Microcircuits in nucleus accumbens' shell and core involved in cognition and reward

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Nucleus accumbens subserves numerous adaptive and goal-directed behaviors. The anatomical substrates for such are the medium spiny projection neurons, at least four different subtypes of local circuit neurons, and inputs from limbic cortical centers and brainstem monoamines. In this review, we show how microcircuits in two parts of the nucleus—the core and caudomedial shell or septal pole—differ subtly in their connections yet permit quite different behaviors. We further show how small differences in synaptic wiring, especially in relation to the local circuit neurons, can facilitate or suppress behavioral activity. Finally, we consider some important organizational principles that underlie cognitive, emotional, and rewarding behaviors.

Nucleus accumbens, which makes up a large part of the ventral striatum, was originally thought to regulate locomotor activity and exert some control over motivational and emotional behavior, including playing a role in the processes underlying schizophrenia (Matthysse, 1978; Stevens, 1973). Early work showed that the pharmacological stimulation of dopamine in this nucleus brought about increases in locomotion (Pijnenburg & Van Rossum, 1973), self-stimulation (Broekkamp, Pijnenburg, Cools, & Van Rossum, 1975), and, with amphetamine administration, stereotypical behavior (Pijnenburg, Honig, & Van Rossum, 1975). When Mogenson, Jones, and Yim (1980) coined the now classical term *limbic-motor interface*, nucleus accumbens came to be viewed as the key site for gating motivational and other emotional signals in order to convert them into adaptive motor responses; dopamine served as the neural facilitator for that translation. Early neuroanatomical studies established links between limbic cortical centers and nucleus accumbens (Heimer & Wilson, 1975) and between the dopaminergic neurons in the ventral midbrain and this nucleus (Nauta, Smith, Faull, & Domesick, 1978). Access to motor circuits was considered to occur via the globus pallidus, a structure from

which locomotion could be elicited with injections of picrotoxin, a GABAergic antagonist (see Mogenson & Yim, 1981, Figure 9). More recent anatomical investigations, however, have shown that the outflow from accumbens, instead of exiting via a single efferent route, follows multiple, parallel pathways to different centers in the forebrain and brainstem (Groenewegen & Russchen, 1984; Heimer, Zahm, Churchill, Kalivas, & Wohltmann, 1991; Zahm & Brog, 1992; Zahm & Heimer, 1988). Moreover, behavioral, physiological, and pharmacological studies suggest that complex synaptic and nonsynaptic interactions within the nucleus itself could account for important nuances in adaptive behaviors (Austin & Kalivas, 1988; Bakshi & Kelley, 1994; Deutch & Cameron, 1992; Kalivas & Duffy, 1995; Ma, Brudzynski, & Leung, 1996; Wan & Swerdlow, 1996). Thus, as more connectional data for nucleus accumbens have become available, its role in gating limbic inputs (Mogenson et al., 1980) has taken on new, more highly complex meanings.

Nucleus accumbens, which is very rich in neurotransmitters and neuropeptides, contains both projection and local circuit neurons that are connected not only with each other but also with diverse inputs from cortical, subcortical, and brainstem centers. Although many details are still lacking, we are now beginning to understand how these cells and their connections form microcircuits, wired to subserve diverse functions. In this review, we will examine these units in some detail in order to provide a basic framework from which to hang broad behavioral concepts. We will look at the structural properties of the circuits with particular reference to their relationship with incoming monoamine pathways and local circuit neurons, and, finally, we will provide some insight into how drugs, lesions, and behavior can alter synapses and, thus, the circuits in which they participate.

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NEUROCHEMICAL ARCHITECTURE

Nucleus accumbens, like the caudate and putamen in the dorsal striatum, is compartmentally organized. The organizational pattern, however, is really very different. In contrast to the bicompartamental, striosome or patch and matrix, pattern in the dorsal striatum, accumbens has two large, neurochemically and cytoarchitecturally complex compartments, termed *shell* and *core* (Figures 1 and 2; Jongen-Rêlo, Groenewegen, & Voorn, 1993; Meredith, Blank, & Groenewegen, 1989; Voorn, Gerfen, & Groene-

wegen, 1989; Záborszky et al., 1985; Zahm & Brog, 1992). A third division, referred to as the *rostral pole*, occupies roughly the foremost one fourth of the nucleus in rats (Zahm & Brog, 1992; Zahm & Heimer, 1993) but has not, as yet, been distinguished in human or other primates (Meredith, Pattiselanno, Groenewegen, & Haber, 1996). While the rostral pole in the rat appears to stand alone on the basis of its efferent connections (Zahm & Heimer, 1993), it does contain rostral extensions of the neurochemical labeling that define shell and core territories (Jongen-Rêlo, Voorn, & Groenewegen, 1994; Meredith,

Figure 1. Drawing depicting the major compartmental divisions at a caudal level of nucleus accumbens, shell, and core. Computerized reconstructions of principal neurons located in the medial shell (to the right), lateral shell (to the left), and core. Note the larger number of primary dendrites and spherical dendritic field of the core and lateral shell neurons, relative to those of the neuron at the septal pole.

Figure 2. Light micrographs illustrating the regional variation in the distribution of the opioid peptides, enkephalin (A) and dynorphin (B), and the rate-limiting enzymes for the production of dopamine, TH (C), and nitric oxide, NOS (D). Photomicrographs are all taken through a caudal level of nucleus accumbens. Core and shell (sh) are labeled in A, and cone area of the septal pole is labeled in C. Stars in A mark enkephalin-rich zones. Medial is to the right of each micrograph, and the scale bar in C, which is equal to 1 mm, is valid for A–D.

Pennartz, & Groenewegen, 1993), thus making it contiguous, at least from a chemical standpoint, with the two compartments.

Sharp regional variations in neurochemical content (Fonnum & Walaas, 1981; Voorn et al., 1989; Zahm & Heimer, 1988), receptor distribution and uptake sites (Bardo & Hammer, 1991; Herkenham, Moon Edley, & Stuart, 1984; Jongen-Rêlo et al., 1993), and afferent and efferent connections (Brog, Salyapongse, Deutch, & Zahm, 1993; Heimer et al., 1991) occur within the two territories. For example, in the core, rostralateral and caudal enkephalin-rich areas (Figure 2A) coincide with opioid receptor patches (Jongen-Rêlo et al., 1993); in the shell, patterns of opioid receptors, cell clusters, dopamine, choline acetyltransferase (ChAT), calcium binding protein D28k (CaBP), and the two opioid peptides, enkephalin (Figure 2A) and dynorphin (Figure 2B), either avoid or overlap one another in marked heterogeneous

patterns (Herkenham et al., 1984; Jongen-Rêlo et al., 1993; Meredith et al., 1989; Meredith, Pennartz, & Groenewegen, 1993; Voorn et al., 1989). Dense substance P and low neurotensin immunoreactivity overlie basal cell clusters ventrally in the caudal shell (Zahm & Heimer, 1988).

To understand the functional bases for motivational behavior, characterizing nucleus accumbens only in terms of shell, core, and rostral pole may not be enough. Beginning with the observations of Chronister, Sikes, Trow, and DeFrance (1981), attention has been increasingly focused on mediolateral differences in neurochemical content and connections of this nucleus (Alheid & Heimer, 1988; Fonnum & Walaas, 1981; Groenewegen & Russchen, 1984; Groenewegen, Vermeulen-Van der Zee, te Kortschot, & Witter, 1987; Meredith et al., 1989; Phelps & Vaughn, 1986; Voorn et al., 1989; Wright & Groenewegen, 1995). Indeed, there is now good evidence to show that caudomedial nucleus accumbens, the *septal pole*

(Figure 1; Voorn, Jorritsma-Byham, Van Dijk, & Buijs, 1986), while an intrinsic part of the shell, is also a transition zone between the extended amygdala and the rest of the striatum (Alheid & Heimer, 1988). The transitional nature of the septal pole becomes obvious when we consider its complex anatomical, hodological, and chemical features. This is where clusters of tightly packed small cells, which are dense in opioid receptors, reside (Herkenham et al., 1984); prefrontal, amygdalar, hippocampal, and midline thalamic inputs intermingle or avoid one another (Wright & Groenewegen, 1995; Zahm & Brog, 1992); dopaminergic fibers, as illustrated in Figure 2C by the distribution of tyrosine hydroxylase (TH) immunoreactivity, are distributed densely to the cone, where they provide a proximal input to the principal cells (Meredith, Pennartz, & Groenewegen, 1993; Voorn et al., 1986); and neuroactive substances, such as cholecystokinin, neurotensin, nitric oxide, as demonstrated via nitric oxide synthase antiserum (Figure 2D), and dynorphin (Figure 2A) are concentrated, and enkephalin (Figure 2A) is weak to moderately dense (Jongen-Rêlo et al., 1993; Van Bockstaele, Sesack, & Pickel, 1994; Záborszky et al., 1985; Zahm & Heimer, 1988).

MORPHOLOGICAL SUBSTRATE

Principal Neurons

The principal neurons (which are often called *densely spiny neurons*) account for roughly 90% of the total number of cells in nucleus accumbens. They use γ -aminobutyric acid (GABA) as a primary neurotransmitter and contain a variety of neuropeptides, including substance P, neurotensin, and the opioids enkephalin and dynorphin (Meredith, Pennartz, & Groenewegen, 1993; Pickel, Joh, & Chan, 1988; Zahm & Brog, 1992). They are small to medium in size, measuring approximately $100 \mu\text{m}^2$ in cross-sectional area or $11.5 \mu\text{m}$ in diameter (a range of $9\text{--}20 \mu\text{m}$) and have three to six primary dendrites that are initially spine-free and farther distally become laden with spines (Chang & Kitai, 1985; Meredith, Agolia, Arts, Groenewegen, & Zahm, 1992; O'Donnell & Grace, 1993b). The axon typically emerges from the cell soma and arborizes in the region of the dendritic tree, where synapses repeatedly occur with neighboring cells, before leaving the nucleus (Chang & Kitai, 1985; O'Donnell & Grace, 1993b). The perikarya are round, with a single large nucleus, one or two nucleoli, and a smooth nuclear envelope and are surrounded by a thin rim of cytoplasm containing all the usual organelles. The perikaryal membrane is often juxtaposed by glia and generally receives few axosomatic synaptic contacts (Meredith, Wouterlood, & Pattiselanno, 1990). Synapses are found on proximal and distal dendrites, and each spine usually receives an asymmetrical input to the head and a symmetrical terminal at the neck (Wilson, Groves, Kitai, & Linder, 1983).

In general, principal neurons in the caudomedial shell have fewer primary dendrites and spines than their coun-

terparts in the core or in lateral parts of the shell (Figure 1; Meredith et al., 1992; O'Donnell & Grace, 1993b). In addition, dendritic trees of medial shell neurons are elongate, whereas those elsewhere are more spherical (Figure 1; O'Donnell & Grace, 1993b). While the structure of core cells is generally uniform, that of shell neurons varies significantly. Spine density, total dendritic length, and number of dendritic branches increase along a medial-to-lateral gradient, such that, laterally, principal neurons more closely resemble those in the core than at the septal pole (Figure 1; Meredith et al., 1992). In line with these site-specific morphologies are regional differences in membrane properties. The mean resting membrane potentials (a range of -90 to -50 mV) are less negative, and the mean input resistances are greater for medial shell than for core neurons (O'Donnell & Grace, 1993b; Pennartz, Ameerun, Groenewegen, & Lopes da Silva, 1993; Pennartz, Dolleman-Van der Weel, & Lopes da Silva, 1992). In addition, neurons in the medial shell (septal pole) have significantly lower membrane time constants than do those in the core (O'Donnell & Grace, 1993b). These differences, when taken together, reflect the overall lower surface area in cells at the septal pole, relative to those more rostral or lateral in the shell or in the core.

Local Circuit Neurons

Local circuit neurons were recognized in early studies of the nucleus accumbens (Chronister et al., 1981), and they may comprise up to 10% of total accumbal neurons (Thomas, Vaid, & Totterdell, 1995). They vary greatly in size (Figure 3); their perikarya may be round or elongated, usually with an eccentric nucleus and an indented nuclear envelope. Their dendrites vary in extent and generally lack spines but are sometimes varicose. They are complex neurochemically: They can be grouped into at least four different, nonoverlapping populations (Hussain, Johnson, & Totterdell, 1996), which, with the exception of the giant cholinergic neurons, are GABAergic (Kawaguchi, Wilson, Augood, & Emson, 1995).

The first two groups of GABAergic neurons contain one of two calcium binding proteins, parvalbumin (PV) or calretinin (Figures 3A and 3C). The PV-positive cells are medium in size ($10\text{--}22 \mu\text{m}$ in diameter) and range from oval to multipolar, usually with two to three primary dendrites (Figure 3A). Some dendrites extend over a considerable distance without further branching, but others branch more often close to the soma. The dendrites appear smooth, being neither varicose nor spiny, and they taper quickly from the cell body. The calretinin-positive neurons (Figure 3C) are usually unipolar or bipolar but rarely multipolar. They all have small perikarya ($8\text{--}14 \mu\text{m}$ in diameter) and long dendrites that branch occasionally and become varicose distally.

The density of PV neurons in nucleus accumbens is lower than in the dorsal striatum, where they decrease in density along a lateral to medial gradient (Bennett & Bolam, 1994). In accumbens, their distribution is not ap-

Figure 3. Light micrographs of subtypes of local circuit neurons found in nucleus accumbens. The range in size of the perikarya can clearly be seen, since all cells are pictured at the same magnification. (A) Multipolar (arrowheads) and bipolar PV-immunoreactive neurons (silver-intensified gold deposit); (B) ChAT-immunolabeled (Vector SG) neurons; (C) calretinin-positive (Vector SG) neurons (note the long, thin dendritic processes); (D) a bipolar somatostatin-immunoreactive neuron (silver-intensified gold deposit); (E) NADPH-diaphorase-stained neurons (note the plexuses of fibers and long, extensive dendrites of the cells); (F) NOS-immunolabeled neurons (DAB) (note the tortuous dendritic processes [arrow] on some cells). Scale bar in D, which is equal to 20 μm , is valid for A–F.

parently linked to the core/shell divisions, although Sadikot, Rudkin, and Smith (1996) report a preferential distribution in the shell. Parvalbumin-positive neurons are more numerous in the rostral pole than they are farther caudally; they are rare at the septal pole but can be found in the ventral shell and core at caudal levels. In contrast, there are more calretinin-positive neurons in nucleus accumbens than in the dorsal striatum (Sadikot et al., 1996, but see Hussain et al., 1996). Moreover, their density medially exceeds that laterally, but there are no obvious core/shell differences. These neurons are also found in the rostral pole, although we have no evidence for an increase in density rostrally as reported in the dorsal striatum

(Bennett & Bolam, 1993). Calretinin-immunoreactive fibers characteristically form a dense but heterogeneous innervation of the medial shell (Hiroi, 1995), whereas they are less dense in the lateral shell and core.

The third major class of medium-sized interneurons is, at least in the dorsal striatum, not only GABAergic but also immunopositive for the neuropeptides, somatostatin (Figure 3D), and neuropeptide Y (NPY) and contains the neuronal form of nitric oxide synthase (NOS; Figure 3F) and NADPH-diaphorase (Figure 3E; Kawaguchi & Kubota, 1995). These neurons have somata that are bipolar, fusiform, or multipolar (compare Figures 3D, 3E, and 3F) and long dendrites, which branch infrequently

and become varicose and highly tortuous distally (Husain et al., 1996). The NOS-positive neurons (Figure 3F) are small to medium in size (8–18 μm in cross-sectional diameter) in both shell and core. There is no overall difference in the distribution of these cells, and fiber staining in the medial part of the shell is not homogeneous—that is, there is a region of low staining intensity at the most dorsal part of the septal pole, which is complemented by the “cone” region immediately below that shows particularly intense fiber staining (Figure 2D).

The local circuit neurons in the final group contain acetylcholine and can be visualized using antibodies to the enzyme, choline acetyltransferase (ChAT). Perikarya (Figure 3B) may be round, fusiform, or triangular with one to three primary dendrites, which are long and smooth and branch infrequently. These neurons are typically large (Figure 3B), measuring 15–35 μm across the long diameter (Phelps & Vaughn, 1986), but are significantly smaller than their dorsal striatal counterparts, which have long diameters of 20–50 μm (Kawaguchi et al., 1995; Phelps & Vaughn, 1986). At the septal pole, the cholinergic cells (a mean diameter of 14 μm) are significantly smaller than those (a mean diameter of 20 μm) in the core (Meredith, Pennartz, & Groenewegen, 1993). Cholinergic neurons are the least dense rostrally, with their density increasing rapidly through the rostral quarter of the nucleus and falling off sharply farther caudally (Meredith et al., 1989). Cell density is greatest in the shell, especially at the septal pole, where it is nearly three times higher than that in the core and five times greater than that at the rostral pole. The increased density also coincides with dense plexuses of immunoreactive fibers. In the core, cells are denser in the regions surrounding enkephalin-positive “patches” than within them (Meredith et al., 1989).

Finally, there are reports of intrinsic neurons containing cholecystokinin (CCK) or vasoactive intestinal peptide (VIP) in the striatum (Tagaki et al., 1984; Theriault & Landis, 1987), but these have yet to be investigated fully.

Receptors

Dopamine plays a powerful role in the regulation of motor activity and emotional and goal-directed behaviors, exerting its effects by interacting with two families of G-protein-coupled receptors: the D1-like and D2-like (Kebabian & Calne, 1979). Other receptors, such as those mediating the actions of excitatory amino acids and opioid peptides, also interact with dopamine and have been implicated in mechanisms of motivationally relevant processes (Churchill, Roques, & Kalivas, 1995; Pierce, Bell, Duffy, & Kalivas, 1996). Therefore, the localization of these receptors to precise morphological sites seems crucial to our understanding of the mechanisms underlying numerous behavioral effects (cf. reviews of Kalivas, Churchill, & Klitenick, 1993, and Mogenson, Brudzynski, Wu, Yang, & Yim, 1993). There are, however, discrepancies between neuroanatomical and pharmacological findings. Often, behavioral effects can only be explained

by the presynaptic activation of receptors; however, ultrastructural studies have not, so far, identified axo-axonic synapses in the striatum, whereas presynaptic actions are well documented pharmacologically. There are also numerous mismatches between the location of receptors and their related synapses (Herkenham, 1987). Nevertheless, other mechanisms of action have been proposed, and it is now widely accepted that dopamine, and perhaps other neurotransmitters, can diffuse some distance from the site of their release to reach extrasynaptic receptor locations (Herkenham, 1987). Furthermore, ultrastructural studies have identified close appositions and other membrane-spanning structures, such as the puncta adhaerens, that may account for some interactions (see, e.g., Gracy & Pickel, 1996; Gracy, Svingos, & Pickel, 1997; Meredith, Ingham, Voorn, & Arbuthnott, 1993; Sesack & Pickel, 1990). Finally, an anatomical substrate for electrical transmission between cells has been described and appears to be regulated by dopamine (O'Donnell & Grace, 1993a; also see O'Donnell, 1999).

Both families of dopaminergic receptors are found in nucleus accumbens, and the D1, D2, and D3 subtypes are found in both the shell and the core (Bardo & Hammer, 1991; Bouthenet et al., 1991). Receptors belonging to the D1 and D2 subtypes decrease in density along a rostral-to-caudal gradient, and D2 receptors are denser in the core than in the shell, whereas D1 receptors are concentrated similarly in both territories (Bardo & Hammer, 1991). The D2 receptor is present in equal proportions in dendrites/spines and axon terminals of GABAergic principal and local circuit neurons in the medial shell (Delle Donne, Sesack, & Pickel, 1997).

Dopaminergic D3 receptors are reported to be denser in nucleus accumbens than in the dorsal striatum (Lévesque et al., 1995) and are densest over the islands of Calleja that line the medial and ventral borders of the shell (Bouthenet et al., 1991; Le Moine & Bloch, 1996). Recent work has shown that up to one quarter of the principal neurons in the shell that contain substance P also express both the D1 receptor and the D3 receptor; in the core, only 16% of these cells have both receptors (Le Moine & Bloch, 1996). Considering the recent evidence for the reduction of D3 receptors in psychosis (Schmauss, Haroutunian, Davis, & Davidson, 1993) and their activation by cocaine (Caine & Koob, 1993), these receptors could potentially play a very important role in mediating the motivational state of individuals.

Opioid receptors, as defined with naloxone binding, form dense aggregates in the rostral and caudal core and overlap small zones enriched with enkephalinergic fibers (Jongen-Rêlo et al., 1993); they also coincide with small clusters of cells in the caudomedial shell at the septal pole (Herkenham et al., 1984). Behavioral studies ascribe the aversive and rewarding effects of opiates to precise neuroanatomical sites, where high densities of mu and kappa receptors are found (Bals-Kubik, Ableitner, Herz, & Shippenberg, 1993), and, recently, μ -opioid receptors

have been localized to dendrites and spines within dense enkephalinergic patches of the core (Svingos, Moriwaki, Wang, Uhl, & Pickel, 1996).

Glutamatergic transmission in nucleus accumbens is mediated primarily by α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate receptors. The *N*-methyl-D-aspartate (NMDA) receptors seem to be activated in the absence of GABA_A receptor-mediated inhibition (Pennartz, Boeijinga, & Lopes da Silva, 1990). There is a greater density of NMDA receptors in nucleus accumbens, relative to the dorsal striatum (Maragos, Penney, & Young, 1988); in the shell, they are found primarily in dendrites but also exist in axons and terminals and occasionally in astrocytes, and they are found in 17% of somata and dendrites of NOS-immunoreactive neurons (Gracy & Pickel, 1996, 1997; Gracy et al., 1997). The core and rostral pole have not as yet been investigated. The compartmental distribution of AMPA receptors in nucleus accumbens is not fully known, but activity at these receptors has been shown for both shell and core territories (Kelley & Swanson, 1997; Pennartz et al., 1990). Both AMPA and NMDA receptors play a role in learning and memory. For example, NMDA receptors in the accumbal core seem to be preferentially involved in learning (Maldonado-Irizarry & Kelley, 1995), and AMPA receptors in the caudomedial shell play a direct role in feeding behavior (Kelley & Swanson, 1997).

SYNAPTIC FRAMEWORK

The neural substrate subserving adaptive behaviors is complex and is dependent not only on the neurochemical compartmentation and extrasynaptic activation of receptors but also on the different structural elements that interact synaptically to form microcircuits. The basic structural unit, whether in shell or core, is the medium-sized, densely spiny projection neuron. The function of such a neuron *in vivo* is likely to depend on the source of its extrinsic inputs, its synaptic relationships with neighboring cells, especially those involved in local circuits, and its ultimate targets. Hence, it is not enough to know that there is a synaptic input from the ventral subiculum in the hippocampus to the projection neurons of the caudomedial shell (Totterdell & Smith, 1989), but it is also crucial to understand that this input makes asymmetrical contacts with the heads of spines of these neurons, as well as synapses with local neurons that, in turn, form symmetrical synapses with proximal dendrites of the projection cells. Thus, the outflow from these neurons may be regulated directly (Yang & Mogenson, 1984) or indirectly through local circuit neurons (Pennartz & Kitai, 1991).

Major excitatory inputs to nucleus accumbens originate in the hippocampus, the entorhinal cortex, the basal amygdala, and the medial and lateral subdivisions of the prefrontal cortex, and project to the nucleus topographically (Brog et al., 1993; Groenewegen et al., 1987; Johnson, Aylward, Hussain, & Totterdell, 1994; Sesack & Pickel, 1992; Totterdell & Meredith, 1997; Wright, Bei-

jer, & Groenewegen, 1996). The full extent of these projections is not known, but, in the case of subicular input, even following extensive lesions, it would seem that no more than 30% of all excitatory terminals in the caudomedial shell of the nucleus are found to be degenerating (Sesack & Pickel, 1990; Totterdell & Smith, 1989). The projection neurons that receive hippocampal input are thus also postsynaptic to a number of other sources: some that could also be excitatory, and others that make symmetrical synaptic contacts and are presumably inhibitory. Axons from cortical centers use an excitatory amino acid, presumably glutamate, as neurotransmitter and form asymmetrical synaptic contacts (Figures 4B and 4C) primarily with spines of principal neurons (Johnson, Aylward, Hussain, & Totterdell, 1994; Meredith, Pennartz, & Groenewegen, 1993; Meredith & Wouterlood, 1990; Sesack & Pickel, 1992; Totterdell & Meredith, 1997). The overwhelming majority of cortical terminals contact the heads of spines (Table 1); indeed, prefrontal and entorhinal fibers terminate almost exclusively on spines (Sesack & Pickel, 1992; Totterdell & Meredith, 1997). However, 10%–15% of hippocampal input to the medial shell and 8% of amygdalar input to the core and the shell synapse with dendrites (Table 1; Johnson et al., 1994; Meredith et al., 1990; Totterdell & Smith, 1989). Axon terminals of hippocampal fibers at the septal pole sometimes form axosomatic contacts with projection neurons and, occasionally, with aspiny interneurons (Meredith & Wouterlood, 1990; Meredith et al., 1990; Totterdell & Smith, 1989).

Another major source of excitation to accumbal cells is from centers in the midline or intralaminar thalamus (Berendse & Groenewegen, 1990). Axons from these centers form asymmetrical contacts with dendrites and spines in roughly equal proportions (Meredith & Wouterlood, 1990). At the septal pole in the medial shell, axosomatic inputs are rare but include contacts with presumed interneurons (i.e., cells with an indented nuclear envelope). Furthermore, midline thalamic terminals provide a major proximal innervation to cholinergic neurons, where they form axodendritic and axosomatic contacts with ChAT-immunoreactive elements (Meredith & Wouterlood, 1990).

Dopamine, which is more plentiful in nucleus accumbens than in the dorsal striatum (Fonnum & Walaas, 1981), provides a major source of symmetrical synaptic input to accumbal neurons. The dopaminergic inputs to accumbens arise primarily from A8 and A10 cell groups in the midbrain and project densely following a medial-to-lateral topography (Domesick, 1981; Groenewegen & Russchen, 1984). Axons from the A8 group project more laterally in the shell than those from A10 cells, and projections from the A9 cells are restricted to the core and lateral shell (Brog et al., 1993). Noradrenergic projections from the locus ceruleus are concentrated in the shell (Berridge, Stratford, Foote, & Kelley, 1997); serotonergic inputs, which are distributed to both core and shell, originate from cells in the periaqueductal gray and the dorsal

Figure 4. Electron micrographs that show the following: (A) A TH-immunoreactive terminal making an asymmetrical contact (arrow) with a dendrite of a medium spiny neuron (asterisk) that projects to the VTA. The medium spiny, principal neuron has been intracellularly filled with the fluorescent dye, Lucifer yellow, immunoreacted, and the DAB reaction product silver–gold intensified (small particles over the dendrite). (B) A somatostatin immunoreactive bouton (presumably from a somatostatin/NOS/NPY interneuron) in symmetrical synaptic contact (arrow) with a spine in the shell region that also receives synaptic input from a bouton on a fiber from the amygdala (asterisk). This bouton, which is degenerating as the result of a lesion of the amygdala, makes an asymmetric synaptic contact (arrow) with the spine. (C) A bouton (asterisk), degenerating following a lesion of the hippocampal input to the nucleus accumbens and making an asymmetrical synaptic contact (arrow), converges with a TH-immunoreactive terminal making a symmetrical synaptic contact (arrow) onto the same postsynaptic target. Scale bars are equal to 0.5 μm .

and median raphe (Li, Rao, & Shi, 1989; Van Bockstaele & Pickel, 1993; Vertes, 1991).

Antibodies to dopamine itself proved hard to produce initially, and many studies have employed antibodies to TH—the rate-limiting enzyme in the production of dopamine. This approach is sometimes criticized, since TH is also present in noradrenergic and adrenergic neurons; however, experience has shown that, in the striatum at least, the TH antibodies are markers of dopamine-containing axons, not noradrenergic fibers (Totterdell & Smith, 1989). Dopaminergic fibers in nucleus accumbens innervate both spiny and aspiny neurons in the shell (Figure 4A) and core (Tables 1 and 2), but their synaptic arrangements differ with respect to location (Zahm, 1992). It was first noted (Freund, Powell, & Smith, 1984) in the dorsal striatum that dopaminergic terminals form symmetrical inputs to spine necks, whereas asymmetrical specializations are found on the heads. Dopaminergic endings also make symmetrical, axodendritic synapses proximal to excitatory inputs, a geometric arrangement

that would suggest that dopamine is in an ideal position to modulate the excitatory afferent input (Freund et al., 1984). At the septal pole of nucleus accumbens, the major proportion of TH-labeled terminals contact dendrites (Figures 4A and 4C) and, often, proximal shafts, whereas in the core, as in the dorsal striatum, the majority of TH-positive axons form axospinous junctions with the necks of spines (Table 1; Meredith, Pennartz, & Groenewegen, 1993; Zahm, 1992). The preferred arrangement with dendritic shafts in the shell could account for the more pronounced effects of dopamine on shell neurons (O'Donnell & Grace, 1993a; Pennartz, Dolleman-Van der Weel, Kitai, & Lopes da Silva, 1992) and presumably underlies the ability of stress to alter dopamine flow in the shell but not the core (Deutch & Cameron, 1992; Kalivas & Duffy, 1995).

The convergence of inputs onto the same postsynaptic target has important implications for the physiological function of accumbal circuits, especially when the proximal-distal arrangement of the inputs is taken into

Table 1
Synaptic Targets (Spine, Dendrite, and Soma) for Extrinsic and Intrinsic Inputs to Nucleus Accumbens' Core and Shell

	Nucleus Accumbens			Septal Pole (Medial Shell)			Reference
	Spine	Dendrite	Soma	Spine	Dendrite	Soma	
Glutamate							
Hippocampus				++++	++	±	Meredith et al. (1990)
Amygdala	++++	+ (core)	0	++++	+	0	Johnson, Aylward, & Totterdell (1994b)
Prefrontal cortex	++++	± (core)	0				Sesack & Pickel (1992)
Midline thalamus				++	+++	+	Meredith & Wouterlood (1990)
Monoamines							
Dopamine (TH)	+++	++ (core)	±	++	+++	±	Zahm (1992)
5-HT	±	+++	0				Van Bockstaele & Pickel (1993)
Opioids							
Enkephalin	+	++++ (core)	+	++	+++	+	Meredith, Ingham, et al. (1993)
Dynorphin	+	++++	+	+	++++	+	Van Bockstaele et al. (1994); Meredith et al. (1997)
Substance P	+	+++	+				Pickel et al. (1988)
Interneurons							
GABA	+	+++ (core)	++	+	+++(+)	+	Johnson et al. (1994a)
Parvalbumin	0	++++ (core)	++				Totterdell & Hussain (1996)
Calretinin	++	++++	+				Totterdell & Hussain (1996)
Somatostatin	++	++++	±				Johnson et al. (1994a)
Acetylcholine	++	+++	++				Phelps & Vaughn (1986)

Note—The following symbols represent the approximate percentages of terminals contacting the target: ++++ = 76%–100%; +++ = 40%–75%; ++ = 10%–39%; + = 3%–9%; ± = ≤2% (rare contacts); 0 = no contacts.

consideration. Table 2 summarizes the convergent arrangements that have been reported to date. Terminals of hippocampal, prefrontal, and amygdalar axons each converge with TH-immunolabeled, presumably dopaminergic, endings onto the same postsynaptic structure (i.e., spine or dendrite; Figure 4C and Table 2). In the medial shell, hippocampal and TH-positive terminals both contact the same interneuron or the same spine or dendrite of medium spiny projection neurons (Figure 4C; Sesack & Pickel, 1990; Totterdell & Smith, 1989). In the core and shell, amygdalar endings converge with TH-immunoreactive boutons on the same spiny projection cell, with the cortical terminal generally making an axospinous contact and the dopaminergic bouton, an axodendritic synapse (Johnson, Aylward, Hussain, & Totterdell, 1994; Johnson, Aylward, & Totterdell, 1994b). Finally, in the core,

medial prefrontal inputs (prelimbic, infralimbic areas) converge with TH-immunolabeled terminals onto spines (Sesack & Pickel, 1990).

Recent work in the septal pole of the medial shell has shown that NMDA receptors are colocalized with TH in axons and terminals (Gracy & Pickel, 1996), an arrangement that could subserve the presynaptic regulation of dopamine transmission. Such an arrangement may provide the basis, at least in part, for the rewarding effects of cocaine, since repeated administration of this psychostimulant augments dopamine transmission in the shell, an event further enhanced by NMDA agonists (Cervo & Samanin, 1995; Pierce & Kalivas, 1995).

Another important source of symmetrical synaptic input to both core and shell neurons comes from the axon collaterals of projection neurons. Their synaptic termi-

Table 2
Neural Elements in Nucleus Accumbens That Have Been Reported to Receive Convergent Terminals

Source of Terminals	Principal Neuron (Medium Spiny)	Local Circuit Neuron (Aspiny)	Dendrite of Unknown Origin	Reference
TH and prefrontal cortex in core	X		X	Sesack & Pickel (1992)
TH and Hippocampus in shell	X	X	X	Totterdell & Smith (1989)
Somatostatin and basolateral amygdala in shell	X			Johnson et al. (1994b)
TH and amygdala in core and shell	X	X	X	Johnson et al. (1994)
GABA and basolateral amygdala in shell	X			Johnson et al. (1994b)
Enkephalin and acetylcholine in core	X		X	Meredith & Chang (1994)
TH and Dynorphin			X	Van Bockstaele et al. (1994)
TH and Substance P	X		X	Pickel et al. (1988)

Note—Convergence is indicated by X.

Figure 5. Electron micrographs illustrating the following: (A) Two enkephalinergic, symmetrical contacts (arrows) with a medium spiny neuron (MSN) in the core (note the smooth nuclear envelope [filled triangles], typical of projection neurons). (B) PV-positive terminal contacting (arrow) a MSN. Inset shows an enlarged view of the synaptic bouton and arrow points to the symmetrical specialization. (C) Calretinin-immunoreactive bouton contacting (arrow) a MSN. The immunolabeled terminal is enlarged in inset and arrow points to the symmetrical synapse. (D) PV-immunolabeled terminal contacting a PV-immunoreactive local circuit neuron (LCN) (note the deep indentations in the nuclear envelope [asterisks] indicative of its interneuronal status). Inset shows the enlarged PV-positive terminal and its symmetrical specialization. Scale bars: A, 1 μ m; B–D, 2 μ m.

nals contain GABA and either enkephalin or substance P and dynorphin. Networks of their local axons are concentrated in restricted parts of the nucleus—that is, large, dense “patches” of enkephalinergic fibers are located in the rostral core, smaller dense “patches” are found in the caudal core (Figure 2A), and substance P or dynorphinergic (Figure 2B) fibers appear to be densest at the septal pole. Local connections have been studied anatomically using antibodies against enkephalin, dynorphin, and

substance P (Meredith, Egan, Tipper, Wong, & Hyde, 1997; Meredith, Ingham, et al., 1993; Pickel et al., 1988; Van Bockstaele et al., 1994), and physiologically with intracellular recordings (Chang & Kitai, 1986; O'Donnell & Grace, 1993b). These principal cells are known to contact local circuit neurons and their medium-sized spiny neighbors (Figure 5A), but autaptic synapses do not appear to occur (O'Donnell & Grace, 1993b). Several studies have suggested that the local collaterals are im-

portant for lateral inhibition (Chang & Kitai, 1985) by presumably "sharpening" the responses to the cortical inputs (Pennartz et al., 1993; Pennartz, Groenewegen, & Lopes da Silva, 1994).

Local terminals of enkephalinergic, dynorphinergic, and substance P-positive neurons primarily contact dendrites, but they also synapse with spines and perikarya of other principal neurons (Figure 5A and Table 1). Enkephalinergic terminals form significantly more axospinous contacts in the shell (19%) and in caudal enkephalin-rich patches (17%) than in the rest of the core, where only 8% of the endings terminate on spines (Meredith, Ingham, et al., 1993). Dynorphinergic terminals do not show such a bias: Axodendritic contacts in both shell and core comprise roughly 75%–80% of the synapses, and axospinous junctions make up 4%–9% in either territory (Meredith & Tipper, 1996). Eight percent of substance P-positive terminals contact spines (Pickel et al., 1988). Enkephalinergic terminals also form contacts with ChAT-positive interneurons, but these are rare and have only been reported in the core (Meredith & Chang, 1994).

The anatomical localizations of the opioid receptors have been little studied. In the core, mu opioid receptors are found primarily in dendrites and spines (Svingos et al., 1996). In the shell, a small percentage of mu opioid receptors are colocalized in the same dendrite or axon with the R1 subunit of the NMDA receptor (Gracy et al., 1997); the delta opioid receptors are concentrated in axons and terminals, which primarily form symmetrical synapses (Svingos, Clarke, & Pickel, 1998). Kappa receptor localization has yet to be examined. Dopamine regulates enkephalin and dynorphin and their receptors, since dopamine depletion or chronic blockade of dopaminergic receptors are known to upregulate enkephalin but have mixed effects on dynorphin in nucleus accumbens (Egan et al., 1994; Meredith et al., 1997; Voorn, Docter, Jongen-Rêlo, & Jonker, 1994). Moreover, disruption of the dopamine supply alters the effects of opioids on locomotion (Churchill, Klitenick, & Kalivas, 1998; Churchill et al., 1995) and raises levels of excitatory amino acids (Lannes & Micheletti, 1994). The intra-accumbal stimulation of enkephalinergic or mu opioid receptors in the dopamine-depleted nucleus accumbens significantly increases motor activity, an action that seems to occur via pathways other than those flowing through the ventral tegmental area (Churchill et al., 1998). Furthermore, blockade of dopamine receptors sensitizes rats to the reinforcing effects of heroin (see Kalivas et al., 1993, for review). The anatomical substrate for this sensitization could involve the dopaminergic input to enkephalinergic neurons and also receive cortical contacts or the dopaminergic input to dendrites that contain opioid and NMDA receptors (Gracy et al., 1997). Such arrangements presumably occur on principal neurons but may also be on interneurons, such as those containing NOS/NPY, which receive inputs (dopaminergic?) from the ventral tegmental area (Totterdell & McFarlane, 1996), contain the R1 sub-

unit of the NMDA receptor (Gracey & Pickel, 1997), and presumably contact opioid-containing projection neurons.

The connections of the interneurons in nucleus accumbens have not been studied extensively, but the role of a particular population is likely to reflect their compartmental distribution, their synaptic interactions with projection and other local circuit neurons, and their relationship with extrinsic afferent inputs. Physiologically, the interneurons are likely to be diverse considering that, in the dorsal striatum, fast spiking, low-threshold spiking, and long-duration after-hyperpolarizing cells have been identified (Kawaguchi, 1993). Limited work (Pennartz & Kitai, 1991; Pennartz & Lopes da Silva, 1994) in nucleus accumbens show that local circuit cholinergic neurons modulate synaptic responses and membrane properties of principal neurons and strongly attenuate both excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) in the nucleus.

In the dorsal striatum, Kawaguchi (1993) found that fast-spiking cells are immunoreactive for PV. Since fornix stimulation results in a monosynaptic EPSP and a disynaptic IPSP that is mediated via both glutamate and GABA in nucleus accumbens, it has been suggested that the PV-containing interneurons are the substrate of feed-forward inhibition (Pennartz & Kitai, 1991). Parvalbumin-positive terminals form symmetrical contacts with principal cells, providing inputs predominantly onto somata (Figure 5B) and proximal dendrites (Table 1; Hussain et al., 1996). Synaptic contacts have been reported between inputs from the basolateral amygdala and PV neurons, although it is likely that the postsynaptic PV neurons in this study were from a very caudal and ventral part of the nucleus (Sadikot et al., 1996). Parvalbumin-positive neurons also receive PV input (Figure 5D; Hussain et al., 1996; Sadikot et al., 1996), presumably from interneurons but possibly also from extrinsic sources, such as the ventral pallidum, where PV has been reported in the GABAergic projection cells (Sadikot et al., 1996). In the dorsal striatum, PV neurons receive excitatory input from the cortex onto all parts of the PV neuron examined (Bennett & Bolam, 1994), and it is possible that PV neurons are the site of convergence of a number of different cortical inputs. However, this has yet to be investigated for ventral parts of the striatum.

Although it is known that calretinin-immunoreactive neurons are postsynaptic to boutons making asymmetrical synaptic contacts (Hussain et al., 1996), as yet no source for these afferent terminals has been identified. Sadikot et al. (1996) did not find input from the basolateral amygdala. These neurons also receive symmetrical synaptic inputs from calretinin-immunoreactive boutons and establish symmetrical and asymmetrical contacts with medium-sized, densely spiny projection neurons (Figure 4C and Table 1; Hussain et al., 1996).

In the dorsal striatum, NADPH-diaphorase reactive neurons have been shown to receive dopaminergic input (Fujiyama & Masuko, 1996); in the accumbal shell, NOS-immunoreactive neurons have been found to be postsy-

naptic to terminals originating from neurons in the ventral tegmental area (Totterdell & McFarlane, 1998). Striatal neurons containing NADPH-diaphorase are also immunopositive for NOS and GABA and probably contain the neuropeptides, somatostatin and NPY (Kawaguchi & Kubota, 1995). Dorsal striatal NPY neurons receive direct input from the cortex (Vuillet, Kerkerian, Kachidian, Bosler, & Nieoullon, 1989), but a cortical input has not yet been confirmed for these neurons in accumbens. The majority of somatostatin-immunoreactive boutons make symmetrical synaptic contacts (Figure 4B) with dendrites (72%), some of which are large and presumably proximal, and spines (27%), but occasionally with somata (1%), percentages that do not differ between core and shell (Table 1; Johnson et al., 1994b). These results suggest that much of the output of these neurons is directed to the projection neurons and also converge with inputs from the amygdala onto spines of medial shell projection neurons (Figure 4B). Some somatostatin terminals may also reach other populations of interneurons.

Cholinergic neurons in the medial shell primarily form symmetrical axodendritic contacts, often with projection neurons. About one quarter of the terminals end on spines, and some of these synapses have asymmetrical specializations (Meredith & Wouterlood, 1990). Cholinergic cells receive inputs from midline thalamic axons onto proximal dendrites and perikarya but only rare inputs from the hippocampus, which form more distal contacts. They also receive axodendritic synapses from other ChAT-positive terminals. In the dorsal striatum, cholinergic neurons receive a dopaminergic input, and acetylcholine release is under dopaminergic control (Dimova, Vuillet, Nieoullon, & Kerkerian-Le Goff, 1993; Lehman & Langer, 1983). However, there is evidence in nucleus accumbens that dopamine and acetylcholine can act independently, especially at caudal levels (Henselmans & Stoof, 1991). Although synaptic contacts between these two elements have not yet been recorded, the pattern of local plexuses of cholinergic fibers matches that of the dopaminergic innervation (Meredith, Pennartz, & Groenewegen, 1993), and TH-immunoreactive fibers have been seen to contact ChAT-immunolabeled neurons in the dorsal striatum (Dimova et al., 1993). Moreover, ChAT-positive neurons, contain both dopaminergic D1 and D2 receptor mRNA (Jongen-Rêlo, Docter, Jonker, & Voorn, 1995). Principal neurons also contain both dopaminergic D2 and muscarinic receptors (Delle Donne et al., 1997; Sugita, Uchimura, Jiang, & North, 1991) and have been shown in independent studies to receive dopaminergic and cholinergic inputs (Meredith & Chang, 1994; Voorn et al., 1986). Finally, dopamine and acetylcholine can interact to influence locomotion, in that cholinergic stimulation potentiates dopamine-stimulated locomotion (De Belle-roche & Gardiner, 1982), and dopamine receptor blockade attenuates cholinergic hyperactivity (Austin & Kalivas, 1988).

MICROCIRCUITS IN BEHAVIOR

Structural Framework Subservient Adaptive Behaviors

Although there is abundant information on the role of the nucleus accumbens in a wide range of behaviors, little of this is presented within the anatomical framework of the nucleus. Pharmacological and lesion studies, with a few notable exceptions (see, e.g., Churchill et al., 1998), seldom take account of the core and shell divisions, and the rostral pole is only rarely considered, although there is a wealth of anatomical data to suggest that these regions are unlikely to function in the same way in different cognitive behaviors. When trying to establish precise circuitry, the compartmental distribution of afferents is particularly important. For example, afferents arising from the amygdala make connections in both core and shell regions (Johnson et al., 1994b), whereas those from the ventral subiculum of the hippocampal formation terminate in medial parts of the shell (Groenewegen et al., 1987; Meredith, Pennartz, & Groenewegen, 1993; Totterdell & Smith, 1989).

The input to the nucleus accumbens most extensively studied in a behavioral context is undoubtedly the dopaminergic input arising from neurons in the midbrain. Dopaminergic afferents reach all parts of the nucleus accumbens, although there are differences between the core and septal pole and in the precise topography of synaptic connections (Zahm, 1992; Zahm & Brog, 1992). The changes in firing pattern of midbrain neurons, between bursts and regular spiking, probably encode different information (Grace, 1991). Behaviorally relevant stimulation causes short-term increases in cell firing and, thus, phasic release of dopamine; tonic release, controlled by afferents from the prefrontal cortex, regulates the intensity of phasic firing by setting the background level of both dopaminergic receptors, auto- and postsynaptic (Grace, 1991; O'Donnell & Grace, 1993a). The fact that dopaminergic afferents apparently contact all projection neurons (Totterdell & Smith, 1989) would suggest that the role of dopamine is likely to be modulatory and possibly independent of the source of the excitatory input to the postsynaptic cell.

It has been proposed that dopamine in the nucleus accumbens plays an important role in determining responses to novelty and stress (Burns, Arnett, Kelley, Everitt, & Robbins, 1996). Dopamine activity is increased both in the prefrontal cortex and the nucleus accumbens in response to footshock or restraint stress (Sudha & Pradhan, 1995) and in the accumbens during execution of a behavioral response to a stressor (Robbins & Everitt, 1992). Dopamine elevations in accumbens are apparently not due to increases in firing rate of the midbrain neurons, but they may result from interactions between the prefrontal cortical afferents and dopamine-containing terminals (Doherty & Gratton, 1996). The influence of the prefrontal cortical input on the accumbens' dopaminergic

Figure 6. Hypothetical, simplified synaptic frameworks subserving motivationally related behaviors. See the Appendix for details.

gic response to stress seems to be specific to the shell region (Doherty & Gratton, 1996; Lacroix, Broersen, Weiner, & Feldon, 1998), where prefrontal cortical glutamatergic afferents make synaptic contacts with dendritic spines of projection neurons and dopaminergic input contact the dendritic shafts of the same neurons. Both dopaminergic and glutamatergic inputs probably contact local circuit neurons as well, and these in turn form synaptic contacts with the necks of spines, each of which also receives an excitatory input (Figure 4B; Johnson et al., 1994b), thus providing a possible site to modulate dopa-

mine release. Although much of the neurotransmission within the nucleus accumbens depends on AMPA receptors, NMDA receptors are important in potentiating fast excitatory responses from the prefrontal cortex to the accumbens (Meredith, Pennartz, & Groenewegen, 1993; O'Donnell & Grace, 1995; Pennartz et al., 1994). Specific to the shell is the presynaptic distribution of NMDA receptors on dopaminergic terminals (Gracy & Pickel, 1996), which may well provide the site for modulation of dopamine release by prefrontal cortical afferent terminals. These anatomical features may underlie the specific

influence of the prefrontal cortex on dopamine release in the nucleus accumbens in response to stress (Kalivas & Duffy, 1995).

Elevations of dopamine in accumbens are also reported in relation to the exposure of rats to novelty (Figure 6A). In a novel environment, rats show increases in locomotor activity (Burns et al., 1996), and the catecholaminergic signal in the prefrontal cortex and shell of the nucleus accumbens is elevated (Rebec, Grabner, Johnson, Pierce, & Bardo, 1997). Both basolateral amygdalar and accumbal lesions increase locomotor activity, whereas prefrontal cortical lesions have no effect, and subicular lesions decrease locomotor activity (Figure 6A; Burns et al., 1996). There are also differences between these cortical afferents in the control of food neophobia (Burns et al., 1996). Rats do not like new foods, but this dislike is attenuated by lesions of the basolateral amygdala or the hippocampus, whereas lesions of the prefrontal cortex affect only initial food choice and latency to begin eating. Excitotoxic lesions of accumbens increase activity generally and decrease neophobia in a comparable way to hippocampal lesions. These experiments led Burns et al. to suggest specific cognitive roles for the afferents to the nucleus accumbens. Mesolimbic dopamine may thus produce a gain-amplification in behavioral responding, but it may also participate in switching and response selection. The basolateral amygdala relays affective information and may be involved in the fearful effects of the novel food rather than its novel taste (Burns et al., 1996). Increased locomotor activity means less fear of the new environment. Ventral subicular lesions may produce a weakened impact of novelty; thus, food neophobia is reduced, and explorative locomotor activity in a novel environment is reduced. Meanwhile, the prefrontal cortex is involved in detection of novelty.

These observations are particularly interesting since they highlight the point that even circuits with apparently similar synaptic connections within nucleus accumbens can have opposite effects on cognitive behavior. The prefrontal cortex, amygdala, and hippocampal axons all project to the shell (Brog et al., 1993), where they make synaptic connections with the spines of projection neurons (Figure 6A; Johnson et al., 1994b; Sesack & Pickel, 1992; Totterdell & Smith, 1989). In all cases, these excitatory inputs are associated with convergent dopaminergic afferents. However, stimulation of the subicular (hippocampal) input to the accumbens results in increased locomotion, whereas stimulation of the amygdala results in "freezing" (Mogenson et al., 1993). These two inputs may feed into functionally independent parallel circuits or possibly interact with the same population of projection neurons, with the inputs being differentially modified by interactions with certain interneuronal populations (Figure 6A). The amygdala apparently relays affective information (fear of novelty, association with reward), whereas the subiculum relays the inhibitory or excitatory effects of novelty on behavioral output (Burns et al., 1996). Behavioral and electrophysiological studies

demonstrate convergence of these different limbic inputs onto single medium-sized, densely spiny neurons (Callaway, Hakan, & Henriksen, 1991; O'Donnell & Grace, 1995), but an anatomical confirmation of such arrangements is still awaited (Johnson, Aylward, & Totterdell, 1994a). Early light microscopic studies tended to emphasize the segregation of the limbic inputs, although, in the case of inputs from the prefrontal cortex and amygdala, the patterns of overlap are proving significant (Wright & Groenewegen, 1995).

These excitatory inputs from limbic cortices may also be differently modulated in the shell by arousal via the noradrenergic input from the locus coeruleus, stress-related serotonin release, or acetylcholine from local interneurons at the septal pole (Berridge et al., 1997; Meredith & Wouterlood, 1990; Van Bockstaele & Pickel, 1993). This caudomedial part of the shell is a common target for prefrontal, hippocampal, and amygdala afferents and is where serotonin-immunoreactive boutons make synaptic contacts more frequently than in the core (Van Bockstaele & Pickel, 1993). Despite physiological studies that show that 5HT depolarizes core neurons, the net result of 5HT action in the shell should be to inhibit the projection neurons (Van Bockstaele & Pickel, 1993). The exact relationship between 5HT and interneurons is not clear.

A role has been proposed for the hippocampal–nucleus accumbens pathway in learning. Ibotenate lesions of accumbens impair spatial discrimination learning, and dopamine depletion in the accumbens impairs working memory; reference memory errors are reported following the injection of glutamate antagonists into the nucleus accumbens (Schacter, Yang, Innis, & Mogenson, 1989). Transfer of information from the hippocampus to the nucleus accumbens is not thought to involve NMDA receptors (Schacter et al., 1989), which is in line with the pharmacological/physiological data, although this receptor type is possibly relevant to learning (Pennartz et al., 1994). It has also been shown that chronic peripherally administered inhibition of NOS decreases the response of rats to novelty, possibly indicating a deficit in working memory (Cobb, Ryan, Frei, Guelgomez, & Mickley, 1995). Although the NOS inhibitors may be acting via cortical regions, it is possible that the cortical input to the accumbens contacts NOS-containing local circuit neurons, which may then presynaptically downregulate transmitter release from the dopamine terminals or indirectly release the projection neurons from inhibition.

Perhaps an even more investigated behavioral relationship is that between dopamine in the nucleus accumbens and reward (Robbins & Everitt, 1992), although it has been suggested that much of the data reflects a loss of mobility rather than a loss of motivation (Salamone, Cousins, & Bucher, 1994). Accumbal dopamine, probably in the shell region, is involved in the maintenance of stimulus–reward association (Everitt, Cador, & Robbins, 1989; Spiegler & Mishkin, 1981) and conditioned reinforcement (Gaffan & Harrison, 1987) and is released in antic-

ipation of reward (Robbins & Everitt, 1992). There is also evidence, however, that dopamine is involved in the aversive aspects of motivation. As described earlier, dopamine is released in response to a wide range of stressful experiences, and dopamine antagonists have been shown to decrease active avoidance (Salamone, Kurth, McCullough, Sokolowski, & Cousins, 1993) at doses that do not impair motor performance. It is possible that the appetitive consequences of dopamine activity are subserved by different subregions of accumbens from those that are activated in response to aversive stimuli. Both conditioned and primary aspects of reward also seem to require an input from the basolateral nucleus of the amygdala (Robbins & Everitt, 1992). The amygdala has a specific role in associating stimuli with specific incentive properties of the reward and is important in determining the salience of the stimulus (Everitt et al., 1989; Robbins & Everitt, 1992). Electrophysiological observations support the idea that amygdalar afferents and mesolimbic dopamine interact in the nucleus accumbens (Yim & Mogenson, 1986), and ultrastructural work shows that these inputs converge onto the same principal neurons (Johnson et al., 1994).

Other limbic afferents of nucleus accumbens could also interact with the amygdalar input. It has been suggested (Weiner, 1990) that input from the rostral basolateral nucleus of the amygdala to the nucleus accumbens is involved in stimulus reinforcement, and this input innervates neurons primarily in the core region (Wright et al., 1996). Stimulation of NMDA receptors in the core is apparently crucial to the establishment of motor responses to reinforcing stimuli (Kelley, Smith-Roe, & Holahan, 1997). The relationship between hippocampal and amygdalar inputs to the nucleus accumbens and their relative influences on cognitive behavior have been considered in some detail (Cools, Van den Bos, Ploeger, & Ellenbroek, 1991). The proposed gating hypothesis, whereby input from the hippocampus impedes the reception of incoming information from the amygdala, suggests that these inputs might converge onto the same cells (O'Donnell & Grace, 1995). These two sets of afferent fibers do indeed overlap in the medial striatum. The feed-forward circuitry via local interneurons (Pennartz & Kitai, 1991) may also provide the anatomical substrate for such gating (see Figure 6A).

Dopamine release in the nucleus accumbens' shell is also related to the rewarding effects of drugs of abuse. There is a significant increase in accumbal dopamine in response to stimulation with cocaine (Bardo, 1998; J. S. Kim & Levine, 1996), although it does seem that different drugs activate different circuits within this nucleus. In addition, NOS blockade significantly inhibits both cocaine- and morphine-induced conditioned place preference (H.-S. Kim & Park, 1995; Kivastik, Rutkauskaitė, & Zharkovsky, 1996), suggesting a role in reward for NOS-containing interneurons in the shell. Some of these interneurons contain the R1 subunit of the NMDA receptor (Gracey & Pickel, 1997) and, thus, presumably receive

input from cortical regions and make synaptic contacts with the projection neurons (Johnson, et al., 1994b). Nitric oxide is a readily diffusible gas that may act extrasynaptically, and it has been proposed as a retrograde messenger in the induction of long-term potentiation (Garthwaite, 1991) by reinforcing the strength of specific synaptic connections following repeated stimulation.

Repeated exposure to amphetamine, which produces behavioral sensitization (Figure 6B), results in long-lasting structural changes (increased numbers of spines and/or longer dendrites) in neurons in both the prefrontal cortex and the nucleus accumbens (Robinson & Kolb, 1997). Development of behavioral sensitization apparently depends on excitatory amino acid inputs to the nucleus accumbens (Pierce et al., 1996), the ventral tegmental area, or both, although different circuits might underpin the different behavioral elements of the development of sensitization to amphetamine (Wolf, Dahlin, Hu, Xue, & White, 1995). There is also a role for interaction between dopamine and the opioid peptides in such behavioral sensitization (Kalivas et al., 1993), since rats treated chronically with dopamine antagonists show greater reinforcement following systemically administered heroin. Enkephalinergic neurons that have had their dopaminergic input blocked certainly respond by upregulating the genes for the production of this peptide (Geffen et al., 1990), a response that is presumably regulated by cortical inputs to these same neurons.

The subtle and complex nature of the behavioral deficits produced by interference with dopamine systems has led to the suggestion that dopamine is involved in sensorimotor function, the ability to use sensory information to regulate motor output (Figure 6C). Prepulse inhibition of acoustic startle (PPI), an operational measure of sensorimotor gating, is the normal reduction in startle reflex that occurs when a startling stimulus is preceded by a weak prepulse that does not itself elicit a response. Increasing dopamine function in the nucleus accumbens by a variety of means disrupts PPI (Wan, Caine, & Swerdlow, 1996). Isolation rearing, which produces a hyperdopaminergic state in rats, also disrupts PPI (Wilkinson et al., 1994). Cholecystokinin, which may be coreleased with dopamine from fibers arising in the ventral tegmental area, is reported to potentiate apomorphine-induced disruption of PPI (Feifel & Swerdlow, 1997), although this could be via intrinsic CCK neurons in the striatum (Tagaki et al., 1984).

PPI is regulated by both core and shell regions (Figure 6C; Kodsi & Swerdlow, 1997). Interactions between the dopaminergic and glutamatergic inputs to the accumbens exert a complex influence over expression of PPI. Although PPI is disrupted by large (Bubser & Koch, 1994) but not small (Lacroix et al., 1998) lesions of the prefrontal cortex, the glutamatergic afferents that have a very important control over PPI expression almost certainly originate in the hippocampus. PPI disruption following subconvulsive doses of NMDA injected into the hippocampus can be reversed by NMDA antagonists in the hippocam-

pus or the accumbens (Klärner, Koch, & Schnitzler, 1997; Wan et al., 1996) but not by dopamine D2 antagonists (Kretschmer & Koch, 1997; Wan et al., 1996). The non-NMDA-induced disruptions of PPI are also dopamine-independent in the shell, although they are reversed by systemic haloperidol in the core (Figure 6C; Wan & Swerdlow, 1996).

Morphological Plasticity

There is now good evidence that the structure and survival of neurons can be altered by dopamine and glutamate acting through their receptors and related second messenger systems. However, there is little information as to how dopamine or dopamine–glutamate interactions mediate structural change. Dopaminergic receptor stimulation controls the release of glutamate. At the septal pole, this process presumably occurs either presynaptically, since D2 receptors have been found on terminals that make asymmetrical contacts (Delle Donne et al., 1997), or postsynaptically through contacts situated close to asymmetrical inputs from the cortex (Sesack & Pickel, 1992; Totterdell & Smith, 1989) or, perhaps, via synapses with local circuit neurons (Hussain et al., 1996; Kawaguchi et al., 1995). While a certain level of glutamate is critical for synaptogenesis and plasticity and is crucial for the development of neuronal circuitry and in the formation and storage of memory (see Malenka & Nicoll, 1993, for review), neurons can be damaged structurally by excessive levels (Michaels & Rothman, 1990; Segal, 1995). Such alterations in structural geometry may be important factors in the production of motor abnormalities. Prinssen, Balestra, Bemelmans, and Cools (1994) have shown that dopaminergic stimulation of neurons in the caudomedial shell, but not the core, can augment chewing movements. Furthermore, removal of tonic excitatory inputs to this same region via blockade of the AMPA receptors enhances feeding activity (Kelley & Swanson, 1997), suggesting that changes in the flow of glutamate to the shell are critical for oral movements. Chronic blockade of D2 receptors with neuroleptic drugs also raises levels of opioid peptides in the nucleus accumbens (Egan et al., 1994) and, in certain susceptible animals (i.e., those that develop abnormal orofacial movements), significantly increases the density of dynorphinergic axospinous contacts, at least in the caudomedial shell (Meredith et al., 1997). Since chronic blockade of D2 receptors elevates extracellular glutamate (See & Chapman, 1994) and kappa receptors regulate striatal glutamate flow tonically (Rawls & McGinty, 1998), it is likely that long-term dopamine receptor blockade also leads to a remodeling of dynorphinergic synapses, at least in the accumbens' medial shell.

We know that dendritic spines serve a neuroprotective function by acting as independent calcium compartments that respond to excitatory amino acid inputs rapidly and in a sustained manner (Segal, 1995). In nucleus accu-

bens, dopamine depletion leads to a loss of spines in the core but not in the shell (Meredith, Ypma, & Zahm, 1995). On the other hand, chronic administration of psychostimulants, such as amphetamine, produce an increase in the density of spines of both shell and core neurons (Robinson & Kolb, 1997). The fact that the removal of dopamine acts differentially to decrease spine density leads us to believe that the mechanism(s) may be regionally specific. However, we would have also expected amphetamine to be site-specific, since repeated cocaine augments levels of dopamine in the shell but not the core (Pierce & Kalivas, 1995; Sorg, Guminiski, Hooks, & Kalivas, 1995). Nevertheless, any change in the structural integrity of neurons, whether regionally specific or not, would alter circuit function and ultimately disturb the balance between pathways flowing out of the nucleus.

CONCLUSIONS

Underlying the complex behavioral functions of nucleus accumbens are structural frameworks of anatomical microcircuits. Although these frameworks can be described in terms of their neurons, synaptic connections, and receptors, it remains difficult to assign specific behavioral functions to a particular circuit. In any one part of the nucleus, topographically organized inputs from cortical and subcortical centers interact with an extensive dopaminergic innervation arising from the midbrain and no fewer than four different populations of interneurons. In addition, the multiple pathways flowing out from the nucleus to different targets mean that any one behavior could be subserved by more than one circuit at any one time.

At the septal pole, where the extended amygdala meets the striatum (Alheid & Heimer, 1988), medium-sized densely spiny projection neurons have long expanses of dendrites, lined with inputs from extrinsic and intrinsic sources, as well as spines that receive cortical and thalamic synapses. In the core, projection neurons have spine-laden dendrites with many of the same inputs. The anatomical substrate for presynaptic interactions may involve the activation of NMDA and/or D2 receptors found at extrasynaptic sites on axons and terminals, the intrinsic connections via interneurons or gap junctions (Delle Donne et al., 1997; Gracy & Pickel, 1996; Gracy et al., 1997; Herkenham, 1987; Kawaguchi et al., 1995; O'Donnell & Grace, 1993a). The anatomical differences in synaptic arrangements between these two territories are subtle. Proximal inputs to core neurons arise from intrinsic sources, and distal contacts are of extrinsic origin, whereas inputs to shell cells are mixed (i.e., of extrinsic and intrinsic origin regardless of the proximity to cell body). Moreover, enkephalinergic terminals end on fewer spines in the core than in the shell; dopaminergic inputs contact dendrites preferentially in the shell, and cortical endings in the core synapse less often on dendrites than in the shell.

There are also shell/core differences in the distribution and density of interneurons, but little is known of territorial differences in their synaptic organizations.

There is now overwhelming evidence that, for a wide variety of behaviors (see, e.g., Figures 6A, 6B, and 6C), different circuits either in the same or in different parts of the nucleus become active. For example, the release of dopamine at the septal pole of the shell under behavioral conditions of reward, sensitization, and stress presumably relies on (1) the proximal arrangement of dopaminergic synapses in relation to cortical inputs to dendrites and spines, (2) the presence of NMDA receptors on TH-immunoreactive axons and terminals, or (3) the synaptic organization of local circuit neurons that produce nitric oxide. Since locomotion is increased with stimulation of NMDA receptors (Kalivas et al., 1993) and the rewarding effects of cocaine are suppressed by blocking the synthesis of nitric oxide (Pulvirenti, Balducci, & Koob, 1996), the NOS-positive interneurons in the shell may be key to understanding the behaviors associated with cocaine.

In the core, synaptic inputs from the prefrontal cortex or amygdala interact with dopaminergic endings primarily at the level of spines of the projection neurons. Stimulation of the glutamatergic AMPA receptors or increasing the dopaminergic activity in the core results in disruption of PPI (Wan & Swerdlow, 1996). The net effect seems to reduce the activity of the projection cells, since blockade of their efferents, farther downstream, also disrupts PPI. Neurons in the core are also vulnerable to changes in dopamine: both its loss by dopamine-depleting lesions and its increase through chronic stimulation with amphetamine (Meredith et al., 1995; Robinson & Kolb, 1997).

As we gather more neuroanatomical data on the synaptic framework of the shell and core circuits, the microcircuits underlying initiating and sustaining motivational and cognitive behaviors, are starting to unfold. We now know that, pharmacologically, behaviorally, and structurally, there are some fundamental differences in how the microcircuits of the accumbal core and the shell, especially at the septal pole, are built and operate.

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APPENDIX

Hypothetical, Simplified Synaptic Frameworks Subserving Motivationally Related Behaviors

Novelty

Both hippocampal and amygdalar inputs to the septal pole region of nucleus accumbens (NAc) may mediate responses to novelty. Their influences are dissociable since lesions of these regions produce qualitatively similar effects on food neophobia but opposite effects on locomotor activity. Hippocampal and amygdalar fibers form excitatory synapses with the spines of medium spiny neurons (MSNs), although not necessarily the same neurons. Dopaminergic input onto dendritic shafts, proximal to the cortical terminals, may modulate this excitatory input. Local circuit neurons (LCNs), unlikely to be PV-containing since such neurons are relatively rare in the septal pole, probably also receive amygdalar and/or hippocampal and dopaminergic innervation. Hippocampal afferents to the NAc are probably im-

portant in switching between behaviors, and those from the amygdala carry information about the animal's emotional state. Convergence of these two inputs would allow individual NAc neurons to integrate their signals. Segregation of inputs to separate populations of MSNs is more consistent with the observed dissociation of behaviors, although MSNs are probably interconnected via their own local axonal connections and via the inputs from LCNs.

Behavioral Sensitization

Behavioral sensitization is reportedly mediated by excitatory inputs to the septal pole region of NAc shell. Since exposure to stress produces cross-sensitization with cocaine, inputs from the prefrontal cortex (PFC) are probably of greatest relevance. In the shell, NMDA receptors are presynaptic on dopaminergic terminals, providing a specific site for the modulation of dopamine release by PFC afferents. The PFC also regulates the burst-firing pattern of the neurons that give rise to dopamine innervation of NAc. Excitatory inputs from the PFC to NAc synapse onto spines and may also innervate PV-containing or somatostatin/ NOS/ NPY-containing LCNs. These LCNs then contact projection neurons, presumably including those that receive direct prefrontal input. Outputs from the septal pole preferentially feed into limbic-related regions. Behavioral sensitization involves increased responsivity to dopamine (via D1 receptors) in NAc, perhaps related to a reported increase in spine density. Such an increase might provide more sites for (presynaptic) interactions between dopamine and cortical afferents and, hence, enhanced dopamine release in response to subsequent exposure to rewarding drugs. Since NOS inhibition significantly inhibits both cocaine- and morphine-induced conditioned place preference,

this population of LCNs may be crucial in the development of increased sensitivity to dopamine.

Sensorimotor Gating

Prepulse inhibition of acoustic startle (PPI), a measure of sensorimotor gating, is regulated in both core and shell regions via complex interactions between the dopaminergic and glutamatergic inputs. Apomorphine-induced disruption of PPI is potentiated by cholecystokinin, either coreleased with dopamine or from LCNs. PPI is disrupted by large lesions of PFC and following subconvulsive doses of NMDA injected into the hippocampus. Glutamate agonist-induced disruptions of PPI are dopamine independent in the shell but are dopamine (D2) dependent in the core. It is possible that core and shell elements of PPI are related to inputs from the PFC and hippocampus, respectively. Fibers from both regions contact spines and dendrites of projection neurons and converge with dopamine input. However, in the shell, excitatory inputs are more often onto dendritic shafts: Spines as specific sites for modulation by dopamine are reduced. Dopaminergic fibers in the shell (but not core) bear presynaptic NMDA receptors that may explain why glutamate-induced PPI disruptions in the shell are dopamine independent. Stimulation of glutamatergic afferents to NAc produces excitation followed by inhibition. Inhibition of neurons in the shell that might project to the ventral segmental area may increase dopaminergic input to both core and shell. In the shell, this elevation might be sufficient to counteract the effects of a dopamine antagonist.

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