Published in final edited form as:

Behav Brain Res. 2011 August 10; 221(2): 412–423. doi:10.1016/j.bbr.2010.11.047.

The cholinergic system and neostriatal memory functions

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Abstract

The striatum is one of the major forebrain regions that strongly express muscarinic and nicotinic cholinergic receptors. This article reviews the current knowledge and our new findings about the striatal cholinergic organization and its role in a variety of cognitive functions.

Pharmacological and genetic manipulations have indicated that the cholinergic and dopaminergic system in the striatum modulate each other's function. In addition to modulating the dopaminergic system, nicotinic cholinergic receptors facilitate GABA release, whereas muscarinic receptors attenuate GABA release. The striatal cholinergic system has also been implicated in various cognitive functions including procedural learning and intradimensional set shifting. Together, these data indicate that the cholinergic system in the striatum is involved in a diverse set of cognitive functions through interactions with other neurotransmitter systems including the dopaminergic and GABAergic systems.

Keywords

Cognitive strategy; T-maze; set-shifting; reversal learning; place navigation; nicotinic; muscarinic; striatum; aging; basal ganglia

1. Introduction

The basal ganglia are a group of nuclei situated at the base of the forebrain. The main components of the basal ganglia are the striatum (the largest component), pallidum, substantia nigra and subthalamic nucleus. The striatum is the main input processing unit of the basal ganglia, extremely rich in acetylcholine (ACh) and its associated enzymes Acetylcholinesterase (AChE; the ACh degrading enzyme), Cholineacetyltransferase (ChAT; the ACh synthesizing enzyme), and cholinergic receptors (muscarinic and nicotinic; mAChRs and nAChRs, respectively). The striatum receives input from virtually all areas of the cerebral cortex. Once the cortical information is integrated at the striatal level, it is conveyed to basal ganglia output nuclei (e.g., the globus pallidus) via the striatal medium spiny neurons (MSNs). The integration is strongly modulated by striatal ACh interacting with dopamine (DA). It has long been recognized that the striatal cholinergic system,

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together with dopaminergic circuitry within the striatum, plays a key role in voluntary movement. In addition, it is widely accepted that the striatal cholinergic system contributes to the cognitive functions of the striatum, which is the focus of this review.

2. Anatomical organization of the striatum

The rodent striatum can be divided into a dorsal and ventral portion based on connectivity and function. The dorsal striatum (or neostriatum) consists of the caudate putamen, and the ventral striatum includes the ventral conjunction of the caudate putamen, the nucleus accumbens, and portions of the olfactory tubercle (Figure 1A). All regions of the neocortex send afferents to the neostriatum in a topographic fashion, and these corticostriatal axons target the major striatal cell type, the GABAergic MSNs, which comprise roughly 95.0 % of the neurons in the rat striatum [150]. These cells have dendrites densely covered with dendritic spines; hence their name. The cortical projections form mainly asymmetrical (excitatory) synapses to MSNs [80,160]. The MSNs send axons to the output nuclei, such as the globus pallidus, also referred to as paleostriatum. These projection neurons project to the internal segment of the globus pallidus, forming the so-called direct, monosynaptic pathway. Other striatal MSNs project to the external segment of the globus pallidus multisynaptically, via intermediate connections, forming the indirect pathway. However, these two pathways are not strictly separated, as some MSNs project to the internal segment of the globus pallidus and also send axon collaterals to the external segment of the globus pallidus [82,115]. The thalamus is another major input region of the neostriatum, with glutamatergic thalamostriatal neurons. The response of the MSNs to cortical and other inputs is key to the functions of the basal ganglia [170]. The neostriatum mainly serves motor related functions [50], and the cortical areas related to sensorimotor functions project to this subdivision [63]. The ventral striatum receives its major glutamatergic input from the prefrontal cortex, hippocampus and amygdala [61,63]. This ventral subdivision serves mainly as the limbic-motor or motivation-action interface and plays a key role in reward-based learning and addiction. For a review of the striatal projections see [161].

Four types of striatal interneurons have been defined [79]. Besides the cholinergic interneurons (see" section 3), three other largely overlapping subtypes of GABAergic interneurons are recognized: 1) interneurons expressing nitric oxide synthase, somatostatin (SS) or neuropeptide Y, 2) interneurons that contain the calcium binding protein parvalbumin (PARV), and 3) interneurons that contain calretinin. These GABAergic interneurons make up approximately 5 % of the neuronal population in the striatum. Nevertheless, these GABAergic interneurons have large spheres of influence. They are placed strategically to integrate and modulate cortical information flows. Notably the PARV-positive interneurons receive cortical input [96], but the other subtypes receive considerable cortical input as well [171].

3. Cholinergic innervation of the striatum

It is known for a long time that the striatum is extremely rich in cholinergic innervation as can be seen in figure 1B for AChE and figure 1C for ChAT [152]. Only a minor cholinergic projection from the pedunculo pontine tegmental area to the neostriatum has been described as an afferent source [198]; other brainstem areas project via monoaminergic afferents to the neostriatum. Hence, the neostriatal cholinergic innervation arises almost exclusively from the intrinsic, relatively large, cholinergic aspiny interneurons. These cells, with smooth dendrites, are distributed in a distinctive spatiotemporal pattern in the different compartments of the neostriatum [162,186]. These neurons most likely correspond to the tonically-active neurons recorded *in vivo* [5,196]. Cholinergic axons are often characterized by small varicosities [32]. In contrast to the very dense neostriatal cholinergic innervation,

relatively few cholinergic synapses have been found [6,32]. This indicates that ACh acts mainly via non-synaptic (paracrine or non-junctional) and diffuse (volume) transmission, released by the varicosities, in addition to synaptic transmission (for review see [42]). This would explain why cholinergic receptors expressed by non-neuronal elements in the neostriatum (e.g. astrocytes and endothelial cells) can be functional in the absence of axonal termination onto these cells.

The neostriatum is characterized by a very high content of AChE (Figure 1B). It could be that this high content of AChE serves to keep ambient ACh levels within physiological limits besides the classical role of eliminating overspill of synaptically released ACh from the extracellular space. The basal levels of ACh in the striatum [40] seems high enough to continuously activate mAChRs and nAChRs [91,137], establishing a baseline and tonic level of cholinergic neurotransmission. The position of the cholinergic varicosities can undergo dynamic changes, by which their exact position in relation to cholinergic receptor-expressing elements (for example releasing more massively ACh in a distal or proximal part of the dendritic tree of an neuron together with local differences in cholinergic receptor densities over the dendritic tree) shifts thereby altering their functional influence [32], adding to functional plasticity within the striatum.

4. The cholinceptive neural substrate of the striatum

The expression of striatal mAChRs (G-protein-coupled receptors acting primarily on either phospholipase c/Protein Kinase C (PKC) and cAMP pathways) and nAChRs (which form ion channels) has traditionally been studied with autoradiography using tritiated agonists. These studies made clear that the striatum is richly endowed with both classes of cholinergic receptors [15,23,62,188,190,191]. Due to the relatively poor anatomical resolution of autogradiographic images, this field of research moved forward by employing poly- and monoclonal antibodies for receptor protein detection. Here we will briefly review these studies.

4.1. Muscarinic receptors

Originally, the immunocytochemical distribution of mAChRs was first described using a monoclonal antibody named M35 recognizing all five receptor subtypes with equal affinity [21,184]. M35 staining gives a good match between cholinergic innervation patterns and mAChR detection, both in brain and peripheral organs [176,182]. Several types of striatal interneurons express mAChRs as determined by M35 staining (Fig. 2 A, B). Numerous MSNs are mAChR-positive, with labeling density varying from moderate to relatively high (Fig. 2B). Cholinergic interneurons are in general more densely stained for mAChRs than the MSNs. This feature differs somewhat from other cholinergic cells that typically express low numbers of mAChRs [179]. The m2 subtype is known to be preferentially expressed by the cholinergic interneurons [3], and the strong mAChR expression suggests an important cholinergic regulation of ACh release via autoreceptors. Striatal SS- and PARV-positive interneurons also express mAChRs as revealed by colocalization studies (data not shown), but less dense than the cholinergic cells and not as abundant as the Striatal SS- and PARV-positive interneurons in the hippocampus [178,181]. The mAChRs in these interneurons can function postsynaptically and/or presynaptically, regulating intracellular signaling cascades or modulating transmitter release, respectively. These staining patterns suggest that mAChRs play a more dominant role in the regulation of ACh release than regulating GABA release in the striatum, whereas the opposite is more often found in other brain regions. The functional impact of ACh release is discussed below.

In aged rats, the expression of mAChRs decreases most strongly in the MSNs, and somewhat less so in the putative cholinergic interneurons (identified based on size,

distribution pattern, and morphology which was confirmed; arrowheads in Fig. 2C). Apparently, mAChR control over ACh release is less aging-sensitive than mAChR control over GABA release. Occasionally, and in contrast to the young striatum, mAChR-positive astrocytes were found in the aging striatum, a feature also found in some other brain regions and species [154,182,185]. Interestingly, food-rewarded learning tasks (e.g. holeboard learning; [11,177]) cause a characteristic alteration in mAChR expression (Fig. 2D). The large cholinergic interneurons remain densely stained, whereas the MSNs are reduced in labeling. In contrast, a considerable increase in mAChR-positive striato-pallidal fiber bundles is seen throughout the neostriatum. This could hint at changes in the presynaptic functioning of cholinergic heteroreceptors, and possibly reflects a stronger striatal output and/or stronger synchronization among MSNs contributing to the formation of striatal memory traces (Figure 3).

Learning and memory-induced increases and decreases in mAChR immunoreactivity have been described in various other brain regions (for review [182]). An increase in M35 immunoreactivity reflects internalization of activated (phosphorylated) mAChRs, usually as a consequence of ACh stimulation or otherwise indirectly by kinase activity (phosphorylating mAChRs) induced by non-cholinergic activity (most notably glutamate) [179,182]. Enhanced and prolonged cholinergic stimulation in the striatum results in internalized mAChRs and redistribution towards intracellular organelles [103]. A decrease in M35 immunoreactivity suggests higher numbers of functional, membrane-incorporated mAChRs. The relatively high staining intensity in experimentally naïve animals is in line with the tonically high level of ACh release in the striatum. The cholinergic cells receive excitatory synaptic input from the thalamus (although a smaller cortical projection is also present; [95,147]), and respond to rewarding and salient stimuli [34]. Reward-based learning apparently alters the dynamics of the otherwise tonic ACh release such that mAChRs become functionally available to respond to the increased but temporally changed overall ACh release to process task-specific information. The functional interpretation of these characteristic striatal alterations awaits further investigation, but it at least demonstrates that certain aspects of performing and mastering a spatial learning task are accompanied by robust alterations in the cholinergic organization of the neostriatum. These aspects could be the reward, the formation of a procedural-memory related trace, enhanced locomotor activity, or a combination of these. Locomotor activity, not related to a memory task, can also induce massive changes in striatal mAChR expression [11].

After the initial studies with M35 antibody that recognizes all subtypes, subtype-selective antibodies became available. These studies confirmed the earlier data, and extended the neuroanatomical knowledge of subtype specific location of action of the five mAChR subclasses [101]. The detailed distribution of mAChRs added significantly to our understanding of distinct populations of striatal neurons and cholinergic/cholinoceptive microcircuitry.

The subtype-specific antibodies revealed that m1 is widely expressed by small to medium sized striatal neurons (Calbindin-positive MSNs; [3]) and also on glutamatergic corticostriatal terminals acting as heteroreceptors (modulating glutamate release via ACh). The m2 subtype is seen in most large neurons (cholinergic interneurons; [3,70,159] and to a lesser degree in SS/NPY-positive interneurons [14,159]. The m2 subtype appeared to be concentrated in the cholinergic axon terminals [149]. Immunostaining for m3 is barely detected but if so, apparent in MSNs, whereas m4 is seen within the neuropil in a patchy distribution throughout the striatum [70]. A comparison between mAChR protein expression and mRNA expression revealed a good match with a ranking of $m1 > m2 \gg m3 > m4$ [71]. It is clear that striatal mAChRs act presynaptically (either as autoreceptors or heteroreceptors) besides their postsynaptic localization at the aforementioned types of

striatal cells. The m1, m3, and m5 subtypes are functionally coupled to mobilization of intracellular calcium, and they have the additional potential to couple to the activation of phospholipase A2, C, and D, and tyrosine kinase. The m2 and m4 subtypes are functionally coupled to the inhibition of adenylyl cyclase and they play an additional role in the augmentation of phospholipase A2 (for review see [52])

The current detailed knowledge of mAChR subtype expression within different compartments of the striatum makes it clear how the cholinergic striatal system can interact with several other transmitter systems in different ways. It explains the wide range of functional consequences of cholinergic striatal neurotransmission, and also makes it clear that the differential position of the mAChR subtypes in the different intrinsic and extrinsic circuits needs to be taken into account to achieve a desired functional alteration of the striatum via cholinergic pharmacological manipulation. Moreover, the plastic effects of learning and memory or motor activity on the expression and localization of mAChRs and shifts in presynaptic activity adds to the complexity and dynamics of striatal cholinergic neurotransmission.

4.2. Nicotinic receptors

The immunocytochemical distribution of nAChRs was first described with monoclonal antibodies directed against the main immunogenic region of nAChRs of *Torpedo* electric organ membranes [43]. In this study, striatal neuropil and some scattered neurons notably in the lateral aspect of the neostriatum were densely labeled. Most likely, the scattered neurons are the cholinergic interneurons. Later on, the antibody mAb270 was used, raised against nAChRs from chicken brain [167]. With this antibody, the striatum appeared to be moderately stained.

Soon thereafter, the monoclonal antibody WF6 recognizing the α -subunit of the *Torpedo* nAChR became available. In contrast to mAChRs, the nAChR-positive MSNs detected with the antibody WF6 were not distributed as evenly throughout the neostriatum but were instead more often observed in patches (Fig. 2E, F). Besides staining in the cell bodies and dendrites, small thin fiber-like structures could be encountered within and between these patches. The staining intensity for nAChRs did not differ strikingly between the large cholinergic interneurons and the other cell types of the neostriatum. In aged rats, a dramatic decrease in immunoreactivity was seen in all striatal elements (Fig. 2G). This decrease exceeded the general decrease seen in other brain regions, suggesting selective vulnerability of the striatal nAChR system in senescence. A strong increase in nAChR-immunoreactivity was seen in all striatal elements after spatial learning (Fig. 2H; holeboard spatial learning; see [11] for procedural details), as is seen for mAChRs.

Using an antibody raised against the β 2-subunit of the nAChR, Hill and coworkers reported that sparsely distributed large neurons (possibly corresponding to the cholinergic interneurons) were intensely stained. Weaker labeling was observed in many MSNs [74]. The entire striatal region appeared to be extremely rich in delicate neuronal processes, which is in line with the presence of nAChRs on axon terminals. The results with this β 2-subunit antibody in general parallels our observations with WF6 antibody (Fig. 2 E–H).

4.3. Striatal microcircuitry and cholinergic neurotransmission

A number of presynaptic and postsynaptic neuronal mechanisms are controlled by nAChRs and mAChRs. The presence of presynaptic nAChRs and mAChRs as autoreceptors on cholinergic cells has been reviewed in [17,34,203] and as heteroreceptors in [17,34,51,93,203]. These pre- and postsynaptic mechanisms regulate cholinergic release, glutamatergic afferents from the cortex and thalamus, and dopaminergic input from the

brainstem regions. See Nakano [114] for a schematic overview of the primate basal ganglia-thalamo-cortical connections. Regarding the dopaminergic innervation, the neostriatum receives dense innervation primarily from the substantia nigra pars compacta (SNc), and to a lesser degree from the ventral tegmental area (VTA) [63]. The ventral striatum receives dopaminergic input primarily from the VTA and to a lesser degree from the SNc. The cholinergic microcircuitry is depicted in figure 3A. The canonical microcircuit of the neostriatum consists of two MSNs, a cholinergic interneuron and a GABAergic interneuron [170]. Except for the cholinergic interneuron, these cells are innervated by glutamatergic input primarily from the cortex and dopaminergic input primarily from the SNc. The functional modulation of MSNs through the striatal cholinergic system will make them more synchronous, enhancing network synchrony [20]. The expression of mAChRs in this circuit and the changes herein following reward-based learning are depicted in figure 3B and C.

Cholinergic interneurons are tonically active [34], responding to rewarding and salient stimuli (see below). These interneurons can significantly change striatal output and functions, due both to their tonic activity and their dense local innervation [83,204]. Interestingly, a novel microcircuit in the striatum has been suggested, in which the cholinergic interneurons are connected and communicate to one another through GABAergic interneurons [164]. This connection depends on the activation of nAChRs and this microcircuit exerts powerful control over the firing activity of cholinergic interneurons. The transient depression of tonic firing of these cells is critical for conditioning involving processing of sensory and motor information [5,146,196].

Many of the striatal mAChR-regulated functions are mediated by protein kinase C (PKC). Nearly all MSNs express PKC β II, PKC γ , and PKC ϵ , whereas the cholinergic interneurons express PKC α [41,200]. As such, PKC α may be important for controlling the release of ACh that influences the basal ganglia circuit and maintaining cholinergic tone [41]. Notably PKC γ is known to be essential for synaptic plasticity and memory formation in many brain regions [47,168,180,183], but whether this holds true for the striatum is less well known although mAChR-mediated modulation of different calcium channels in neostriatal neurons by PKC has been described [131]. Interestingly, part of the cholinergic striatal neurotransmission via mAChR may depend on A-kinase anchoring protein (AKAP) 150 [174], which is highly expressed in the striatum [121]. AKAPs compartmentalize cAMP signaling by forming complexes of kinases, phosphatases and substrates [157]. It has recently been shown that AKAP150 is critically involved in learning and memory [118,121,174]. AKAP150 could link mAChR activation to potassium channel regulation [72,75]. This provides another way by which the cholinergic and dopaminergic systems may interact (as discussed below) in the regulation of potassium currents [165]; AKAP150 anchors PKC regulated via ACh whereas PKA anchoring is regulated via dopamine.

5. Interaction of the cholinergic and dopaminergic system

The dopaminergic and cholinergic system are the primary and "secondary" largest neuromodulatory systems in the striatum and their interaction plays a key role in coordinating striatum-mediated behavioral responses. A large body of data suggests that these systems can bi-directly modulate one another's function. Initial studies suggested that activation of the dopaminergic system generally inhibits the release of ACh [100]. However, these findings were biased by the fact that the originally developed DA-receptor agonists preferentially modulated dopamine receptor 2 (D2) activity rather than dopamine receptor 1 (D1) activity [92]. Indeed, later studies showed that D2 activation reduces whereas activation of the D1 receptor using specific agonists facilitates ACh release [1,16,29,31,35,36,45], for review see [46].

In addition to the dopaminergic system modulating the cholinergic system, the cholinergic system also affects activity of the striatal dopaminergic system. Although it has been widely accepted that presynaptic mAChRs can modulate DA release, whether or not mAChRs facilitate or inhibit this process remains a matter of debate. The studies by De Belleruche and Bradford [37] indicated that muscarinic receptor-evoked DA release could be facilitated by using high levels of the muscarinic antagonist atropine. Other studies described similar findings [44,90]. In contrast, Giorguieff and colleagues [57] showed that application of the muscarinic antagonist atropine blocked ACh-mediated DA release indicating that presynaptic mAChRs facilitate DA release, a finding confirmed by others [69,99,144]. It was suggested that the original findings of De Belleruche and Bradford [37] were confounded by the use of inappropriately high levels of agonists and antagonists. In addition to pharmacological studies aimed at determining the modulatory role of the presynaptic mAChRs, genetic approaches have been undertaken to elucidate the role of the cholinergic system in striatal DA release. Using mutant mice lacking AChE, Hrabovska et al [76] showed that this manipulation resulted in a marked decrease in D1 and D2 receptors besides the previously-described reduction in m1, m2 and m4 mAChRs in the brain [189]. The reduction in D1 and D2 receptor expression in the AChE knockout mice was hypothesized to be a consequence of increased DA release due to mAChR overstimulation. This critical dopamine-acetylcholine misbalance has recently been suggested to underlie the cognitive dysfunctions in Parkinson's disease [18]. Furthermore, selective loss of m1 cholinergic receptors resulted in upregulation of dopaminergic transmission that was accompanied by increased locomotor activity, and stronger activation of the dopaminergic system in response to amphetamine treatment [56]. These studies confirmed the previous pharmacological findings described above suggesting that blocking muscarinic cholinergic activity facilitates rather than inhibits dopaminergic transmission indicating that the cholinergic system acts as a constraint on the dopaminergic system. This antagonistic function of the dopaminergic and cholinergic system was further strengthened by the fact that both facilitating dopaminergic signaling or inhibiting cholinergic signaling rescued the motor dysfunctions seen with Parkinson's disease [8,134].

nAChRs, as discussed previously, are located on pre-synaptic axon terminals [78], and can directly facilitate or inhibit DA release [148,201,202]. To date, 5 nAChR subtypes are known to be expressed on dopaminergic nerve terminals [59]. Three of these subunits contain the $\alpha 6$ subunit ($\alpha 4\alpha 6\beta 2\beta 3$, $\alpha 6\beta 2\beta 3$, $\alpha 6\beta 2$) whereas the other two contain the $\alpha 4$ -subunit ($\alpha 4\beta 2$, $\alpha 4\alpha 5\beta 2$) with the later being more numerous than the $\alpha 6^*$ containing subtypes and the $\alpha 4^*$ containing subtypes having the highest affinity for nicotine [59]. ACh released by cholinergic interneurons activate these nAChRs which maintain the background DA levels [202]. However these same nAChRs restrict DA release in response to burst firing of dopaminergic neurons since a reduction of nAChR activity facilitates this process [148,201]. A recent study by Drenan et al [49] indicated that transgenic overexpression of $\alpha 6$ -channels hypersensitive to endogenous ACh or exogenous nicotine resulted in greatly augmented DA release and increased DA neuron firing.

6. Interaction of the cholinergic and GABAergic system

Because most of the striatal neurons are GABAergic, it is fair to assume that the cholinergic system also mediates GABA release in addition to modulating DA release [17]. Activation of postsynaptically localized mAChRs on striatal projection neurons have been suggested to inhibit GABA-mediated synaptic potentials [17]. Besides postsynaptically-mediated alteration of GABAergic signaling, the cholinergic system may also presynaptically mediate GABA release. Both nicotinic and mAChRs have been reported to be expressed in GABA-releasing presynaptic terminals [60,88,102,105,106,163], with the $\alpha 4\beta 2$ -containing subtypes of nicotinic cholinergic receptors being the major modulators of GABA release based on

studies using genetic [132], or pharmacological approaches [105]. A recent study by Grilli et al [60] showed that mAChRs and nAChRs (of the $\alpha_4\beta_2$ subtype) co-exist on GABAergic nerve terminals and that nicotinic-mediated release of GABA was prevented by activation of M4 mAChRs (that are strongly expressed in the striatum (see figure 2, and also [135]), suggesting an antagonistic function of mAChRs and nAChRs regarding GABA release from presynaptic terminals.

As mentioned above, a novel microcircuit in the striatum is suggested in which the cholinergic interneurons are connected and communicate to one another through GABAergic interneurons [164]. This interaction between the striatal cholinergic system and GABAergic signal transduction could be pivotal for proper striatal functioning.

7. Associative memory functions and the striatal system

Initial studies on the function of the striatum in learning and memory indicated that the striatum is a critical region for specific forms of learning. For example, lesions of the striatum impaired avoidance learning [4,81,112,116,136,197] and performance in the cued version of the Morris water maze where a visual mark indicated the location of the platform [193,194]. Packard and colleagues [124] tested the effect of either bilateral caudate nucleus or bilateral fimbria-fornix lesions in two versions of the radial-arm maze. The first version was a 'win-shift' version in which each of the eight arms was baited once and the number of revisits to a previously baited arm was measured. This working memory version of the task was used to assess the capability of the animals to remember which arm(s) were already visited and which arms were not. Memory was indicated by no revisits. The second version of the task was a 'win-stay' version of the same task in which the location of 4 randomly selected baited arms was signaled by a light at the entrance to each arm. Rats had to learn to selectively visit the arms signaled by light, a form of habit or skill learning. Fimbria-fornix lesions impaired learning in the working memory-dependent 'win-shift' task, but enhanced performance in the win-stay version of the task. In contrast, lesions of the caudate nucleus did not affect learning in the win-shift version of the task, but markedly impaired performance in the win-stay version of the task indicating that the striatum plays a crucial role in habit learning. This study together with other studies indicated that different memory systems exist in the brain. A similar habit memory or 'skill' learning deficit was later demonstrated for amnesic patients and patients with Parkinson's disease [84]. More detailed analyses indicated that the dorsal striatum and ventral striatum have different functions. The ventral striatum is indirectly involved in driving instrumental responses by allowing cues associated with reward (for instance cocaine) to exert a general motivational influence on responding [19,155,192,195]. The dorsal striatum, on the other hand seems to play a crucial role in adaptive motor control and procedural memory [54,89,199]. The latter will be discussed in more detail below.

8. Place navigation and the striatal cholinergic system

A general theme in behavioral neuroscience is that distinct "memory systems" mediate dissociable aspects of memory. In place navigation, these distinct memory system mediate different navigational strategies [58,77,113,122]. These systems predominantly rely on specific brain regions, such as the hippocampus, the striatum and the amygdala. The existence of distinguishable neuronal systems is supported by many studies in various species including rats [119,124,126,151], mice [98], monkeys [205,206] and humans [25,66,84]. For example, Packard and McGaugh [126] demonstrated that rats with hippocampal or fimbria/fornix lesions are impaired in place learning which depends on the use of a configuration of extra-maze cues to locate a submerged escape platform, although they are not impaired in a cued version of the task in which a visible platform directs the

rat's escape. In contrast, rats with lesions of the dorsal striatum are impaired in the 'visible platform' version of the task, while performance was not affected in the spatial version of the task where the rats had to use extra-maze cues to find the platform. These findings indicate that the hippocampus, but not the dorsal striatum, plays a crucial role in spatial learning (also known as allocentric learning; making responses based on external cues). In contrast, rats with dorsal striatal lesions were impaired in the cued version of the water maze task, but not in the spatial version suggesting that the dorsal striatum is important for response learning (i.e. "egocentric" learning; making responses based on their own body orientation in space). The neuronal systems underlying the different behavioral strategies used for place navigation have been further studied using other behavioral paradigms including a modified version of the T maze also known as cross maze [28,127], originally described by Tolman [172,173]. For instance, rats in which the striatum was inactivated were impaired in a right-left discrimination paradigm [33], as well as non-spatial versions of the Morris water maze and modified version of the T-maze [28,127]. Likewise, glutamate injections into the striatum was shown to facilitate response learning [123], whereas blocking the activity of N-Methyl-D-Aspartate (NMDA) receptors in the dorsal striatum impaired response learning, leaving place learning unaffected [38,128].

The role of the cholinergic system in striatum-mediated egocentric learning has also been determined. Kobayashi and Iwasaki [85] showed that striatal lesion of the cholinergic system selectively impaired egocentric learning, but not allocentric learning. Interestingly, McIntyre and colleagues [109] showed that the profile of ACh release in the dorsal striatum relative to the hippocampus indicates the preferred behavioral strategy used by a particular rat; high ratios of striatal versus hippocampal ACh release were found in individuals that preferentially used a dorsal striatal-dependent response strategy, rather than a hippocampus-dependent spatial strategy. In line with these observations, Vetreno and colleagues [187] showed that preferential use of an egocentric response facilitated ACh release in the striatum. ACh levels were found to be enhanced in both hippocampus and striatum, when rats were trained in either a place or response version of the task. However, the increase in striatal ACh release was significantly higher in the task in which rats could selectively use a response strategy. This parallel increase in ACh release in both hippocampus and striatum suggested that in case of the cholinergic system, both systems are activated in parallel, but that the striatum predominates the hippocampus under specific conditions, for example when a striatum-dependent response strategy is required, as a result of stronger cholinergic activation. The principle of multiple parallel memory systems has been described previously and under certain conditions these systems can complement or compete with each other. The findings described in the paragraphs above suggest that the cholinergic system in both hippocampus and striatum are activated in parallel but that if the striatal activation is stronger it can overrule the hippocampal system.

Several studies have indicated that during acquisition in a place navigation task both humans and rodents preferentially use a hippocampus-dependent spatial strategy rather than a striatum-dependent response strategy. With extended training, humans as well as rodents switch to using a response-strategy [22,120,123,127]. It is interesting to note that this shift in behavioral strategy is paralleled by a transition in ACh release from hippocampus to striatum. Chang and Gold [22] showed that with ongoing training in a T-maze reference task, rats shifted from using a spatial to a response strategy, and that this shift was accompanied by a gradual increase in ACh release from the striatum. ACh release from the hippocampus did not decrease but remained high, indicating that the striatum was activated at the time rats started to use the striatum-dependent response strategy. The authors argued that the hippocampus remains active, but that the striatum can override hippocampal activity when fully engaged by repeated training. In addition to the different levels of activation of

the striatal and hippocampal cholinergic system, similar observations have been made using general activity markers including c-fos, phospho-CREB and c-Jun [26,27,169].

9. Cholinergic involvement in intra- and extradimensional set shifting

The basal ganglia play a crucial role in motor planning, procedural learning, non-declarative forms of memory and motivation [55,73,89,117,125,199]. In addition to these functions, the dorsomedial region of the striatum is involved in the adaptation of previously acquired behavioral responses (e.g., behavioral flexibility) [65,86,104,133,140,141] for review [138]. It has strong connections with the orbitofrontal cortex and pre-limbic area [13], two prefrontal cortex areas both known to be critically involved in behavioral flexibility [139].

One of the various behavioral paradigms used to study the molecular mechanisms underlying the adaptation of previously learned responses is (place) reversal learning, also known as intradimensional set shifting [7,39,130,145]. In a symmetrical T or Y maze, rodents are initially trained to retrieve a food reward that is located in either of two accessible goal arms. After the animals have learned which of the two arms is baited, indicated by a strong significant preference to visit the baited arm, the food reward is relocated to the previously non-baited arm. Initially the animals will tend to visit the previously-baited arm, but gradually they will learn that the previously non-baited arm is now baited, indicated by a strong preference to visit that arm. The latter is referred to as reversal learning. Previous studies have indicated that place learning and reversal learning differentially impact hippocampal plasticity [67,68]. Similar to the hippocampus, the dorsomedial striatum has been shown to be differentially involved in both processes; lesions or electrical stimulation of the dorsomedial striatum results in impaired spatial reversal learning [65,86,104,156], as well as non-spatial reversal learning [12,24,133]. These findings were confirmed by Ragozzino and others which locally infused anesthetics to temporally inactivate the dorsomedial striatum (for review see [138]).

Because the cholinergic system is a key modulatory system in the dorsomedial striatum, the question that remained to be answered was whether the striatal cholinergic system also had a prominent role in intradimensional and extradimensional reversal learning, for example through alterations in striatal ACh release. For this purpose, Ragozzino and Choi [140] subjected rats to training and reversal training in a spatial discrimination task and measured ACh release from the dorsomedial striatum. They found that ACh levels were increased during spatial reversal learning, but not during the initial training suggesting that the medial-striatal cholinergic system is differently involved in spatial learning and spatial reversal learning. Similar observations were made by Palencia and Ragozzino [129]. In parallel with these findings that intradimensional reversal learning induces changes in ACh levels in the dorsomedial striatum, pharmacological studies have been undertaken to determine the role of specific cholinergic receptors in reversal learning. Ragozzino et al [141] delivered muscarinic or nicotinic cholinergic antagonists into the dorsomedial striatum during training and reversal training in a response discrimination task. They found that the muscarinic cholinergic blocker scopolamine did not interfere with the initial acquisition of response learning, but did impair reversal learning of the previously acquired response. In contrast, infusion of the nicotinic cholinergic antagonist mecamylamine did not affect either the acquisition or reversal learning, suggesting that specifically mAChRs in the dorsomedial striatum play a crucial role in the reversal of a previously acquired response. To determine whether the M1-type or M4-type mAChR was involved in place reversal learning, the laboratory of Michael Ragozzino did similar experiments, using m1-type or m4-type specific mAChR and demonstrated that specific blockage of the m1-type receptor impairs reversal learning, but not acquisition [108,175].

In addition to the fact that the dorsomedial striatum is important for intradimensional set shifting, as described above, the dorsomedial striatum has shown to be involved in extradimensional set shifting, the switching from using a spatial strategy to using a response strategy and *vice versa* in a cross maze reference task. Ragozzino et al [142] showed that temporal inactivation of the dorsomedial striatum using tetracaine did not impair acquisition of egocentric learning or allocentric learning. However, it markedly impaired the shifting from using one strategy to the other, and *vice versa*. However, to our knowledge, no experiments have been conducted to determine whether the cholinergic system in the dorsomedial striatum is critically involved in extra-dimensional set shifting as it is in intra-dimensional set shifting.

10. Behavioral flexibility and the striatal cholinergic system

Loss of behavioral flexibility (impairment of intra- or extradimensional reversal learning) is one of the first hallmarks of non-pathological ageing and the development of major dementing illnesses like Alzheimer's disease [94,107] for review [2], and Parkinson's disease [48,53]. Similar observations have been made in rodents. For instance, two-year old mice perform similarly as young mice during acquisition in a two-arm reference memory task, but are impaired during intra-dimensional reversal learning (Figure 4). As such, the training and reversal training Y-maze paradigm is very suitable to detect aging-specific deficits besides the functional interaction between the striatum and hippocampus [64,67,68]. Other studies have also reported that the ability to adapt previously acquired responses is the first to be affected by ageing [110,111,143]. In terms of the cholinergic system, the deficits in behavioral flexibility may be due, in part, to a selective loss of mAChRs in the striatum [158], see also Figure 2. Likewise, several studies reported alterations in the balance of ACh release in the dorsomedial striatum and hippocampus with aging [30,153] and development of neurodegenerative diseases. Changes in ACh release have been observed with the development of Alzheimer's disease and Huntington's disease [10,166]. Lazari and colleagues [97] showed that aging-accompanied impairments in procedural memory could be rescued through intra-striatal delivery an M2-type muscarinic receptor antagonist. Future studies are needed to determine whether manipulation of ACh release from the dorsomedial striatum (and hippocampus) is sufficient to overcome the reduced behavioral flexibility and other cognitive deficits observed with pathological and non-pathological aging.

11. Conclusion and future directions

The striatum robustly expresses both muscarinic and nicotinic cholinergic receptors that modulate the function of striatal dopaminergic and GABAergic systems. Behavioral studies have shown that the striatal cholinergic system is important for procedural learning and intradimensional set-shifting although a role in extradimensional set-shifting remains to be elucidated. It will be of great value to determine whether aging-induced changes in ACh release from the hippocampus and dorsomedial striatum are paralleled by changes in the preferred behavioral strategy used by young and aged animals in a Y or T-maze reference task. For instance, the ratio of ACh release from the hippocampus and dorsomedial striatum may predict the behavioral strategy used in aged animals as was demonstrated for young animals by McIntyre and colleagues [109]. This is of great significance since Barnes and colleagues [9] showed that aged rats preferentially use a striatum-dependent strategy, in contrast to young rats that prefer to use a hippocampus-dependent strategy. Altogether, these studies would indicate whether a shift in the preferentially used behavioral strategy is due to alterations in the balance of hippocampal and striatal cholinergic activity with pathological and non-pathological aging. Understanding how the balance between striatal and hippocampal cholinergic activity controls behavior and memory may result in novel approaches to rescue aging-related cognitive decline.

Acknowledgments

We thank Joshua Hawk and Dr. Sara Aton for valuable comments on a previous version of this manuscript. We thank Jan Keijser for his help with making the photomicrographs. This work was supported by The Netherlands Organization for Scientific Research (NWO-Vernieuwingsimpuls E.A.V.d.Z. (Grant 016.021.017)) and by P50 AG 017628 (A. I. Pack, PI).

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Figure 1.

A schematic drawing of a coronal section of the striatum of the rat adapted from [87] (A). The expression of acetylcholinesterase (AChE; B) and choline acetyltransferase (ChAT; C) is very high in the striatum. The striped box in A depicts the location of the photomicrographs of figure 2. AC = anterior commissure; CC = corpus callosum; CPu = caudate putamen; NAc = nucleus accumbens; OTu = olfactory tubercle; Sep = septum. Scale bar = 900 μ m

Figure 2.

Cholinergic receptor immunoreactivity in the rat neostriatum (caudate putamen; see striped box in Figure 1A for location). Expression of mAChRs (upper panels) and nAChRs (lower panels) in young (A, B, E, F; 3 mo of age), aged (C, D; 32 mo of age), and holeboard-trained rats (D, H; 3 mo of age) are shown. The boxes in A and E are enlarged in B and F, respectively. Scale bars in A and F = 100 μ m; in B–D and F–H = 50 μ m.

Figure 3.

A schematic representation of the canonical microcircuit (A) of a cholinergic neuron (ACh), two medium spiny neurons (MSN), and an interneuron (Int). The MSNs and Int receive massive glutamatergic input from the cortex and dopaminergic input from the substantia nigra compacta (SNc). The MSNs provide the output of the microcircuit. The cholinergic neurons innervate the Int at the MSNs. The density of mAChR immunoreactivity in the neostriatal microcircuit, as detected with the monoclonal antibody M35, is indicated in B and C. B represents the mAChR situation of experimentally naive (home cage) control rats (black = high immunoreactivity; dark grey = moderate immunoreactivity, and light grey = low immunoreactivity). C represents the situation after a spatial learning task (holeboard) has been completed. It should be noted that the rats performed at 90% correct choices for several days [11]. Low M35 staining indicates a relative open circuit, with free, functional mAChRs located in the cell membrane ready for processing cholinergic input. High M35 staining indicates activated and subsequently internalized mAChRs, reflecting a relative closed circuit, internally processing acquired information [182]. The hippocampus of these holeboard-trained animals showed dense staining for mAChRs already halfway training while the neostriatum still resembles that of control rats (unpublished observations and [11]; for mice see [177]). This suggests that the neostriatum starts processing holeboard task information in a later phase, and/or continues processing this information longer than the hippocampus does. Thickness of the arrows corresponds to the level of output activity.

Figure 4.

Aged mice are impaired in intra-dimensional reversal learning Performance of young ($n=7$) and aged C57Bl6/j mice ($n=8$) in the Y maze during training and reversal training. Both groups gradually learned to locate the baited arm (ANOVA $F_{6,78} = 8.880$, $P < 0.001$). Aging did not affect the rate of acquisition during training (ANOVA $F < 1$). Although both young and aged mice both improved their performance during reversal training (ANOVA $F_{6,78} = 22.564$ $P < 0.001$), rate of acquisition during reversal training was reduced in aged mice (ANOVA $F_{1,13} = 8.208$, $P < 0.05$).