA and a lateral aspect innervated by the SNc (Fallon and Moore, 1978), the two separated by a broad district in which VTA and SNc projections overlap (e.g., Nauta and Domesick, 1984). Nevertheless, SNc projects mainly to the CPu and in lesser abundance to cortical structures, amygdala and STN (Fallon and Moore, 1978; Fallon et al., 1978; Loughlin and Fallon, 1983; Gerfen et al., 1987; Jimenez-Castellano and

Graybiel, 1987b; Lavoie et al., 1989; Smith and Villalba, 2008). It should be noted that the density of terminations of the mesostriatal DA projection as revealed with a modern promoter-driven expression of reporter molecule (Matsuda et al., 2009) appear to be much greater than demonstrated in any previous conventional tract tracing study. This may reflect a lesser capacity of axonally transported tracers such as PHA-L to reach all of the terminations of mesostriatal neurons, although it can be said that the photographed axonal terminations shown in Matsuda et al. (2009) appears less dense than the graphically illustrated ones (compare Figs. 1 and 3 – 7). Nonetheless, the data therein mainly are consistent with previous studies indicative of a specificity in these projections beyond gross topography, in that the ventral tier of the SNc projects preferentially to the striatal patch compartment (Gerfen et al., 1987; Jimenez-Castellanos and Graybiel, 1987).

The VTA projects most robustly to the Acb and olfactory tubercle, but also innervates the orbitofrontal and motor cortices, striatum, lateral septum, ventral pallidum, EA, subventricular zone, LHb, entorhinal cortex and hippocampus, including the ventral subiculum and stratum oriens of CA1 and CA3 (Fallon and Moore 1978; Fallon et al., 1978; Scatton et al., 1980; Swanson, 1982; Verney et al., 1985; Gasbarri et al., 1994, 1997; Goldsmith and Joyce, 1994; Gaykema and Zaborsky, 1996, 1997; Shammah-Lagnado et al., 1999; Hasue and Shammah- Lagnado, 2002; Santiago and Shammah-Lagnado, 2005; Del-Fava et al., 2007; Ikemoto, 2007; Hosp et al., 2011; Lennington et al., 2011). Whereas axonal projections originating from neurons in the VTA are mainly unbranched and thus target one structure, those from the SNc were reported to project more abundantly via axon collaterals to subcortical structures and the cortex (Fallon, 1981; Fallon and Loughlin, 1982; Swanson, 1982; Loughlin and Fallon, 1984; Sobel and Corbett, 1984; Takada and Hattori, 1986; Chandler et al., 2013). However, there has never been uniform agreement on the subject of the collateralization of mesofugal axons (e.g., Febvret et al., 1991) and a recent study with a modified, GFP-expressing virus injected into single SNc DA neurons revealed no significant collateralization of SNc DA axons (Matsuda et al., 2009), suggesting that collateralization observed in earlier studies may have involved non-DA neurons.

The RRF and the PAGvl (which contains the A10dc neurons) also project to numerous forebrain structures but most prominently to the EA. The issue of which outputs from these structures are DAergic is exacerbated by the substantial proportions of non-DA projection neurons in the RRF and PAGvl. The RRF projects to the olfactory tubercle, striatum, Acb, interstitial nucleus of the posterior anterior commissure, BST, amygdala, and pyriform and entorhinal cortices (Jimenez-Castellanos and Graybiel, 1987; Arts et al., 1996), but with particular density to EA structures (Deutch et al., 1988 Shammah-Lagnado et al., 1999; Hasue and Shammah-Lagnado, 2002). Outputs from the PAGvl terminate in the Acb, caudate putamen, medial prefrontal cortex, lateral septum, hippocampus, magnocellular basal forebrain, LHb, BST, and amygdala (Pohle et al., 1984; Descarries et al., 1986; Semba et al., 1988; Yoshida et al., 1989; Stratford and Wirtshafter, 1990; Li et al., 1993), but, again, most strongly in the EAc (Hasue and Shammah-Lagnado, 2002). Hasue and Shammah-Lagnado (2002) found that of all TH immunoreactive projections to the central amygdaloid nucleus (CeA) and lateral division of the BST almost half arise from neurons in the PAGvl, indicating that the A10dc group of neurons provides a main catecholaminergic input to the EAc. It is notable that A10dc neurons are reported to utilize L-DOPA rather than DA as a

catecholamine neurotransmitter (Misu et al., 1996). An early report that the CeA (in cat) projects strongly to the SNl (Shinonaga et al., 1992), suggested that the SNl might, in turn, provide a main nigroamygdaloid projection. However, Moriizumi et al. (1992) demonstrated that the SNl projects mainly to the inferior colliculus via GABA neurons and to the superior colliculus, caudoventral CPu and, as later confirmed by Hasue and Shammah-Lagnado (2002), modestly to the amygdala with GABA and DA neurons.

A somewhat similar situation may exist vis a vis a dense projection from the supramammillary nucleus to the lateral septum (Shepard et al, 1988; Vertes, 1992), of which about 40% of the neurons of origin are dopaminergic neurons (Swanson, 1982) residing in Hökfelt's et al. (1984b) A10rv group. Like the projection from A10dc to extended amgydala (Hasue and Shammah-Lagnado, 2002), that from A10rv to the lateral seputm supplements a substantial dopaminergic projection to the septum from the main body of the VTA (Lindall and Stenevi, 1978). A10rv neurons that give rise to this projection are reported to have several electrophysiological characteristics resembling nigral and VTA dopamine neurons (Shepard et al., 1988). Terminations of dopaminergic projections to the the lateral septum form pericellular baskets (Gall and Moore, 1984) around MdSNs that exhibit somatic spines (Jakab and Leranth, 1990).

Striatal DA-GLU interactions and the synaptic triad

DA and GLU inputs characterize all MdSN-containing structures and are particularly strong in the CPu, Acb and striatal districts of the olfactory tubercle. Very dense plexuses of DA (TH-imunoreactive) axons and axon varicosities are present in these striatal structures (Lindvall and Björkland, 1983; Voorn et al., 1989; Pickel et al., 1975; Bouyer et al., 1984), which also exhibit an abundance of VGLUT1-containing cortical and cortical-like inputs and equivalently dense, VGLUT2-containing thalamic inputs (e.g., Fremeau et al., 2001; Härtig et al., 2003). DA-GLU interactions thus play a major role in shaping functional potency in these structures (Wan et al., 1995; Morari et al., 1998), but in ways reflecting considerable mechanistic heterogeneity depending on the specific afferent systems involved (David et al., 2005). A so-called striatal synaptic triad, first described in neostriatum (Freund et al., 1984), has been the subject of considerable interest as regards striatal DA-GLU interactions. The triad comprises an MdSN dendritic spine with an asymmetrical synapse (excitatory, GLU), typically on the spine head, and a symmetrical synapse (DA), typically at the spine neck (Freund et al, 1984; Sesack and Pickel, 1990), an arrangement that may confer special capacity for the integration of DA and GLU influences in the striatum, possibly via gating of the GLU signal by the DA signal (Freund et al., 1984). However, Wilson et al. (1983) had estimated that in neostriatum only about 8% of spines get the symmetrical input and Bennett and Wilson (2000) later pointed out that only half of the symmetrical contacts are DA. Similar data are not available for ventral striatum, but one might anticipate similar numbers, or perhaps even fewer DA contributions to the spine innervation, particularly in the Acb shell (Zahm, 1992). These quantitative data suggest that the importance of the triad as a predominant substrate for MdSN DA-GLU interactions may be overstated.

Non-DA efferent connections

It has long been recognized that GABA cells are intermingled with DA neurons throughout the midbrain (Mugnaini and Oertel, 1985; Steffensen et al., 1998; Olson and Nestler, 2007); however, little is known regarding their efferent projections. One region known to receive VTA GABA input is the Acb (Van Bockstaele and Pickel, 1995; Carr and Sesack, 2000a; Van Zessen et al., 2012), wherein preferential VTA-derived GABA input to cholinergic interneurons has been reported (Brown et al., 2013). The mPfC is also innervated by VTA GABA neurons (Carr and Sesack, 2000a).

Interestingly, the rostral linear subnucleus of the VTA (VTArl), which is reported to contain few DA neurons (Ikemoto, 2007), has efferent connections that differ from the rest of the VTA. Specifically, VTArl projects heavily to a number of structures that receive modest DA inputs, including the ventral pallidal parts of the olfactory tubercle, magnocellular preoptic nucleus, lateral hypothalamus, central division of the mediodorsal thalamic nucleus, and the lateral part of the LHb (Del-Fava et al., 2007). Accordingly, a recent chemicogenetic study in mice revealed a general complementarity in the forebrain distributions of GABA and DA VTA projections (Taylor and Picciotto, 2013). In addition, Gorelova et al. (2012) remarked on the abundance of anterogradely labeled fibers that co-express the GLU marker VGLUT2 following injections of anterograde tracer into the rostral linear nucleus.

GLU neurons are present in all VTA subnuclei and project to both the mPfC and Acb (Yamaguchi et al., 2007, 2011; Gorelova et al., 2012; Hnasko et al., 2012). Whereas the Acb clearly gets heavier DA than GLU input, the opposite pattern is observed in the mPfC (Yamaguchi et al., 2011; Gorelova et al., 2012). Additional studies in mice have revealed that GLU neurons that reside in the medial part of the VTA and exhibit electrophysiological characteristics of medial VTA DA neurons preferentially target the Acb, mPfC, amygdala, ventral pallidum and LHb. Interestingly, those projections, like GABA input to the forebrain, are densest in areas of lesser DA input (Hnasko et al., 2012). These workers also noted that mice appear to have a lesser GLU VTA projection to the mPfC than rats.

Co-transmission in DA neurons

Longstanding evidence for co-release of GLU from midbrain DA complex DA neurons and axons (Kocsis and Kitai, 1977; Sulzer et al., 1998; Joyce and Rayport, 2000; Chuhma et al., 2004; Dal Bo et al., 2004; Descarries et al., 2008; Broussard, 2012) has been bolstered by recent technical advances. Optical stimulation of DA terminals in the Acb shell, but not dorsal striatum, of adult mice evokes GLU-mediated postsynaptic responses in MdSNs. The GLU signal is abolished by genetic deletion of VGLUT2 in mesoaccumbal but not mesostriatal DA axons (Stuber et al., 2010; Tecuapetla et al., 2010), which indicates that GLU is co-expressed by DA neurons in the VTA, but not SNc. Consistent with this, researchers have been able to detect little VGLUT2 expression in SNc DA neurons (Hnasko et al., 2010; Yamaguchi et al., 2013). It is unclear if DA and GLU are packaged together in the same synaptic vesicles of VTA DA neurons or even occupy the same axon terminals. That is, one study in rat found that VGLUT2 co-immunoprecipitates with the vesicular monoamine transporter 2 (VMAT2) from striatal synaptic vesicles (Hnasko et al., 2010), but

no double-labeling of TH and VGLUT2 was detected in axon terminals in the mouse Acb in another study (Bérubé-Carrière et al., 2012).

It also seems that GABA is co-expressed in some ventral midbrain DA and GLU neurons (Rodriguez and Gonzalez-Hernandez, 1999). Remarkably, striatal DA terminals that co-labeled with VMAT2, but not the vesicular GABA transporter, can co-release GABA, which in turn postysnaptically inhibits striatal MdSNs (Tritsch et al, 2012). Blockade of VMAT2 prevented the inhibitions, suggesting that GABA is packaged by VMAT2 in these terminals. There also is emerging evidence that a unique population of LHb-projecting VTA neurons co-expresses GLU and GABA. Early reports indicated that VTA efferents to the LHb are mainly GABA (Swanson, 1982; Skagerberg et al., 1984; Del-Fava et al., 2007), but it was recently determined that about 50% of LHb-projecting VTA neurons are DA (Gruber et al., 2007). Stamatakis et al. (2013), however, observed that optogenetic stimulation of neurons targeted by their DA phenotype caused no detectable release of DA in the LHb, but instead produced a GABA inhibition of LHb neurons. Alternatively Root et al. (2013) demonstrated that close to 90% of meso-habenular neurons expresses both GAD and VGLUT2 and when VGLUT2 was targeted for optogenetic stimulation of these neurons, a GABA A receptor-mediated inhibitory response was elicited in the LHb (Mejias-Aponte et al., 2013). Although these reports are mutually supportive in spirit, the details need to be further ironed out. Incidentally, optical stimulation of VTA VGLUT2-expressing fibers in the ventral pallidum also elicits short latency inhibitory postsynaptic responses, indicative of GABA co-transmission in GLU, ventral pallidum-projecting VTA neurons (Hnasko et al., 2012).

As regards DA neurons that co-express neuropeptides, CCK is expressed by VTA DA neurons that project to the Acb, olfactory tubercle, septum and orbitofronal cortex, while SNc neurons that co-express CCK project to the striatum and anterior cingulate cortex (Hökfelt et al., 1980b; Seroogy and Fallon, 1989). Other VTA DA neurons projecting to the Acb and mPfC express NT (Hökfelt et al., 1984a; Kalivas and Miller 1984; Studler et al., 1988) and a subset of DA neurons that co-expresses both CCK and NT has been reported (Seroogy et al., 1987, 1988).

Heterogeneity of VTA DA neurons by projection target

Accumulating evidence indicates that VTA DA neurons are physiologically heterogeneous. A variety of morphological, electrophysiological and molecular biological characteristics of VTA DA neurons vary with their projection targets. Earlier studies showed that DA neurons in the medial part of the VTA projecting to medial Acb are smaller and have fewer and shorter dendritic branches as compared to lateral VTA neurons projecting to more lateral parts of the Acb (Tan et al., 1995). Lammel et al. (2008) extended these findings in a recent study that employed experimental neuroanatomical, electrophysiological, immunohistochemical and laser-dissection techniques to demonstrate one group of neurons centered in the medial VTA that projects to the mPfC, Acb medial shell and core, and basolateral amygdala and another positioned mainly in the lateral VTA that projects to the Acb lateral shell and ventrolateral caudate-putamen. Whereas medial VTA neurons are fast-firing and have low dopamine transporter (DAT)/TH mRNA ratios, lateral VTA neurons have a “classical” slow firing pattern reminiscent of SNc DA neurons and express DAT more

robustly. DA neurons projecting to the mPfC were uniquely unresponsive to (normally inhibitory) stimulation of somatodendritic D2 autoreceptors, an effect apparently due to their low levels of D2 receptor and GIRK2 potassium channel expression (but see Margolis et al., 2008). Lammel et al. (2011) also found that the modulation of excitatory synaptic potentials elicited in VTA DA neurons by rewarding and aversive stimuli also varies as a function of projection target. Administration of cocaine increased AMPA/NMDA ratios in medial VTA DA neurons projecting to Acb medial shell, whereas infusion of formalin into the hindpaw (subchronic pain) increased AMPA/NMDA ratios in medial VTA DA neurons projecting to the mPfC. In contrast, both reward and pain increased AMPA/NMDA ratios in lateral VTA neurons projecting to the Acb lateral shell. Finally, Ford et al. (2006) showed in mice that VTA DA neurons projecting to the Acb have a greater inhibitory response to administration of kappa opioid agonist than amygdala-projecting VTA neurons. Interestingly, Margolis et al. (2006) observed the opposite, i.e., more kappa-mediated inhibition in amygdala-projecting VTA neurons, in the rat.

Rodent versus primate

Notable differences exist between rodents and primates in the patterns of midbrain DA projections to cortical and thalamic regions (Berger et al., 1991; Lewis and Sesack, 1997; Garcia-Cabezas et al., 2009). In the rat, robust DA innervation is observed in prefrontal, anterior cingulate, insular, piriform, entorhinal and perirhinal cortex, whereas there is only light innervation in posterior cingulate, motor, parietal and temporal regions (Berger et al., 1991). The functional impact of even a modest cortical DA innervation, however, may be profound (e.g., Bao et al., 2001). In contrast to the rodent, DA innervation in the primate targets all cortical regions, most densely in prefrontal and motor areas (Lewis et al., 1987; Gaspar et al., 1989; Berger et al., 1991; Williams and Goldman-Rakic 1993; Lewis and Sesack, 1997). Rat and monkey also exhibit regional differences in laminar density of DA inputs. In the rat, cortical DA innervation is limited mainly to deep layers, whereas both superficial and deep layers exhibit robust DA inputs in the primate (Descarries et al., 1987; Berger et al., 1991, Williams and Goldman-Rakic 1993; Lewis et al., 2001). The differences between rat and primate lead to speculation that DA innervation of cortical regions in the human brain may be even more expanded and dense. However, the results of a recent study comparing DA innervation in human and chimpanzee brain were not consistent with this expectation, insofar as DA projections to the cortex of humans were not obviously more extensive as compared to chimpanzees. Subtle differences in the patterns of DA innervation of the human as compared to chimpanzee cortex were evident, however, wherein humans show a sublaminar pattern of DA input in layer I of cortical areas 9 and 32 that is absent in the chimpanzee (Raghanti et al., 2008). It is also noteworthy that primates exhibit as much DA innervation of dorsal thalamic nuclei (including midline, mediodorsal, lateral posterior, and ventrolateral) as they do of cortical regions, whereas rodents have little DA innervation in comparable thalamic regions (Groenewegen 1988; Papadopoulos and Parnavelas 1990; Sanchez-Gonzalez et al., 2005; Garcia Cabezas et al., 2007, 2009). In contrast, related species differences involving the DA innervation of ventral thalamic nuclei and the epithalamus are not apparent (Garcia Cabezas et al., 2009).

Prospectus

The main purpose of investigating brain morphology and axonal connections is to provide clues about how to investigate brain function. The midbrain DA complex is famously uncharitable in this regard, insofar as its connections, including intrinsic, afferent and efferent, are so numerous and diverse and, in part, so apparently indiscriminate in distribution, as to tend to obscure rather than clarify mechanisms that may subserve its contribution to overall brain function. But this is the nature of reticular formation to which we would argue the midbrain DA complex belongs. About all that distinguishes structures comprising the midbrain DA complex from reticular formation are the dense projections of the midbrain DA complex to deep telencephalic nuclei and cortex. However, a variety of other structures that have been associated with, actually included within, reticular formation also have robust rostropetal projections. The midline-intralaminar thalamic nuclei (Ramon-Moliner, 1975) project massively to striatum and prefrontal cortex. The lateral hypothalamus-preoptic continuum (McMullen and Almli, 1981) has substantial projections to telencephalic deep nuclei and cortex. Basal forebrain cholinergic cell groups (Mesulam, 1995) project very strongly to cortex and, less so, thalamus. A common portrayal of reticular formation as ‘diffusely’ organized is falsified by the subtlety and sophistication with which it orchestrates the interactions of neuroendocrine, autonomic and somatomotor effectors (Swanson and Mogenson, 1981). Moreover, careful attention to structure that might have been regarded as diffuse, e.g., the projections of midline-intralaminar thalamic nuclei to cortex and striatum, clearly revealed that it is not (Groenewegen and Berendse, 1994; van der Werf et al., 2002). To the contrary, organization said to be ‘diffuse’, including that of the midbrain DA complex, despite the elusiveness of its underlying principles, undoubtedly ranks with the most elegant in brain.

The complexity of the local DA, GABA, GLU and neuropeptide network(s) of the midbrain DA complex in combination with uncertainty about the extent to which afferent influences are exerted on select neuron subpopulations versus extended functional-anatomical networks renders functional analysis of the midbrain DA complex a formidable undertaking. As regards outputs, an evidence-based impression that all DA neurons burst fire and inactivate in unison in response to presentations of reward predicting cues and omissions of expected rewards, respectively (Mirenowicz and Schultz, 1996; Schultz et al., 1997; Hollerman and Schultz, 1998; Schultz, 1998; Hong et al., 2011), is disputed by the work of Matsumoto and Hikosaka (2009) and Matumoto and Takada (2013), whose findings, in turn, are incongruous with other functional-anatomical evidence for a hedonic-aversive duality in midbrain DA complex input-output pathways (Lammel et al., 2008; 2011; 2012; 2014; Roeper, 2013). Despite the elegance and transformative impact of these and other studies afore-cited in this review, how the organization of the midbrain DA complex permits its contributions to all of the various functional realms that it is reported to modulate (see refs. in Introduction) remains a topic for continuing research.

We would argue that the depth of our understanding of the functional role of the midbrain DA complex will continue to increase only if accompanied by continued elucidation of its neuroanatomical relationships. Conventional experimental neuroanatomical studies continue to be valuable, having recently revealed, on one hand, important gross organizational

principles, such as, e.g., the topographical relationships between sectors of the midbrain DA complex and various basal forebrain functional-anatomical macrosystems (Fig. 3), and, on the other hand, fine details of synaptic organization that yield only to determined ultrastructural investigation (e.g., Bayer and Pickel, 1990; Carr and Sesack, 2000a; b; Omelchenko et al., 2009; Balcita-Pedicino et al., 2011). In the same vein, it was a keen sense of neuroanatomical organization revealed with traditional methods that led to the discovery of the RMTg (Jhou, 2005; Perrotti et al., 2005), which has provided a new perspective from which to view the afferent regulation of the midbrain DA complex (Jhou et al., 2009a; Lavezzi and Zahm, 2011; Bourdy and Barrot, 2012).

More and more, however, it appears that future developments in our comprehension of the neurobiology of the midbrian DA complex will most depend upon continuing creative applications of modern chemicogenetic and optogenetic technology to reveal specificity of connections with the aid of viral delivery of promoter-specific, neuron-filling reporter molecules and provide optogenetic-electophysiological validations (Smedemark-Margulies and Trapani, 2013; Williams and Deiserroth, 2013). Roeper (2013), however, has pointed out some pitfalls and conflicing reports that have emerged in the interpretation of behavioral patterns elicited by optogenetic stimulations, which introduce into brains large neuronal activations and inactivations in unnatural, isolated spatial and temporal patterns that otherwise would never occur.

Indeed, one wonders if the role of the midbrain DA complex in the modulation of behavior can be captured in its essence by modern hyper-reductionist technology. A capacity to define circuit specificity does not diminish the reality of how abundant is the seemingly ‘irrational’ connectivity that characterizes the inputs and outputs of the midbrain DA complex. Even hints that occult specificity can underlie confusingly converged projections (MacAskill et al., 2012) do not deter our sense that the next leap in our understanding of functional-anatomical organization in the midbrain DA complex may come from an entirely different direction - something that helps us appreciate the neurobiological logic and adaptive value of mapping connectional specificity onto a background of connectional promiscuity.

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List of Abbreviations

Acb	accumbens
BST	bed nucleus of the stria terminalis
CeA	central nucleus of the amygdala
CCK	cholecystokinin
CPu	caudate-putamen

DA	dopamine and dopaminergic
DAT	dopamine transporter
c	caudal
dc	dorsal, caudal
dl	dorsolateral
EA	extended amygdala
EAc	extended amygdala, central division
EPN	entopeduncular nucleus
GABA	gamma-aminobutyric acid and GABAerg
GAD	glutamate decarboxylase
GLU	glutamate and glutamatergic
GP	globus pallidus
GPb	globus pallidus, border region
GPi	globus pallidus, internal segment
LDTg	laterodorsal tegmental nucleus
LHb	lateral habenula
m	medial
MdSN	medium densely spiny neuron
MeA	medial nucleus of the amygdala
mfb	medial forebrain bundle
NT	neurotensin
PAG	periaqueductal gray
PfC	prefrontal cortex
PHA-L	*Phaseolus vulgaris* leucoagglutinin
PPTg	pedunculopontine tegmental nucleus
RMTg	rostromedial tegmental nucleus
RRF	retrorubral field
SNc	substantia nigra pars compacta
SNl	substantia nigra pars lateralis

SNr	substantia nigra pars reticulata
STN	subthalamic nucleus
TH	tyrosine hydroxylase
tVTA	tail of the ventral tegmental area
VGLUT1	vesicular glutamate transporter 1
VGLUT2	vesicular glutamate transporter 2
vl	ventrolateral
VMAT2	vesicular monoamine transporter 2
VTA	ventral tegmental area
VTArl	rostral linear nucleus of the VTA

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Highlights

- Intrinsic organization and connections
- Afferent connections
- Efferent connections
- Prospectus

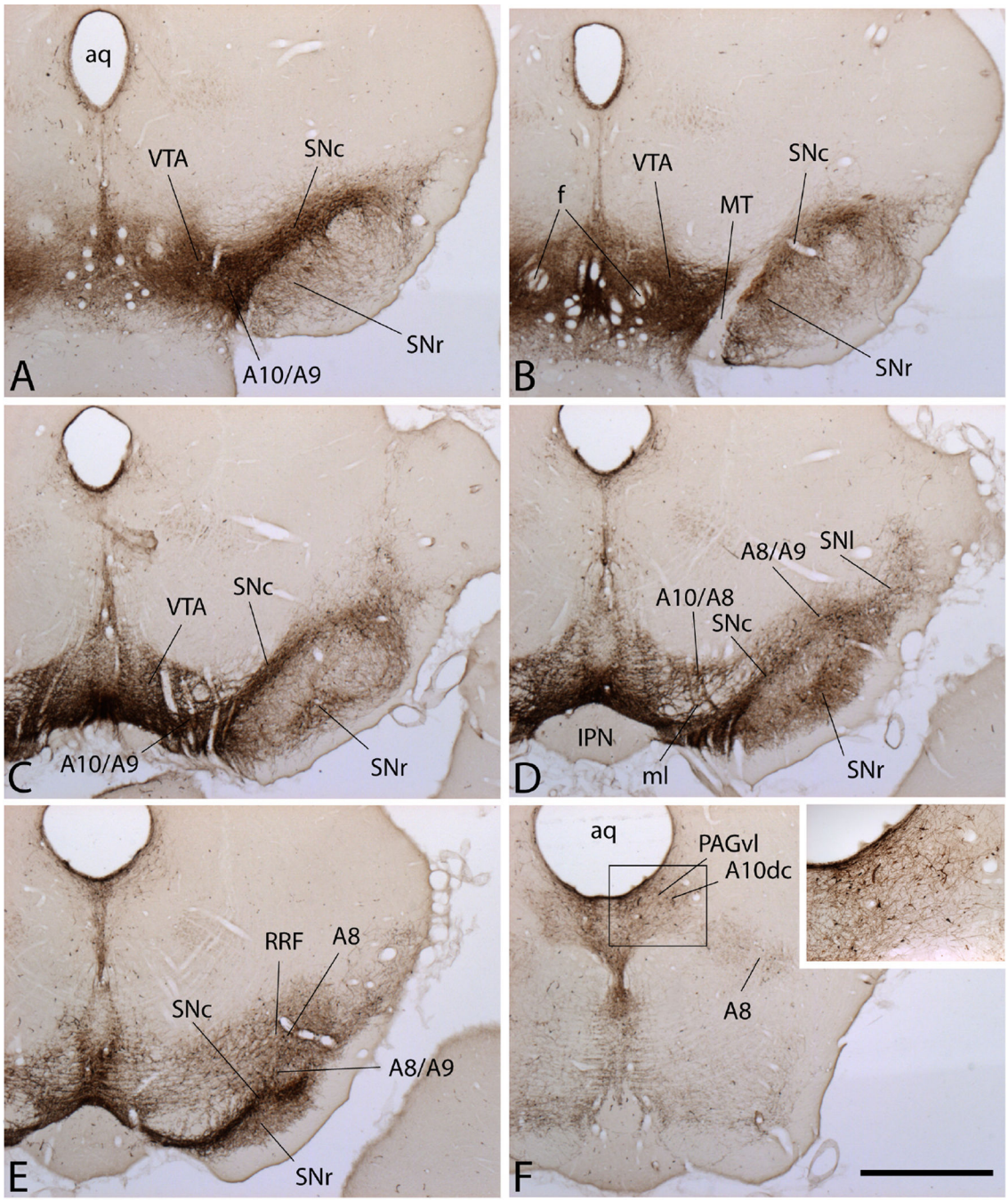

Figure 1.

Micrographs illustrating sections through the rat ventral mesencephalon in rostrocaudal sequence from A through F processed for tyrosine hydroxylase (TH) immunoreactivity (brown reaction product), which shows the continuities between various parts of the midbrain dopaminergic complex provided as names of structures, including the ventral tegmental area (VTA), substantia nigra compacta (SNc), retrorubral field (RRF) and ventrolateral quadrant of the periaqueductal gray (PAGvl), and as the catecholeamine-fluorescing dopaminergic (DAergic) cell groups (A10, A9, A8 and A10dc) that occupy the

respective structures. Note that much TH immunoreactive material, including neurons, dendrites and axons is present in the substantia nigra reticulata (SNr), belying its common designation as a non-DAergic basal ganglia structure. A10/A9, A10/A8 and A8/A9 designate regions of transition between the respective cell groups. The inset in panel F shows the numerous TH-immunoreactive neurons in the PAGvl. Additional abbreviations: aq - cerebral aqueduct; dc - dorsal, caudal; f - fornix; IPN - interpeduncular nucleus; ml -medial lemniscus; MT - mammillothalamic tract; SNl - substantia nigra pars lateralis. Scale bar: A-F - 1 mm; inset F - 0.5 mm.

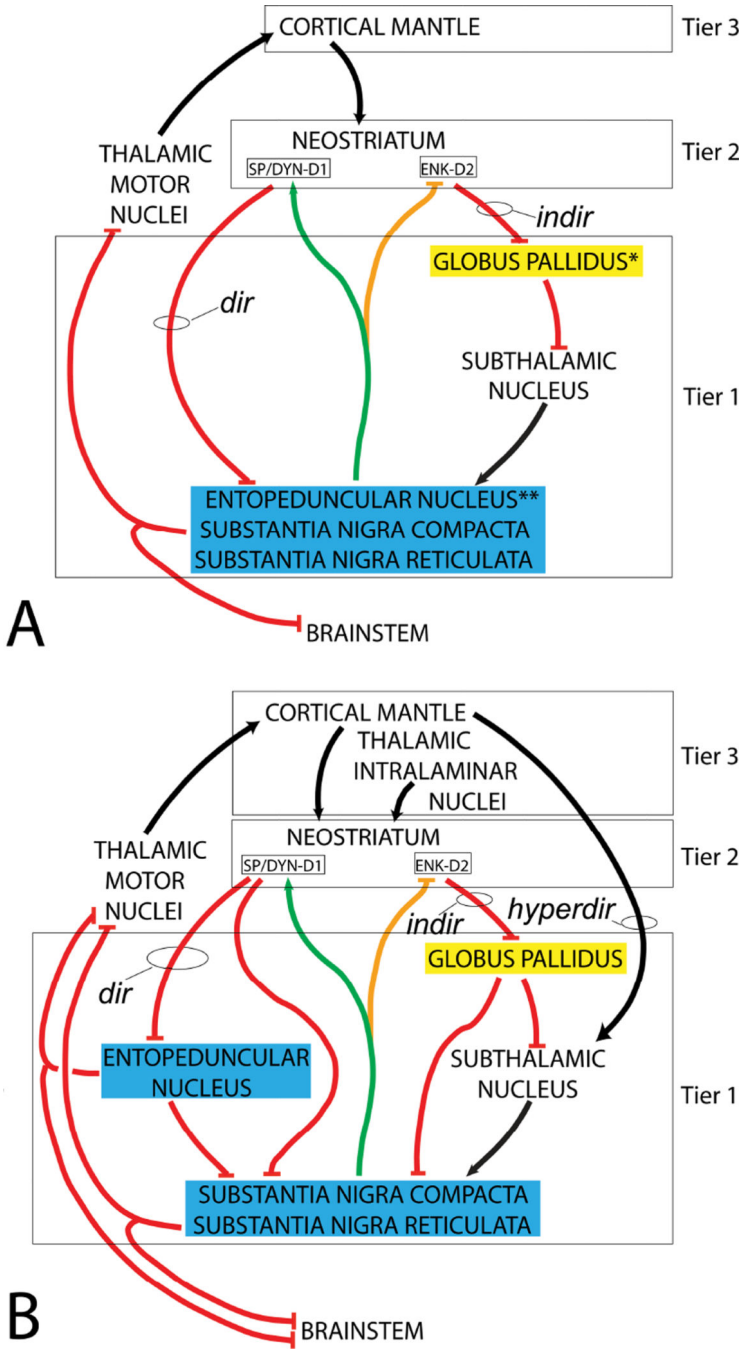

Figure 2.

Diagram depicting the ‘balkanized’ connectivity of the basal ganglia as commonly shown (A) and in a more inclusive rendering (B). Spontaneously active structures are in Vcolored boxes and include output nuclei (blue - note that the substantia nigra compacta is not an output nucleus, but is embedded within the substantia nigra reticulata, which is) and intrinsic nuclei (yellow). Black and green (for dopaminergic) lines depict excitatory connections; inhibitory connections are shown as red and orange (for dopaminergic). Boxes just beneath NEOSTRIATUM indicate medium densely spiny neurons expressing substance P (SP),

dynorphin (DYN) and dopamine (DA) D1 receptors that are the origin of the *direct* pathway *(dir)* and enkephalin (ENK) and D2 receptors that give rise to the *indirect* pathway *(indir)*. Summation of the signs of the connecting links shows how the direct pathway may inhibit the output nuclei, thus disinhibiting the thalamocortical and brainstem targets, and how the indirect pathway may activate output structures, which suppresses the thalamocortical and brainstem targets. Note that DA acting at D1 receptors facilitates the activity of the direct pathway (green line) and, acting at D2 receptors, attenuates that of the indirect pathway (orange line). Panel B shows additional connectivity not typically included in discussions of the direct and indirect pathways. Conventions in B are as in A. Note, for example, that the entopeduncular nucleus (EPN) is split out from the substantia nigra reticulata (SNr) because it has no DA neurons. Serial inhibitory connections from SP/DYN neurons to the SNr, via EPN, would oppose the action of the direct pathway. More pathways not included in the original theory include the hyper direct pathway *(hyperdir)* from cortex to subthalamic nucleus and a pathway from the globus pallidus (GP) to the SNr. GP also projects to EPN (not drawn). Note also in B that the thalamic intralaminar nuclei are shown. These are important inputs to the direct and indirect pathways not typically regarded in the original format of the theory. Three tiers of innervation of DA neurons are indicated by black boxes and on the right. * Globus pallidus in the rat is homologous to the lateral (a.k.a. external) pallidal segment in primate. ** Entopeduncular nucleus in the rat is homologous to the medial (a.k.a. internal) pallidal segment in the primate.

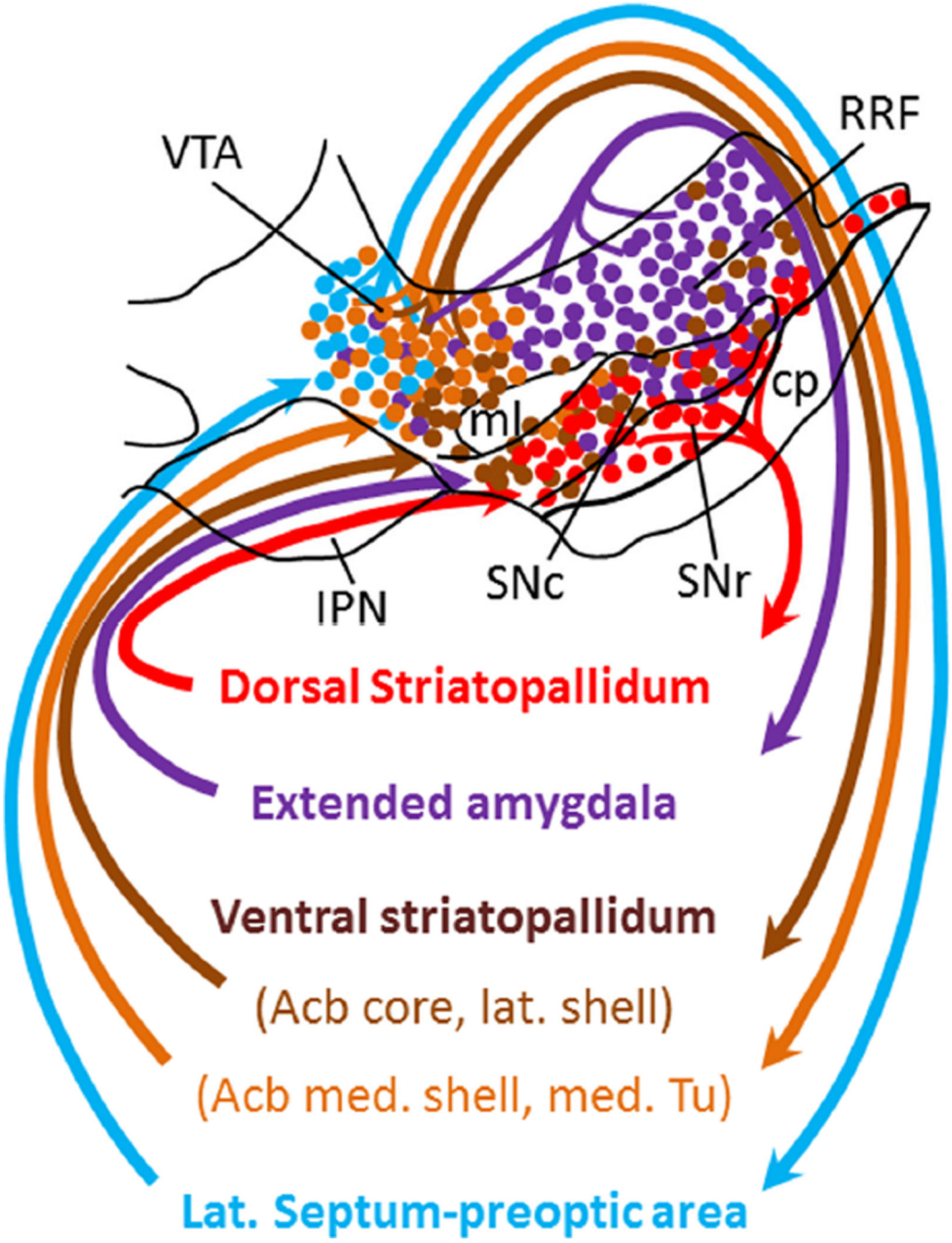

Figure 3.

Diagram depicting topographic input-output relationships (inputs and outputs are same colors) that relate various sectors of the midbrain dopaminergic (DA) complex to basal forebrain functional-anatomical macrosystems. Dots (color coded respectively) indicate the regions of terminations of direct and transynaptic (e.g., striato-ventral pallido-nigral) afferents of the macrosystems within the midbrain DA complex. Thus, the medial part of the ventral tegmental area (VTA) gets input from and gives output to the lateral septal-preoptic system. Much of the VTA receives from and projects to the medial accumbens (Acb),

including the shell, and its ventral pallidal projection area. The Acb core and its ventral pallidal target area project to lateral parts of the VTA and much of the substantia nigra pars compacta (SNc) and gets output from them, where as the caudate-putamen and topographically related parts of the pallidum (dorsal striatopallidum) projects mainly to the SNc. The central division of the extended amygdala projects most strongly to lateral parts of the SNc, RRF and ventrolateral periaqueductal gray (PAGvl) and gets outputs from these regions. Note that the SNc has the most heterogeneous input of the entire complex, due to the circumstance that all of the macrosystems (except lateral septum-preoptic area) have projections that enter the complex in topographical relation, but diverge lateralward through the SNc enroute to the lateral retrorubral field (RRF) and PAGvl. Additional abbreviations: cp - cerebral peduncle; IPN -interpeduncular nucleus; lat. - lateral; med. - medial; ml - medial lemniscus; SNr - substantia nigra compacta; Tu - olfactory tubercle

Table 1

Structures containing retrogradely labeled neurons following injections of FluoroGold into the VTA (adapted from Geisler and Zahm, 2005)

Telencephalon:
dorsal peduncular, infralimbic, prelimbic *, cingulate and agranular insular **cortex; claustrum, endopiriform nucleus**, olfactory tubercle, **core, shell and rostral pole of the accumbens, bed nucleus of stria terminalis**, anterior amygdaloid area, **medial nucleus of amygdala**, central nucleus of amygdala, **ventral pallidum, sublenticular sub s tantia innominata**, dorsal, **intermediate** and ventral divisions of the **lateral septum, septofimbrial nucleus, medial septum/diagonal band nuclei, lateral preoptic area, medial preoptic area** magnocellular preoptic area, median preoptic area.
Diencephalon:
anterior hypothalamus, hypothalamic paraventricular nucleus, ventromedial hypothalamus, **perifornical hypothalamus, lateral hypthalamus, dorsal hypothalamus, tuber cinereum** parafascicular nucleus, **zona incerta**, thalamic paraventricular nucleus, **lateral habenula medial habenula**, supramammillary nucleus
Mesencephalon:
superior colliculus deep layers, periaqueductal gray, substantia nigra pars compacta and reticulata, **deep mesencephalic field, anterior**, dorsal and **ventral tegmental nuclei**
Pons and Medulla:
oral pontine reticular field, dorsal raphe, median raphe, paramedian raphe, raphe pontis pedunculopontine tegmental nucleus, **laterodorsal tegmental nucleus**, cuneiform nucleus, **parabrachial nucleus, nucleus reticularis pontis, locus coeruleus**, lateral reticular field, intermediate reticular field, gigantocellular reticular field
Cerebellum:
dentate nucleus

* robust inputs are bolded