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The structural basis for mapping behavior onto the striatum and its subdivisions

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Abstract

The striatum can be divided into dorsal (caudate-putamen) and ventral parts. In the ventral division, the nucleus accumbens, which subserves adaptive and goal-directed behaviors, is further subdivided into shell and core. Accumbal neurons show different types of experience-dependent plasticity: those in the core seem to discriminate the motivational value of conditioned stimuli, features that rely on the integration of information and enhanced synaptic plasticity at the many spines on these cells, whereas shell neurons seem to be involved with the release of predetermined behavior patterns in relation to unconditioned stimuli, and the behavioral consequences of repeated administration of addictive drugs. In the core, the principal neurons are medium sized and densely spiny, but in the medial shell, these same neurons are much smaller and their dendrites, significantly less spiny, suggesting that morphological differences could mediate unique neuroadaptations associated with each region. This review is focused on evaluating the structural differences in nucleus accumbens core and shell neurons and discusses how such different morphologies could underlie distinguishable behavioral processes.

Keywords

dopamine; nucleus accumbens; glutamate receptors; dopamine; shell; core

Introduction

In his long and productive research career, Lennart Heimer was particularly focused on the organization of the basal forebrain, the unravelling of which he saw as being essential for our understanding of drive and motivation, and of associated psychiatric disorders. In considering the neural substrates that initiate and maintain motivated behavior, we, like Lennart Heimer and his associates (Heimer et al. 1993), naturally focus on the nucleus accumbens (Acb) of the ventral striatum, the functional interface between motivation and movement (Mogenson et al.

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†Dr. Ann Kelley died on August 5, 2007, before this manuscript was complete. We would like to honor and remember both Dr. Heimer, who died on March 12, 2007, and Dr. Kelley, distinguished neuroscientists, both of whom made profound contributions to our understanding of the ventral striatum. Indeed, the conceptual framework for this article grew out of discussions that occurred at the 1999 conference, “Advancing from the ventral striatum to the extended amygdala,” held in honor of Dr. Heimer’s retirement. Drs. Heimer and Kelley respected each other’s work enormously, and it pleased Ann Kelley that her work would be represented in this tribute to Lennart Heimer. Both scientists sincerely hoped that, just as their own work had been inspired by the great neuroanatomists of the twentieth century, the next generation would carry on the excitement and intellectual adventure of trying to uncover the biological basis of that which makes us most human- our emotional life.

1980; Mogenson and Yang 1991). Heimer and Wilson (Heimer and Wilson 1975) were the first to recognize the significance of the parallel input-output relationships of the dorsal and ventral parts of the striatum. They realized that while the dorsal striatum was the primary target of sensory and motor cortices, the ventral striatum received the bulk of its cortical innervation from allocortical regions, such as the amygdala and hippocampus, regions that process affect-related information, and from neocortical areas, such as the prefrontal cortex, that are associated with the executive modulation of emotional expression (Kelley et al. 1982a; Kelley and Domesick 1982b; McGeorge and Faull 1989; Heimer et al. 1991b; Heimer and Van Hoesen 2006). The cortex provides the major glutamatergic innervation and the ventral tegmental area (VTA) and substantia nigra (SN), the dopamine supply to the Acb (Beckstead et al. 1979; Kelley et al. 1982a; Kelley and Domesick 1982b; Brog et al. 1993). Dopamine from the mesolimbic system (VTA), which innervates large parts of the Acb, is of particular importance for reward-related stimuli (Scheel-Krüger and Willner 1991). Neural processing in the Acb is also critically dependent upon the relationships with the basolateral amygdala, hippocampus, and prefrontal cortex, the 'affect'-related cortical connections (Alheid and Heimer 1988).

The Acb was first linked to motivational processes early in the last century when Herrick (Herrick 1926) suggested that it was involved in locomotion and feeding. Subsequently, Mogenson and Wu (Mogenson and Wu 1982) reported that pharmacological manipulations of dopamine in the Acb could inhibit or enhance feeding and drinking. Mogenson and colleagues then went on to propose the influential idea that the ventral striatum could be a 'limbic-motor interface' where processing related to motivation and emotion gains access to the motor system (Mogenson et al. 1980). Heimer and colleagues carried the concept further in a series of seminal works defining and refining the descriptions of basal forebrain systems, including the Acb (Alheid and Heimer 1988; Heimer et al. 1991b; Heimer and Alheid 1991c; Heimer et al. 1993; Alheid and Heimer 1996; Heimer et al. 1997).

In focusing specifically on the Acb, there is now considerable evidence that dopamine is a critical substrate for goal-directed behaviors and the incentive salience associated with reward. However, conditioned behavior also requires glutamate, and drug-induced changes in glutamate transmission in the Acb seemingly produce the long-term plasticity that underlies addiction (Wolf 1998; Kelley et al. 2003; Wolf et al. 2004). Nevertheless, considerable debate continues regarding the precise behavioral process or set of processes governed by the Acb, in part, because the ventral striatum itself can be further subdivided into functionally discrete parts.

In 1985, working with Lennart Heimer, Zaborszky and colleagues (Zaborszky et al. 1985) made the important observation that the Acb could be divided morphologically into two regions, the shell and core. Others have recognized these subdivisions subsequently using hodological, morphological, and histochemical criteria, see e.g. (Alheid and Heimer 1988; Meredith et al. 1989; Voorn et al. 1989; Groenewegen et al. 1991; Heimer and Alheid 1991c; Meredith et al. 1992; Brog et al. 1993). The anatomical delineation has also been matched by behavioral, electrophysiological, and neurochemical studies that have demonstrated distinctive Acb core and shell associations with specific motivated behaviors, e.g. (Chang et al. 1994; Betancur et al. 1997; Kelley and Swanson 1997; Stratford and Kelley 1997; Barrot et al. 2002).

It might be thought that the various behaviors could be consequences of different information being provided to core and shell neurons, and there is some evidence for this view. For example, the ventral hippocampus projects primarily to the shell whereas more dorsal parts of the subiculum innervate the core (Groenewegen et al. 1991). The amygdala supplies the shell strongly, but innervate only small compartments (the patches or striosomes) in the core (Ragsdale and Graybiel 1988; Wright et al. 1996). There are also differences in the

dopaminergic innervation of the Acb, since the inputs to the shell arise almost exclusively from the VTA whereas those to the core are mixed, coming from the SN as well (Brog et al. 1993). Moreover, projections from different sources may well end up on the same neurons, as has recently been demonstrated for ventral subicular and amygdalar inputs that converge on the same principal neurons in the shell (French and Totterdell 2003).

Although divergent connectivity provides a framework for many of the shell-core functional differences, we shall argue here that it is the heterogeneity in the structure of Acb neurons themselves that confers distinctive information-processing capabilities to these regions. We expect the differential ability of these neurons to integrate or adapt to changes in their inputs and to undergo the plastic changes that underlie motivational behavior (Meredith and Totterdell 1999b) to account for, at least in part, the alignment of certain functional responses to a particular region. We evaluate here some of the evidence for functional heterogeneity in the ventral striatal territories and review how this correlates with various behaviors.

Mapping behavior onto the shell and core

Kelley and colleagues were among the first to report distinguishable behavioral effects of selective pharmacological manipulation of the shell versus core (Maldonado-Irizarry and Kelley 1994). They demonstrated that infusions of the NMDA-receptor antagonist, AP-5 into the “central accumbens” (placements were in the Acb core and partially in the lateral shell, immediately lateral to the anterior commissure) produced decrements in locomotor activity, rearing, and novel object exploration that were much more pronounced than similar infusions into the “medial accumbens” (placements were in the medial shell). A conceptually similar result was reported two months later by Pulvirenti et al. (Pulvirenti et al. 1994), who showed that hyperactivity induced by systemic cocaine treatment was attenuated by intra-Acb infusions of AP-5 into the core but not the medial shell.

These initial studies suggested that glutamate transmission in the Acb core plays a more important role than in the shell in modulating goal-directed exploratory activity. This would mean a stronger involvement of the core neurons in connecting motor output with motivationally salient environmental contexts or stimuli. This idea has been further refined in numerous subsequent studies. To cite just a few: the development and expression of Pavlovian conditioned approach responses to a stimulus predicting food (Parkinson et al. 2000), the ability of drug-associated Pavlovian stimuli to support operant lever-pressing (Ito et al. 2004), and the motivational consequences of outcome devaluation, which tests an animal's ability to respond appropriately to a recent change in the motivational significance of a stimulus (Corbit et al. 2001), are all impaired by lesions of the Acb core, but not those of the medial shell (Parkinson et al. 1999; Di Ciano et al. 2001; Kelley 2004). In addition, inactivation of the Acb core, but not the medial shell, impairs performance in a set-shifting task (Floresco et al. 2006). Electrophysiological studies have found that a greater proportion of units recorded in the Acb core, relative to those in the medial shell, display excitatory responses when an animal is orienting to a novel environment or about to perform a motor response (lever-press) to receive drug reinforcement (Wood and Rebec 2004; Hollander and Carelli 2005). Moreover, studies using fast-scan cyclic voltammetry have demonstrated pre-lever press increases in dopamine release in the Acb core but not the medial shell (Phillips et al. 2003c). Based in part on these findings, a consensus is emerging that the Acb core plays a relatively more prominent role than the shell in selecting and executing motor responses to complex, changing contexts, or to stimuli whose motivational significance has been recently updated or modified by previous conditioning, e.g. see (Cardinal et al. 2002). Thus, neurons in the core appear to integrate the motivational value of reward-related stimuli and context-dependent associations, and translate these into motor actions.

In contrast, the Acb shell, and here we mean the medial sector, may be more selectively involved in governing unconditioned responses, including the release of predetermined motor patterns, in association with unconditional stimuli. For example, stronger spontaneous locomotor and investigatory responses are elicited by dopamine or D1 receptor agonist infusions into the medial shell compared to those in the core (Swanson et al. 1997; Baldo et al. 2002; Hernandez et al. 2005). Although lesions of the medial shell do not affect the ability of a Pavlovian conditional stimulus to support instrumental responding (conditioned reinforcement, CR), these lesions strongly attenuate the ability of amphetamine to enhance CR responding (Parkinson et al. 1999), and see (Phillips et al. 2003a), and weaken the psychostimulant actions of cocaine (Ito et al. 2004). Indeed, the unconditioned dopamine response to morphine and cocaine is significantly greater in the shell compared to that in the core (Pontieri et al. 1995).

The neural network that mediates the stimulant drug effects appears to lie in the shell, for the magnitude of the dopamine response with psychoactive drugs is dependent upon an intact shell (Everitt et al. 1999). Even stronger evidence of the somewhat ‘fixed’ nature of the Acb shell-mediated behavioral responses comes from the work of Kelley and colleagues on the Acb’s mediation of feeding. In several studies, this group showed that pharmacological inactivation of the medial shell output, whether by AMPA-type glutamate receptor blockade, or by stimulation of GABA receptors, produces a voracious feeding response in *ad libitum*-fed animals (Kelley and Swanson 1997; Stratford and Kelley 1997). These effects are not seen with similar microinfusions into the Acb core, lateral shell, or other parts of the striatum (Kelley and Swanson 1997; Basso and Kelley 1999). The feeding response is very stereotyped, and is not taste- or macronutrient specific, as it is with opioid receptor stimulation in the core (Zhang et al. 1998; Basso and Kelley 1999). Perhaps more germane to this discussion, shell-mediated hyperphagia does not translate into enhanced operant responding for food (Zhang et al. 2003). Moreover, hyperphagia-inducing shell manipulations during operant training enhance the acquisition of responding for food reward (Hanlon et al. 2004; Baldo et al. 2005). Thus, the feeding response elicited from the shell appears to resemble the *release of fixed-action feeding patterns*, in a manner reminiscent of stimulus-driven feeding elicited from the lateral hypothalamus (Kelley et al. 2005b; Baldo and Kelley 2007). In further agreement, opioid enhancement of unconditional palatable taste reactions are selectively enhanced by stimulation of the same medial shell region that supports GABA-mediated hyperphagia (Pecina and Berridge 2005; Baldo and Kelley 2007).

It is straightforward to invoke an argument based on hodology for these differences in the behavioral responses being mediated by the Acb core vs. medial shell. The topographic organization of basolateral amygdala-Acb projections (Kelley et al. 1982a; Wright et al. 1996) could perhaps account for the core/shell differences in mediating Pavlovian processes, and the unique Acb shell-lateral hypothalamus projection (Heimer et al. 1991a) in shell-mediated feeding responses. Nevertheless, intrinsic differences in the information-processing capabilities of the Acb neurons must be important contributors to the observed behavioral differences.

Two potential mechanisms that come to mind are the ability to *integrate information* arriving from convergent neural inputs, and the capacity to *consolidate or store information* through mechanisms of cellular plasticity. The involvement of these two processes, and in particular the latter, in the Acb control of behavioral processes is controversial. Yet, there is compelling evidence from behavioral studies to suggest that instrumental learning-related plasticity occurs in the Acb, and that neuronal plasticity is differentially expressed in the Acb core vs. medial shell. For example, intra-Acb core NMDA receptor blockade produces a stronger disruption of spatial learning and performance in a food-foraging holeboard task (Maldonado-Irizarry et al. 1995) and in a radial arm maze (Smith-Roe et al. 1999) compared to identical manipulations

in the medial shell. One of us (Kelley et al. 1997) has shown a striking dissociation between the effects of NMDA receptor blockade in the core compared to the shell on the acquisition of a food-reinforced operant lever-press response. Intra-Acb core infusions of AP-5 during training strongly inhibited acquisition, but had no effect on the response of rats that had already learned the response. Infusions into the shell had no effect on acquisition or performance. Finally, infusions of the protein synthesis inhibitor, anisomycin (a drug known to disrupt the consolidation of fear memories in the amygdala), into the Acb core, but not the medial shell, disrupted the acquisition of operant lever-pressing for food reinforcement (Hernandez et al. 2002). In this experiment, the drug was infused immediately *after* the training sessions, ruling out non-specific performance effects and suggesting a mechanism of post-trial disruption of memory consolidation. A subsequent study showed that pre-trial blockade of AMPA, NMDA, or dopamine D1 receptors in the Acb core disrupted instrumental learning, but post-trial infusions had no effect (Hernandez et al. 2005), implicating both transmitter systems in the learning. It is therefore important to consider whether structural and synaptic patterning of innervation in the Acb core and shell could account for putative differences in information integration and plasticity. The following section reviews the evidence for compelling differences between the core and shell in morphology and synaptic arrangements of dopamine and glutamate.

The structural basis for motivation and reward in the shell and core

Ramón y Cajal's (Ramón y Cajal 1911) description of striatal neurons, being medium in size and densely spiny implies a homogeneity throughout the region for which in fact there is scant evidence as applied to the Acb. In the Acb, as in the dorsal striatum, principal neurons use GABA as their primary neurotransmitter, contain various peptides and comprise 90–95 percent of the total population (Meredith and Totterdell 1999b). However, they differ noticeably in their dendritic organization and spine densities, as can readily be seen in figure 1 (Meredith et al. 1992).

In the dorsal striatum, the neurons are indeed medium-sized (12–18µm in cross-sectional diameter), and their dendrites are densely covered with spines, except for the most proximal branches (Wilson et al. 1983; Bolam 1984; Ingham 1989). But in the ventral striatum, the morphology of principal cells differs significantly between regions (figs. 1-2 and table 1). Thus, in the Acb core and lateral shell, the cell bodies are smaller than those located in the dorsal striatum, but the spine density is similar (Meredith et al. 1992). The principal neurons in the medial shell are even smaller and have fewer dendritic arbors and 20% fewer spines than do neurons in the core, lateral shell or dorsal striatum (figs. 1-2). Accordingly, medial shell principal neurons have as much as 80% less surface available for synaptic contact than do neurons in other dorsal or ventral striatal regions (Meredith et al. 1992). There are differences between shell and core neurons include their connections, as has been reviewed by others (Voorn et al. 2004), synaptic arrangement and receptor distribution.

One of the most interesting features of striatal spiny neurons is the way synapses are arranged on their spines. Each spine has an asymmetrical input at its the head (Kemp and Powell 1971) that is presumably glutamatergic, and a dopaminergic supply to its base (Bolam 1984; Freund et al. 1984), a grouping, often referred to as a 'triad', that could enable the dopaminergic synapse to influence the efficacy of the glutamatergic signal (reviewed in (Dani and Zhou 2004). However, this synaptic arrangement is not found throughout the Acb. Indeed, in the core, only about half of the dopaminergic inputs contact the necks of spines, and in the medial shell, only a third of these terminals even synapse on spines (Zahm 1992). In fact, the more medial and caudal a neuron's location in the Acb, the more dopaminergic contacts are found on its dendrites (Zahm 1992). The origin and density of the synapses also differ between regions. Dopaminergic neurons in the SN pars compacta (dorsal tier), along with some neurons

in the retrorubral fields, project to patches in the Acb (Gerfen 1987a), whereas dopaminergic neurons in the VTA terminate predominantly ventromedially in the Acb shell and in medial parts of the core (Brog et al. 1993). The densest dopaminergic innervation to the Acb is in the medial shell (Voorn et al. 1986), where the terminals arise from VTA axons and synapse primarily on the dendrites of principal neurons (Zahm 1992), and often on proximal dendrites (unpublished data, Meredith, 2001).

The D1 receptor appears to be differentially distributed between the medial shell and core. Dumartin and colleagues (Dumartin et al. 2007) have identified presynaptic D1 receptors at one-quarter of all asymmetrical synapses in both shell and core but a significantly greater proportion in the shell are found on dendrites when compared to the core (Hara and Pickel 2005). Significantly more of the D1 receptors co-localize with NMDA receptors on dendrites in the medial shell when compared to the core (Hara and Pickel 2005) and where this co-localization occurs, the diameter of the target dendrites is greater in the shell than in the core, suggesting that more proximal dendrites in the shell have both D1 and NMDA receptors (Hara and Pickel 2005). This is not surprising, for we have shown that dopaminergic synapses more often contact proximal dendrites in the shell than the core (unpublished results, Meredith 2001). In the shell, NMDA receptors are also found presynaptically on dopaminergic endings (Gracy and Pickel 1996), where they could influence the release of dopamine, an arrangement that might be responsible for the preferential release of dopamine in the shell observed during the acquisition of Pavlovian associations (Phillips et al. 2003b).

The distribution of AMPA receptors has been studied in the dorsal striatum. Approximately 60% of the two subunits, GluR2 and GluR3, are concentrated at asymmetrical synapses on spines (Bernard et al. 1997) and these colocalize postsynaptically with the NR1 subunit of the NMDA receptor at greater than 80% of axospinous synapses (Bernard and Bolam 1998). The distribution of AMPA receptors has yet to be fully explored in the Acb, but they are present on virtually all principal neurons and overlap the distribution of D1 and D2 receptors on approximately 80% of these cells (Lu and Wolf 1999). While presumably located at excitatory synapses on spines and dendrites, it is not yet known whether these AMPA receptors are differentially distributed between shell and core.

Alterations in glutamatergic activity can impact synaptic efficacy and give rise to changes in synaptic shape. We know that the competitive blockade of the NMDA receptor with AP-5 produces profound learning deficits in an instrumental learning task but only during its acquisition (Maldonado-Irizarry and Kelley 1994; Kelley et al. 1997). As this motor learning is fully dependent upon neurons in the Acb core, which are densely endowed with spines, each of which has a glutamatergic synapse, NMDA receptor-mediated plasticity could form the basis for the learning that has been so commonly observed in this part of the Acb. A spine forms a biochemical compartment, with NMDA receptors that are permeable to calcium ions, and has a thin neck where the movement of calcium into the dendrite could be gated (Koch and Zador 1993). Additional data implicate D1-NMDA interactions in the control of learning-related plasticity (Wolf et al. 2003). For example, DA D1 receptor antagonists that block instrumental learning (Hernandez et al. 2005), may do so through their actions on the synaptic 'triads' of core neurons.

The medial shell appears to play a less prominent role in the acquisition of new operant responding, although it does exhibit different types of experience-dependent plasticity, such as the long-lasting depression of excitatory synaptic transmission elicited by chronic cocaine administration (Thomas and Everitt 2001). As we have seen, shell neurons have many fewer spines than do core neurons, their afferent dopaminergic inputs are made onto proximal dendrites rather than on spines, and although D1 and NMDA receptors co-localize, they do so more often on dendrites, or presynaptically on spines (Hara and Pickel 2005; Dumartin et al.

2007). Thus, shell principal neurons seem less prepared for typical NMDA-mediated synaptic plasticity than are core neurons and, accordingly, shell cells may require synaptic or dendritic growth to support any behavioral change.

Dendritic spines are the favored sites for plastic changes in the striatum. Over three decades ago, Rall (Rall 1974) through modeling studies, and later Wilson and colleagues (Wilson et al. 1983) using high voltage electron microscopy found that synaptic efficacy can be rapidly and persistently altered if spine number or shape is modified. Several studies that have manipulated synapse form have revealed differences between shell and core neurons. For example, the number of spines on core but not on medial shell neurons decreases, when the dopaminergic innervation is removed (Meredith 1995). Shell neurons, however, increase dendritic length, spine density and change spine shape after chronic administration of cocaine or amphetamine (Robinson and Kolb 1999). Considerable synaptic remodeling of shell neurons occurs, including an increase in spine numbers follows long-term administration of haloperidol, but only when rats develop an abnormal (dyskinetic) motor response (Meredith et al. 2000). Thus, principal neurons in both the shell and core seem able to adapt structurally to prolonged changes in their inputs and such neuroadaptation could support long-lasting behavioral change.

Conclusions and future directions

We have summarized the evidence that suggests that there may be a structural basis for the distinguishable behaviors mediated by Acb core and shell, particularly with regard to information-processing and storage as mediated by convergent dopaminergic and glutamatergic inputs onto intrinsic striatal neurons. We conclude that the plasticity that accompanies core-mediated learning is rapid and, therefore, could require enhanced synaptic efficacy at numerous spine synapses, presumably through a mechanism such as long-term potentiation. In contrast, the behavioral responses mediated by the medial shell may be more fixed, and would require robust changes at dendrites rather than spine-based synaptic modification.

Other mechanisms, however, are likely to be involved. There are, for example, numerous neuroactive substances in the Acb, other than dopamine and glutamate, whose role in cellular plasticity is only beginning to be understood, and whose distribution and functional effects differ between shell and core. To outline just a few examples, it has been shown that methionine-enkephalin depresses IPSCs more strongly in the shell than in the core, and that Acb shell neurons lack the adenosine-mediated inhibition of EPSCs observed in the core (Brundage and Williams 2002). There is a noradrenergic projection to the striatum that is provided mainly by the A2 cell group in the nucleus of the solitary tract that innervates the posterior medial shell, but avoids the core and dorsal striatum (Delfs et al. 1998). In addition, there are several recently discovered hypothalamic peptides, such as the feeding- and arousal-related peptides, orexin/hypocretin, and the melanin-concentrating hormone (Bittencourt et al. 1992; Peyron et al. 1998; Baldo et al. 2003), that innervate the Acb shell far more densely than the core. It is interesting to note that these projections arise from neurons that are localized entirely within the lateral hypothalamic area, a region that receives a major projection from the Acb shell (Heimer et al. 1991a). Finally, the ventral striatum contains abundant binding sites for amylin, a member of the CGRP peptide family that is co-released with insulin in connection with feeding and energy balance-related signals; these binding sites are concentrated most heavily in the Acb shell and fundus striati (Sexton et al. 1994; van Rossum et al. 1994). Hence, there is a particularly close relationship between the Acb shell and systems that convey arousal-related autonomic, visceral, and peripheral energy balance-related information, and this association has led the shell being referred to as the “viscero-endocrine striatum” (Kelley 1999). Although the roles of these modulators in the information-integration and plasticity functions of the Acb neurons have yet to be determined (indeed, the

ultrastructural arrangements of their synaptic contacts are still largely unknown), we can speculate that if they participate in cellular plasticity, they are likely to do so in the context of automatic, reflexive, or highly over-learned behavioral processes (feeding, unconditioned patterns of investigatory behavior, etc).

This review has provided evidence that the core with medium sized densely spiny neurons relates to new instrumental learning and behavioral responses to conditioned stimuli, and the shell with smaller, sparsely spiny cells mediates predetermined behavior patterns in relation to unconditioned stimuli. It remains to be seen whether new findings will support these designations and realize the potential that swstructure can bring to behavioral funding.

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Figure 1.

Digitized reconstructions of principal neurons located in the (A) core – small to medium size densely spiny neuron, (B) lateral shell of nucleus accumbens – small to medium size densely spiny neuron, (C) medial shell of nucleus accumbens – small size sparsely spiny neuron. These reproductions were made from neurons reconstructed after intracellular filling with Lucifer yellow and then immunoreacted to produce a permanent record. Note the differences in the spread of the dendritic fields (Reproduced, with permission from psychobiology, Meredith and Totterdell 1996b).

Figure 2. Golgi-impregnated neurons in the (A) dorsal striatum, (B) core and (C) medial shell of the Acb. Note the differences in spine density and dendrite orientation of principal neurons in these regions

Table 1

Structural, synaptic and receptor framework of the Acb shell and core

	mean spine density ¹	dendrites ¹	glutamatergic synapses ²	NMDA receptors	AMPA receptors ³	dopaminergic synapses ⁴	dopaminergic receptors ^{5,6}
medial shell	14 spines/10µm	5 primary dendrites	95% corticostriatal synapses on spine heads	NR1 distributed uniformly	overlap with D1 and D2 receptors on principal neurons	70% on dendritic shaft	D1 + NR1 presynaptic co-localization
core	17 spines/10µm	3–8 dendritic trees	5% corticostriatal synapses on dendritic shafts	NR1 co-localized with D1 on significantly more dendrites than in core	NR1 + D1 presynaptic co-localization NR1 distributed uniformly	30% on dendritic spine	29% of all D1 receptors are presynaptic asymmetrical synapses
		total dendritic length: 1300 µms	2% hippocampal synapses on cell soma	NR1 co-localized with D1 on significantly fewer dendrites than in shell		37% on dendritic shaft	D1 + NR1 presynaptic co-localization
		6 primary dendrites	+/- 100% corticostriatal synapses on spine heads			51% on dendritic spine	25% of all D1 receptors are presynaptic asymmetrical synapses
		3–11 dendritic trees					
		total dendritic length: 2425µms					

¹ (Meredith et al. 1992)
² (Meredith 1999a)
³ (Lu and Wolf 1999)
⁴ (Zahm 1992)
⁵ (Hara and Pickel 2005)
⁶ (Dumartin et al. 2007)