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COGNITIVE AND SOCIAL FUNCTIONS OF THE MAMMALIAN STRIATUM

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by

Kari L. Hanson

Committee in charge:

Professor Katerina Semendeferi, Chair
Professor Margaret Schoeninger
Professor Shirley Strum

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

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ABSTRACT OF THE THESIS

Social and Cognitive Functions of the Mammalian Striatum

by

Kari L. Hanson

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Professor Katerina Semendeferi, Chair

The striatum is formed by a group of subcortical nuclei in the brain with analogues shared by all vertebrates, and as such, it has frequently been described in the literature as being evolutionarily "conserved." However, its extensive connections with the neocortex, and its involvement in a variety of complex cognitive and behavioral processes, particularly those associated with social cognition, indicate phylogenetic modification that bears further exploration in an evolutionary context. Here, I will explore the anatomy and cognitive functions of the striatum, highlighting its role as an

integral part of the social brain. I will assert that major modifications in its connectivity with the dynamically evolving neocortex yield important functional differences across species, contributing to derived cognitive specializations in the primate lineage. Finally, I will raise questions regarding the chemical anatomy of the striatum across species, calling for further investigation of interspecific differences in chemical anatomy. These differences in connectivity and chemical anatomy likely underlie features of primate and human cognition representing uniquely evolved specializations.

INTRODUCTION

It would be a fair assessment to say that modern evolutionary neuroscience embraces a corticocentric perspective. There is a strong focus on the mammalian neocortex as the most obvious site of novelty and enlargement, as it is the hallmark of mammalian brain evolution, and it has greatly increased in size in many mammalian orders. In the lineage that gave rise to the great apes and humans, neocortical expansion accounts for a large proportion of the total increase in overall brain size, and the allometric relationships between neocortical and total brain volume show that humans and great apes share an enlarged neocortex relative to other anthropoids (Rilling & Insel 1999, see also Semendeferi et al. 2002). Many cortical areas have been added or enlarged as the brain expanded in primate evolution (Butler & Hodos 2005), and given the involvement of the cortex in higher-order sensorimotor and cognitive function, it is unsurprising that these areas are targeted as sites for analyzing structures involved in uniquely human cognitive specializations.

Often, subcortical structures are described as being highly conserved. The basic mammalian Bauplan shows little innovation in terms of the gross structures found in the basal ganglia, limbic system, and other subcortical areas at a macroscopic level (Butler & Hodos 2005), though a more careful examination of these areas often yields evidence of substantial reorganization in terms of morphology, cytoarchitecture, and connectivity. Given that these subcortical regions share diverse connections with the cerebral cortex, and in light of the phylogenetically dynamic nature of cortical modification, we should

expect to find that subcortical structures reflect the changes in the cortical areas with which they share connections.

Indeed, the limbic system shows signs of major reorganization, and in the amygdala in particular, differences in its morphology may underlie some crucial differences in hominoid social cognition. Nicole Barger's (2007) work has shown enlargement of the lateral nucleus of the basolateral amygdala as compared to other apes, and that African great apes show a very different pattern of organization compared to orangutans. Further, hippocampus size and connectivity varies substantially across phylogeny as a function of ecology and foraging strategies (Brown 2001).

Strikingly, the thalamus, a structure once canonically written off as being phylogenetically conserved and quite primitive, has also shown remarkable evolutionary modification. Este Armstrong's work has shown evidence of mosaic evolution in components of the thalamus, particularly the pulvinar and lateral posterior nuclei, which have shown evidence of substantial morphological reorganization (Armstrong 1982).

In light of these data that seem to reflect the mosaic evolution of various subcortical systems, a critical reconsideration of the comparative function and morphology of other subcortical structures is warranted. In the thesis that follows, I will consider one group of subcortical structures and their important role in cognition and social behavior. The striatum is a group of nuclei that serve as the primary input for cortical projections to the basal ganglia, a diverse group of structures in the medial forebrain involved in a variety of motor and cognitive functions.

Chapter I reviews the basic anatomy and general morphology of the basal ganglia and striatum with specific reference to functional connectivity. Chapter II addresses the

function of the striatum with respect to cognitive processes, as discussed relative to studies of normal and pathological function in humans and non-human experimental animals. Chapter III details the role of the striatum, and the ventral striatum in particular, in regulating processes associated with social interaction and those underlying social organization, particularly mating systems. Chapter IV reviews some of the basic comparative anatomy research describing derived specializations in the striatum in mammalian and primate brains. Finally, I conclude with a general discussion of material presented.

Overall, the aim of this thesis is two-fold: I will show that the striatum, classically considered with respect to motor function, also plays a crucial role in cognitive processes and social behavior. I will conclude by highlighting what is still unknown about the function of the striatum from a comparative perspective, paving the way for future research to address specializations of these important structures. I hope to frame the evolution of the striatum as a dynamic set of structures with important connections to the neocortex that show substantial modification with major implications for the evolution of the brain as a whole. As the cortex does not evolve in isolation, we must consider the nature of subcortical reorganization in order to gain a holistic perspective on the evolution of the brain.

CHAPTER I. ANATOMY OF THE BASAL GANGLIA AND STRIATUM

GENERAL ORGANIZATION OF THE BRAIN AND INTRODUCTION TO ITS ANATOMY

The brain can be subdivided into several primary regions that are unique in their organization and development, which include the cerebrum, the cerebellum, and the brainstem. The cerebrum, also known as the telencephalon, consists of the bilateral cerebral hemispheres and the diencephalon, which can be further subdivided into thalamic and hypothalamic areas. During development, the dorsal region of the telencephalon gives rise to the cerebral hemispheres, whereas the basal ganglia develop from the ventral telencephalon (Nolte 2009).

THE BASAL GANGLIA

The basal ganglia include a diverse grouping of subcortical nuclei in the basal portion of the telencephalon. Authors vary substantially in terms of what is included in the definition of the basal ganglia, and early definitions included all areas of gray matter within the interior of the brain, including the thalamus (Jenkins 1978). More modern definitions frame the basal ganglia as a network of interconnected structures distinct from the limbic system and thalamus, including the caudate nucleus, the putamen, the nucleus accumbens, the globus pallidus, the subthalamic nuclei, and the substantia nigra (Nolte 2009).

Martin (2003) divides the nuclei of the basal ganglia into three distinct categories relative to their connections: input nuclei, output nuclei, and intrinsic nuclei. The striatum includes the major input nuclei of the basal ganglia, and is further subdivided into the caudate nucleus, the putamen, and the nucleus accumbens. Output nuclei include the

internal segment of the globus pallidus, the substantia nigra pars reticulata, and the ventral pallidum, which project to the thalamic nuclei, which in turn project to areas of the frontal lobe. Four intrinsic nuclei of the basal nuclei include the external segment of the globus pallidus, the subthalamic nucleus, the substantia nigra pars compacta, and the ventral tegmental area, which maintain connections between structures of the basal ganglia. Discrete components of the basal ganglia are separated by white-matter fiber tracts of the internal capsule in primates during development, separating the striatum into its three component parts, and dividing the internal segment of the globus pallidus from the substantia nigra pars reticulata. Figure 1 shows some structures of the basal ganglia in the human brain.

The basal ganglia can further be described in terms of anatomical “loops,” organized functionally and connecting areas of the cortex to basal ganglia and thalamic nuclei. Two well-understood sensorimotor loops run through the basal ganglia in parallel circuits. The motor loop receives inputs from the primary somatosensory and motor areas and projects back to the frontal motor cortex, integrating sensory information and playing a role in the control of facial, limb, and trunk musculature. The oculomotor loop participates in the control of saccadic eye movements such that inputs from the frontal eye field and the posterior parietal association cortices project to the caudate, substantia nigra, and internal segment of the globus pallidus, which in turn project to the frontal eye movement control centers of the brain, controlling the speed and direction of eye movements.

Less well-understood are the two non-motor loops that course through the basal ganglia. The limbic loop receives inputs from the medial and lateral temporal lobes, the

limbic association cortex, and the hippocampal formation, engaging the ventral striatum and ventral pallidum, and projecting back to the limbic association cortex of the anterior cingulate gyrus. The cognitive loop receives inputs from a diverse arrangement of association cortices to the head of the caudate, and to the substantia nigra pars reticulata and internal segment of the globus pallidus, projecting to the dorsolateral prefrontal cortex. This loop is involved in a variety of cognitive and behavioral functions, including planning of behavior, and is unique to primates. Figure 2 illustrates the loops of the basal ganglia with respect to sensorimotor, limbic, and cognitive organization.

The four parallel loops of the basal ganglia work together in integrated circuits in ways that, at present, are not well understood, but aspects of their organization suggest that striatal neurons may play a key role. Dendrites of striatal neurons have the unique capacity to extend beyond their own loops into adjacent loops, receiving information from a great variety of cortical areas. Striatal neurons in all loops additionally project back to the substantia nigra pars compacta, which suggests that the loops' axon terminals may converge on dopaminergic neurons and interneurons in this area, integrating information from all of these loops.

Chemical Anatomy of the Basal Ganglia: Neurotransmitters and Neuromodulators

A variety of neurotransmitters and neuromodulatory substances play key roles in modulating neuronal activity in the basal ganglia. Among these, the inhibitory neurotransmitter γ-aminobutyric acid, or GABA, is found in the medium spiny neurons of the striatum. These neurons also contain either enkephalin, or substance P and dynorphin. GABA is also present in both internal and external portions of projecting neurons of the globus pallidus and the substantia nigra pars reticulata, and outputs of the basal ganglia

are inhibitory. Dopamine is present in the ventral tegmental area and substantia nigra pars compacta, which also contains neuromelanin. Acetylcholine is common in striatal interneurons, important for the function of local circuits (Martin 2003).

ANATOMY OF THE STRIATUM

Bridges of gray matter across the internal capsule (a white-matter fiber tract connecting the cortex to the medulla) between the putamen and the caudate nucleus give this region a striped appearance in many planes of section. The caudate and the putamen, in conjunction with the nucleus accumbens, form the striatum (Nolte 2009). The striatum is the primary target of cortical input to the basal ganglia, and it is considered to be phylogenetically newer than other areas of the basal ganglia (Jenkins 1978), and will be the focus of this thesis.

The neostriatum consists of the caudate nucleus and putamen, separated by fibers of the internal capsule, and covered by subcortical white matter to form the dorsal striatum. The term “ventral striatum” refers specifically to the nucleus accumbens. A variety of histochemical techniques have been employed to determine the cellular organization and connectivity of the striatum, revealing that it is highly heterogenous with respect to cell types and their distributions, and diverse in its cortical connections and projections.

Cell Types

The striatum is characterized by the presence of several types of neurons and interneurons. Medium spiny neurons comprise the vast majority of cells present in the striatum, and have many arborizations emanating from their axons. Additionally, Deiter’s neurons are present in small numbers in the striatum, and are distinguished by their

resemblance to pallidonigral neurons, with large arborizations with few branches. Several varieties of interneurons are also present in the striatum, and can be broken down into cholinergic and GABAergic types (Braak & Braak, 1982). Cholinergic interneurons are morphologically distinct in primate brains as compared to rodent brains, having very dense local innervations, and may play an important role in learning and reward (Zhou, Wilson, & Dani, 2002). GABAergic neurons include parvalbumin-expressing and somatostatin-expressing interneurons, both of which pertain to dopamine expression, and calretinin-expressing interneurons (Braak & Braak, 1982).

Afferent Connections of the Striatum

Afferent projections include input fibers that carry information from the cortex toward the striatum. Major afferent projections to the striatum include corticostriatal fibers arising in the ipsilateral neocortex to various locations in the striatum. Sensorimotor projections comprise the greatest number of these projections, with few projections from the visual cortex. Cortical projections enter the caudate nucleus via the internal capsule and fasciculus, and the putamen by way of both the internal and external capsules. A few contralateral projections from the sensorimotor cortex and Brodmann's area 5 in the parietal cortex also cross the midline to enter the striatum. Projections from the thalamus connect to the striatum, and are exclusively ipsilateral and topographically organized anteroposteriorly. Nigrostriatal pathways have also been shown to project to the striatum, originating in the substantia nigra pars compacta, reaching the head of the caudate and the rostral putamen, and are regarded as primarily dopaminergic inputs. Serotonergic projections from the raphe nuclei of the mesencephalon have been shown using tracing techniques, and terminate throughout the caudate, most numerously in its

caudal aspect. Further projections to the striatum may include bilateral projections from the locus coeruleus (Grofová 1979).

Efferent Connections of the Striatum

Efferent projections emanate from the striatum to carry information to other locations in the brain, and an interesting pattern of organization of these projections can be observed. The striatum forms tiny bundles of poorly-myelinated fibers within its nuclei, known as Wilson's pencils, which project to the globus pallidus and substantia nigra. These projections are topographically organized, and fibers from the caudate terminate in the dorsal region of the globus pallidus, whereas fibers from the putamen project more ventrally. Striatonigral fibers project to both parts of the substantia nigra, with fibers from the ventromedial part of the caudate head terminating medially, and fibers from the posterior aspect of the putamen terminating laterally.

DEVELOPMENT OF THE STRIATUM

Early in fetal development, the rostral portion of the neural tube gives rise to what becomes the diencephalon and cerebral hemispheres. Structures that develop from the diencephalon include the thalamus, hypothalamus, and the retina. Anterior to the diencephalon lie the developing cerebral hemispheres, each of which contains a lateral ventricle. The striatum, along with the amygdala, develops from the corpus striatum in the floor of the lateral ventricle. Developing neurons migrate along the ventricular zone, guided by specialized radial glial cells, to form the layers of the cortex and subcortical structures. Many of the GABAergic neurons of the cortex originate in the corpus striatum. In a pattern that is reportedly unique to primates and distinct from rodents and

other mammals, GABAergic neurons follow a path of migration to the dorsal thalamus to the enlarged pulvinar and medial dorsal nuclei.

The developing cerebral hemispheres encircle the diencephalon, lending a C-shape to underlying structures, particularly the caudate nucleus. The head of the caudate in the frontal lobe extends to the body in the parietal lobe, with the tail terminating in the temporal lobe. The putamen and nucleus accumbens develop into a more spherical structure (Martin 2003).

Recently, evidence for adult neurogenesis has been examined in the primate striatum, though different techniques have produced conflicting results. Two different studies (Bedárd et al. 2002, Dayer et al. 2005) used BrdU tracing techniques to target newly generated cells in the primate striatum, finding evidence for migration of immature cells to the striatum from the subventricular zone in adult rhesus monkeys. However, work by others (Benraiss et al., 2001; Pencea et al., 2001; Teramoto et al., 2003) failed to find evidence for adult neurogenesis in the striatum. Whether or not development in the striatum includes the addition of new neural cells in the adult brain remains, at present, widely debated.

CHAPTER II. COGNITIVE FUNCTION AND DYSFUNCTION IN THE STRIATUM

In order to understand the basic functions of the striatum, we may rely on several lines of evidence from pathological studies to determine the role of these structures in motor and cognitive processes. Lesion studies in experimental animal models have yielded direct evidence of associations between tissue damage and cognitive and motor impairments. Additionally, disease processes that target specific brain areas result in pathological change to the structure and function of certain tissues, allowing us to draw conclusions about the function of these areas. Further, functional imaging studies allow for inferences to be made about the recruitment of brain areas in real time in a variety of behavioral tasks in non-pathological subjects. Here, these major sources of data will be reviewed with respect to their contributions to the knowledge of what functional role the striatum plays in individual cognition and behavioral output.

Lesion Studies

Much of what is known about the function of the brain, and of the basal ganglia and striatal complex in particular, has been determined using experimental animals that are surgically altered in controlled conditions to produce lesions in exact locations to correlate behavioral impairments with neurological damage. Due to practical concerns, most studies have focused on rat models, though several studies have utilized cats, and a few non-human primate models have also been used.

Chozick (1983) reviews some of the early lesion studies focusing on the striatal complex in experimental animal models, with specific emphasis on cognitive impairments resulting from lesions to the striatum. Lesions to different areas of the

caudate nucleus inhibit performance in a wide variety of learning tasks, including in tasks involving delayed alternation, whereby rats in a T-maze were required to alternate behavioral sequences to obtain rewards. Rats with lesions to the anteromedial portion of the caudate demonstrated severe deficits in retention of the behavioral sequence that could not be corrected with further training, whereas rats with lesions to the anterolateral caudate showed some impairment, but were able to regain preoperative levels of performance. Rats with posterolateral caudate lesions retained preoperative levels on task performance, indicating no role of this area in task alternation. Given the connectivity of the anteromedial caudate with the frontal cortex, and the similarity of the behavioral effects of lesions in this area to those produced when the rat frontal cortex is lesioned, it is strongly suggested the anteromedial caudate and frontal cortex cooperatively participate in the planning and execution of task alternation. Further, lesions of the corpus striatum prevented stereotypical behavioral effects in rats administered amphetamines and other neuroleptic drugs that act on the dopaminergic system that could be reversed with the administration of exogenous dopamine agonists (specifically, l-dopa).

Interestingly, lesions to the striatum have also been associated with hyperactivity. Rats with both dorsal and ventral lesions to the caudate nucleus exhibited significantly higher activity levels in conditions of high baseline activity, including in the dark, and when deprived of food. The effects of caudate lesions on sleep are complex, however. Despite the lack of quantitative differences in amount of slow-wave sleep and waking between lesioned and control groups, caudate-lesioned rats have been demonstrated to have spent considerably longer portions in the paradoxical stage of sleep (REM). This

likely reflects inhibitory influences of the caudate on structures that trigger paradoxical sleep.

The striatum also appears to serve important functions in emotional states as well. Stimulation of the caudate has been shown to result in aggressive and dominant behaviors toward conspecifics. Additionally, lesions of the caudate in rats have been associated with heightened states of arousal and sensitivity to stimuli, and may exhibit heightened activity related to fear as demonstrated through significantly higher levels of thigmotaxis[1] and defecation and lower levels of grooming and environmental exploration. Caudate-lesioned rats also appeared to react more strongly and with higher levels of activity to strong levels of illumination.

The most profound effects produced by lesions in the striatum correspond to major deficits in learning and memory. Rats with bilateral lesions to the dorsal caudate demonstrate deficits in active avoidance of aversive stimuli, though these deficits were less profound in animals with unilateral dorsal and bilateral or unilateral ventral caudate lesions. In tasks targeting avoidance learning, with foot-shocks as aversive stimuli, amnesia for escape routes was noted in rats with hippocampal and caudate lesions in short-term intervals, but caudate lesions only produced corresponding amnesia in animals that had been trained previously, suggesting a role of the caudate in long-term memory for aversive events.

Additionally, cats with bilateral caudate lesions committed more perseverative errors and were less successful in ipsilateral and contralateral bar-pressing tasks. The cats

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[1] thigmotaxis: the tendency of an animal in an open-field maze to remain close to its walls, a common indicator of anxiety (Simon et al. 1994).

appeared to understand the necessary behavioral response to receive rewards, but had difficulties in producing proper behavioral sequences, and failed extinction trials where rewards were not administered. Cats with unilateral lesions performed better than cats with bilateral lesions, but exhibited greater difficulties in task acquisition than unlesioned cats. Cats and kittens with caudate lesions also exhibited heightened responsivity to auditory stimuli.

Grahn et al. (2009) further review some of the more recent experiments that focus on lesions of the striatum in laboratory animals. Distinct functions of the striatum in the formation of habit and as a mechanism for task-switching and behavioral flexibility are examined, and lateral regions of the dorsal striatum seem to be involved in instrumental stimulus-response habit, whereas the medial dorsal striatum seems to correspond to goal-directed action. Further, the ventral striatum seems to support more classically-conditioned responses to stimuli.

The striatum also seems to participate in consolidation of stimulus-response learning, and infusions of dopamine agonists into the striatum following training sessions dramatically enhance subsequent performance in a variety of learning tasks. Behavioral flexibility, by contrast, is dramatically impaired when the striatum is damaged, and more recent studies have shown that lesions to the medial dorsal striatum impair inhibitory control, disrupt reversal learning, and impair the ability of subjects to switch behavioral strategies. Rats with lesions to the striatum also show deficits in extinction when rewards are removed, and commit more perseverative errors when the target behavior is modified.

The caudate seems to be an important site of integration for goal-directed behavior. Lesions of the posterior medial dorsal striatum (but not the anterior medial

dorsal striatum) in rats result in disruptions of the rats' ability to respond to changes in the value of reward stimuli. Connectivity of this region with limbic areas associated with incentive learning, including the basolateral amygdala, which further projects to the orbital and medial prefrontal cortex, suggest that this functional circuitry is extremely important for integration of goal-directed and incentive-based learning.

Beyond the caudate, the globus pallidus and putamen are thought to function cooperatively to integrate sensorimotor regulation of tasks involving forelimb control and operant responsivity, as demonstrated through deficits in bar-pressing tasks in lesioned rats (Chozick 1983). Additionally, lesions of the ventral putamen in rhesus monkeys have been shown to result in postoperative deficits in learning in visual, but not auditory discrimination tasks (Buerger et al. 1974).

Lesions to the striatum have a profound effect on cognitive functions associated with cortical processes (Goldman-Rakic 1988). The striatum appears to be a site of major convergent input from the neocortex in all mammals, and in primates, this convergence seems to be of particular importance for integrating higher-level cognitive processes. In primates, this convergence heavily implicates frontocortical circuitry. Disrupting this connectivity, as in lesion studies targeting either the caudate or putamen, leads to major dysfunction in processes that rely on this circuitry (Butler & Hodos 2005).

Disease States Affecting the Striatum

Due to its location deep beneath the cortical surface, the striatum is not a common site of trauma and accidental injury in humans. However, several disease processes differentially affect striatal function, producing lesions in areas of the striatum yielding profound motor and cognitive deficits. Huntington's Disease (HD) is a heritable, terminal

condition primarily affecting individuals of Western European ancestry. Mutations of the gene that codes for synthesis of huntingtin, a protein crucial for normal development via the up-regulation of Brain-Derived Neurotrophic Factor (BDNF), yield irregularities in the normal protein interactions within cells that cause inclusions of protein aggregates that damage the cell.

Due to its specificity in the early degeneration of the basal ganglia, Huntington's disease offers the clearest example of the neuropathological effects of striatal lesions on cognitive performance. Cell death in the caudate and putamen are characteristic of the early manifestations of Huntington's disease, and substantial atrophy in these areas has been noted in pathological specimens. Medium spiny neurons are most vulnerable to the effects of pathological aggregates of the mutant huntingtin protein and polyglutamine, and enkephalin- and substance-P-containing cells are also affected. Interneurons are generally not affected by the disease. Overall, a pathological "gain of function" has been suggested as the characteristic manifestation of Huntington's within the striatum, whereby polyglutamine overexpression results in cell death, and aggregates of the mutant huntingtin protein inhibit cellular function and communication by interfering with synaptic transmission and glial cell support of neurons. Further, release of cortical neurotrophic factor in corticostriatal neurons has been shown to interfere with intrinsic function of neurons within the striatum.

Behaviorally, the most immediately noticeable effects of Huntington's disease are on motor processes. The "chorea" characteristic of early stages of the disease includes characteristic jerking, uncontrollable movements, and additionally, motor impersistence and slowing of saccadic eye movements have been noted. Cognitive dysfunction in

Huntington's patients is usually not severe enough to warrant concern in the earliest stage of the disease, but can include irritability, disinhibition and impulsivity, anxiety, restlessness, and difficulty multitasking (Walker 2007).

As the disease progresses, and typically after the onset of motor symptoms, deficits in cognitive ability increase in severity, particularly with respect to executive function. Organizational behavior and planning are severely impaired, as is task alternation. Language function declines progressively, though speech production deteriorates faster than comprehension. Interestingly, though short-term memory is affected, the disease generally spares long-term memory. Further, affective symptoms, including depression, do not seem to progressively become more severe. Suicidal ideation has been noted as a common symptom in Huntington's disease, though it could be argued that this is not a surprising outcome resulting from diagnosis with a terminal degenerative disease (Walker 2007).

Parkinson's Disease (PD) is another neurodegenerative disorder that affects the function of the striatum. It is characterized by more extensive systemic disruptions in the basal ganglia, though some conclusions about the function of the striatum can be drawn from examining the cognitive and motor deficits associated with its associated disease processes. Parkinson's disease affects the striatum through the destruction of dopaminergic cells and through the accumulation of protein aggregations, known as Lewy bodies, that disrupt connectivity and supportive glial cell function, and the destruction of nigrostriatal dopaminergic pathways leads to excessive inhibition of striatal function. As in Huntington's disease, the most immediate and debilitating symptoms are

in the disruption of motor function, but a variety of cognitive processes are also disrupted in patients with Parkinson's disease (Samii et al. 2004).

The typical cognitive profile associated with Parkinson's disease is marked by a deficit in executive function, and difficulties in planning behavior, problem-solving, rule and set formation, task-switching, and attentional shifting have been noted. In contrast to patients with frontal lesions alone, who demonstrate perseverative behavior, Parkinson's patients tend to have greater difficulty in discriminating against non-relevant stimuli and maintaining adaptive responses to distractors, and are susceptible to interference in divided-attention tasks. Working memory is also greatly impaired, and intrastriatal administration of dopamine has been shown to have therapeutic effects in treating these deficits (Whitehead & Brown 2007).

The psychoaffective symptomatology of Parkinson's disease can include depression and apathy, most commonly attributed to the deficits associated with the depletion of dopaminergic innervation throughout the brain, particularly areas associated with reward. Anxiety is also a commonly reported symptom and frequently manifests in hyperarousal (Gallagher & Schrag 2009), which is particularly interesting in light of the hypersensitivity to external stimuli demonstrated in animals with caudate lesions (Chozick 1983).

Sleep disturbances and fatigue are also common in patients with Parkinson's disease, and seem to be linked to disturbances in the dopaminergic innervation of the brain, including the striatum. Similarly to the effects experienced by rats with caudate lesions, Parkinson's patients seem to exhibit intrusions of REM sleep during sleep

cycling (Trotti & Rye 2009), lending support for the assertion that the caudate is involved in the inhibition of REM and paradoxical sleep (Chozick 1983).

Other neuropsychiatric disorders are also characterized by pathologies of the striatum. Schizophrenia is a psychological disorder characterized by disruptions in normal socioemotional and cognitive function, resulting frequently in bizarre behavior and inappropriate emotional responses. Immunochemical analysis of post-mortem specimens from schizophrenic patients have shown that they have significant reductions in numbers of cholinergic interneurons within the striatum. As cholinergic interneurons cease firing in response to behaviorally salient and reward-related stimuli, the reduction in numbers of these neurons in schizophrenics likely contributes to associated difficulties in the processing of reward-related and social stimuli (Holt et al. 1999).

Further, disruptions in the development of the striatum have been noted in autism. Autism is a developmental disorder characterized by an array of cognitive and behavioral impairments, including disordered social attachment, deficits in learning, and a tendency toward ritualized behavior and routine. In a structural MRI study, increases in caudate volume in autistic subjects as compared to normal, age-matched subjects were observed (Langen et al. 2009). The authors suggest that these pathological caudate enlargements likely relate to the stereotyped and repetitive behaviors that characterize some behavioral aspects of the disorder. Additionally, it may be suggested that the abnormalities in the development of the caudate may further be implicated in pathologies of social function, as the caudate plays a significant role in social behavior which will be further discussed in the next chapter.

Functional Imaging Studies

Taken together, pathology and lesion studies help to paint a picture of the functional role of the striatum in integrating cognition and behavioral output by highlighting deficits that correspond to striatal damage. However, as Damasio and Damasio (1989) have importantly noted, the localization of damage does not equate to the localization of function, and further evidence from functional imaging studies allows for greater understanding of the striatum's role in cognitive and behavioral processes in non-pathological subjects.

In a number of functional imaging studies in humans, different portions of the striatum show activation in response to behaviorally-salient and rewarding imagery. For example, the putamen showed greater activation bilaterally for selecting larger gain or loss options in situations involving greater risk in humans in a monetary incentive task (Ino et al. 2010). Further, the anterior and lateral portion of the ventral striatum have shown differential activation for determining reward outcome, and the posterior and medial ventral striatum showed greater activation in gauging reward magnitude (Yacubian et al. 2007). The ventroanterior striatum was also implicated in preferential selection of immediate versus delayed rewards, whereas the insula was more closely associated with selection of delayed rewards (Wittman et al. 2010). Consistent with these findings, increased levels of ventroanterior striatal activity, correlated with immediate reward-seeking behavior, have been found to correlate with impulsivity in alcoholics (Beck et al. 2009).

Additionally, high levels of activation of the ventral striatum have been observed in individuals viewing inherently pleasurable stimuli, including erotic images (Walter et

al. 2008), smoking-related pictures in smokers, but not non-smokers (David et al. 2005), and visual arts (Lacey et al. 2010). However, the striatum is not simply a site of reward processing: activation of the caudate nucleus has been observed in tasks involving aversive learning, as well as in response to viewing unpleasant visual stimuli (Carretié et al. 2009).

Conclusions

As we have seen from a variety of studies that focus on pathological and non-pathological subjects, the striatum is marked by a great degree of regional functional specialization. The ventral striatum is heavily implicated in the processing of reward-related stimuli. The caudate nucleus has a variety of important cognitive functions that show impairments when lesioned, and disturbances in sleep and normal arousal mechanisms indicate crucial inhibitory function of this area. In addition to its importance for stimulus-response and reward-based incentive learning, the ventral striatum in particular also plays a role in modulating aspects of social behavior, which will be the focus of the next section of this thesis.

CHAPTER III. SOCIAL COGNITION AND THE VENTRAL STRIATUM

Whereas the caudate and putamen of the dorsal striatum serve important roles in learning and memory, it is the ventral striatum in particular that is most heavily implicated in the reinforcement of a variety of complex social behaviors. The nucleus accumbens is largely regarded as the brain's reward center, and the dopaminergic system innervating this area is key to the experience of the pleasurable feelings associated with all manner of gratifying behaviors, from appetitive feeding behaviors, to the mechanisms of drug addiction, to the physiological reinforcement of the maternal-offspring bond (Ikemoto & Panksepp 1999, Beck et al. 2009, Numan & Insel 2003).

Mammalian brains in particular seem to be hard-wired to experience pleasure as the result of physical contact and social interaction. By definition, mammals reproduce sexually and give birth to live offspring dependent on their mothers for warmth and milk, so it is easy to see the adaptive value in these behaviors providing physiological reward. Before elucidating the mechanisms by which specific social behaviors are reinforced in the brain, it is important to gain an understanding of how the nucleus accumbens participates in the reward circuit and in the reinforcement of behavior generally.

THE PHYSIOLOGY OF REWARD

Though there is no direct evidence of dopamine providing subjective hedonic effects in model animals, there is substantial evidence to imply that the infusion of dopamine into putative reward pathways in the brains of experimental animals greatly facilitates behavior in a manner that indicates that it is essential for the establishing incentive saliency. As such, dopamine is at the center of our understanding of the reward system, and a putative anatomical model of this system has been asserterted.

According to this model, dopamine is released into the nucleus accumbens by the projections of dopaminergic cell bodies from the ventral tegmental area, in the ventromedial mesencephalon deep within the midbrain. The nucleus accumbens can be subdivided into the shell, which sends projections to the ventral pallidum, the amygdala, the lateral preoptic area, lateral hypothalamus, entopeduncular nucleus, ventral tegmental area, mediodorsal substantia nigra pars compacta, mesopontine reticular formation, and periaqueductal grey. The core sends projections to the lateral ventral tegmental area, dorsolateral ventral pallidum, entopeduncular nucleus, and substantia nigra. Nucleus accumbens dopamine innervates these areas, and may bind to either DA1 or DA2 receptor subtypes (Ikemoto & Panksepp 1999). See Figure 3 for a representation of nucleus accumbens projections and reward circuitry.

The exact mechanisms by which dopamine interacts with various neuromodulators in the nucleus accumbens and other brain areas remains unknown, but there is evidence to suggest that nucleus accumbens dopamine receptors, particularly the D2 subtype, may function cooperatively with other neuropeptides, including oxytocin (Liu & Wang 2003, Aragona et al. 2006). Oxytocin is a peptide hormone unique in mammals that functions as a neurotransmitter in the brain, and it is best know for its involvement in female reproduction. A surge in levels of oxytocin in the brain and body is an essential antecedent of parturition and lactation, and it is released in modest quantities in response to vaginocervical or areolar stimulation. It has further important roles for social partner recognition, trust, the formation of partner preference and pair-bonding, and parental care (Numan & Insel 2003). Dopamine and oxytocin are an essential part of how social behavior is modulated by the striatum, and the actions of

these important neurotransmitters with respect to a diverse array of social behaviors will now be discussed.

SOCIAL BEHAVIOR AND ITS REINFORCEMENT

The Social Neuroscience of Pair-Bonding

A considerable body of literature has addressed the neural correlates of pair-bonding in monogamous mammal species as compared to closely-related species with different reproductive strategies. The pair-bonded prairie vole forms a long-term bond with a single mate with which it rears its offspring cooperatively, and males devote a significant portion of their time to caring for pups. By contrast, in male montane voles, paternal investment in offspring does not occur, and interaction with female mates does not transcend copulation.

When the brains of female, pair-bonded prairie voles are contrasted with those of female montane voles, a striking difference in oxytocin and dopamine binding sites can be observed in the nucleus accumbens. Female prairie voles were found to have a dramatically greater density of oxytocin binding sites in the nucleus accumbens than montane voles (Young et al. 2001) (see Figure 4 for comparison). Further, when dopamine antagonists were used to block D2 receptor binding sites in the nucleus accumbens of female prairie voles, the formation of partner preference and pair-bonding was inhibited. Blockage of D1 binding sites did not have a profound effect on the formation of partner preference and pair bonds (Liu & Wang 2003).

For males, there is greater emphasis on the importance of the effects of arginine vasopressin in the ventral pallidum on the formation and maintenance of pair bonds. The ventral pallidum receives major projections from the shell of the nucleus accumbens,

which provide dopaminergic innervation, and it shares extensive connections with the limbic system. Arginine vasopressin, or AVP, is a mammalian peptide hormone best understood for its role in regulating fluid balance and blood pressure in the body, but it has been shown to correlate with pair-bonding in male prairie voles. As compared to montane voles, male prairie voles have a much higher density of AVP receptors of the V1a type in the ventral pallidum (see Figure 5). During mating, AVP is released that activates V1a receptors in the ventral pallidum, and likely contributes to the formation of partner preference (Young et al. 2001).

In a manner similar to the effects of reward learning, nucleus accumbens dopamine seems to underlie the formation of partner preferences and bonding with a mate. Aragona and colleagues (2003) have shown that the administration of dopamine antagonists blocked the formation of pair bonds in male prairie voles, whereas administration of dopamine agonists induced partner preference formation—without mating. So it would seem that the dopamine release that occurs in the nucleus accumbens as a result of copulation is an essential part of pair-bonding, and not unlike addictive mechanisms, the combination of oxytocin-mediated social recognition and pleasure have powerful synergistic effects with a profound impact on social structure.

It is important to note that there are two subgroups of dopamine receptors, and they appear to serve different functions for the formation and maintenance of pair bonds. Aragona and colleagues (2006) found that activation of D2-like receptors facilitated the formation of partner preferences, whereas D1-like receptor activation actually prevented it. D1-like receptor activation, by contrast, seems to have an important role in the maintenance of pair bonds, rather than in their initiation. Male prairie voles showed

increased D1-like receptor binding after 2 weeks of exposure to a mate, and this was correlated with increased aggression toward other females and greater affiliative behaviors toward the mate. In sum, the authors suggest, binding of dopamine in the nucleus accumbens to D2-like receptors facilitates partner preference formation and the initiation of pair-bonding, whereas D1-like receptor binding aids in the maintenance of the pair bond.

Most of the work addressing the neural correlates of mating strategies has focused on rodents, and voles in particular, though a few monkey species have been compared. Monogamous marmosets have a higher density of V1a receptor binding in the ventral pallidum than non-monogamous rhesus monkeys (Young et al. 2001). Additionally, Bales and colleagues (2007) used positron emission tomography (PET) co-registered with structural magnetic resonance imagery (MRI) to examine glucose uptake in monogamous male titi monkeys both before and after being caged with a female. Males who were caged with their partners, with whom they had formed long-term monogamous bonds, showed significantly higher levels of glucose uptake in the nucleus accumbens of the striatum, as well as the ventral pallidum, than males who were caged with non-partners. According to the authors, this increased glucose uptake indicates a critical shift in neural activity consistent with plasticity in the dopaminergic system underlying both short-term and long-term pair-bonding.

Further research by Hinde and colleagues (2010) has shown through MRI/PET that D1 dopamine binding potential increases in the nucleus accumbens as a function of time after initial pairing with a mate in male titi monkeys over the course of eight weeks. Interestingly, increased D1 binding potential in the caudate-putamen was observed early

on in the initiation of pair-bonding, which has not been observed in voles. These results seem to suggest that D1 dopaminergic involvement in the caudate-putamen of primates, but not voles, may serve an important role early in the formation of the pair bond.

Intrinsic Reward of Parental Behavior

The role of oxytocin in the physiology of childbirth has been well understood for many years. Spikes in blood and brain oxytocin levels immediately precede the onset and persist throughout the duration of labor and delivery, and the maintenance of high levels of oxytocin following parturition are essential for lactation and the release of milk into the subareolar sinuses. Oxytocin is an essential part of the onset of maternal care and behavior in mammals, and rats administered oxytocin antagonists fail to rear their pups normally (Numan & Insel 2003). Despite the dramatic differences in oxytocin receptor distribution in the nucleus accumbens of monogamous prairie voles and non-monogamous montane voles, however, major differences in females' rearing of pups and maternal behavior toward them have not been observed.

Insel (2003) summarizes the function of the reward system in the reinforcement of maternal behavior. When exposed to pups, dopamine is released in the nucleus accumbens, and a protein called fos is activated. Lesions to the ventral tegmental area or nucleus accumbens in female rats, inhibiting dopamine and fos release and uptake, inhibit maternal behavior by reducing approach and interaction with pups. Lesions of the medial preoptic area also associated with disruptions in normal maternal behavior. The medial preoptic area shares both efferent and afferent connections with the shell of the nucleus accumbens, and together with the ventral tegmental area, a circuit underlying the reinforcement of maternal behavior is formed.

Paternal behavior in mammals is rare, and only around 6% of mammalian species exhibit bi-parental care. Strikingly, this pattern shows a marked deviation in primates, with some 40% of genera showing the incidence of some manner of bi-parental care for offspring (Kleinman & Malcolm 1981). The neurobiological mechanisms of paternal behavior, though still somewhat poorly understood, seem to be different from those influencing maternal care for offspring. This is unsurprising since the behavioral mechanisms of paternal care are different, and include aggressive behavior directed at other males in defense of mates and offspring, which seems to be modulated in part by testosterone and vasopressin (Numan & Insel 2003).

Vasopressin further plays a role in paternal behavior that is likely reinforced by dopaminergic innervation of the ventral pallidum by the nucleus accumbens. When a viral vector was used to increase the expression of V1a receptors in the ventral pallidum, male prairie voles showed a significant increase in affiliative behavior toward juveniles. These effects were not demonstrated, however, with increased V1a receptor expression in the caudate-putamen (Young et al. 2001).

Alloparenting and the Striatum

Given the importance of the nucleus accumbens in the reinforcement of parental behavior, Olazábal and Young (2006) sought to determine if similar mechanisms were involved in the responsiveness of virgin juvenile females to a conspecific's pups. Intra- and interspecific differences were observed in oxytocin receptor density in the nucleus accumbens, caudate-putamen, and lateral septum when juvenile female rats, mice, prairie and meadow voles were compared. Prairie voles, who exhibit a high degree of alloparental care and responsivity to pups, had the highest density of oxytocin receptors

in the nucleus accumbens and caudate-putamen. Mice had the lowest density of oxytocin receptors in these areas, and rats and montane voles had intermediate levels. This ordinal scale of oxytocin receptor density seems to vary consistently with interspecific differences in amount of time spent in alloparental care: prairie voles show greater levels of juvenile-directed affiliative behavior toward juveniles and mice the least, with montane voles and rats falling in between.

Further, they measured time spent by individual females licking and hovering over pups, and compared these data with measures of oxytocin receptor density. Higher levels of alloparental care were positively correlated with density of oxytocin receptors in the nucleus accumbens and caudate-putamen. An inverse pattern was observed in the lateral septum, where interest in pups was negatively correlated with oxytocin receptor density. Given the close association of the nucleus accumbens and caudate-putamen with the reward system and habit learning respectively, these results may further suggest the interaction of dopamine with oxytocin, providing greater intrinsic reward for parental behavior and the formation of social relationships with younger conspecifics.

Social Grooming, Affiliative Behavior, and the Striatum

Allogrooming of conspecifics is an extremely important facet of social behavior in mammals, and primates in particular devote a large amount of time and energy in physical contact with conspecifics. Being groomed is associated with the release of endorphins, and dopamine in particular. In fact, when dopamine antagonists were administered in talapoin monkeys, an insatiable solicitation of grooming was observed, indicating an essential function of grooming in the release and uptake of dopamine. In light of the important role dopamine plays in bonding, this is particularly interesting, and

grooming has further been associated with the release of oxytocin. Further, the anxiolytic effects of oxytocin may be at the heart of why social grooming is an essential part of reconciliation after bouts of conflict in primate groups (Dunbar 2010). Given the involvement of dopaminergic reward system and oxytocin in the striatum, it is likely that social grooming activates these systems within the nucleus accumbens, and possibly the caudate-putamen as well.

Social Status, Stress, and the Striatum

Evidence suggests that dopamine in the striatum is correlated with social status and acute and chronic stress. Isovich and colleagues (2001) demonstrated that social isolation following defeat in bouts of conflicts with conspecifics resulted in reduced striatal dopamine transporter binding in male rats. Interestingly, these effects were not observed when rats were housed with social partners after defeat, suggesting a role for social interaction and support in mitigating the negative effects of acute stressors.

Lower-status animals, experiencing the complex physiological effects of chronic stress, have been shown to exhibit decreases in D2 receptor numbers in the nucleus accumbens (Papp et al. 1993). Cynomolgus monkeys *(Macaca fascicularis)* of low status show significant reductions in the binding potential of a D2 receptor ligand when compared to conspecifics of high social status, indicating decreased uptake of and sensitivity to the positive effects of dopamine (Grant et al. 1998). As lower-status primates tend to have fewer grooming partners, an indicator of pro-social relationships (Dunbar 2010), chronic stress associated with low social status may form a vicious circle together with the lack of physical contact that can ameliorate the negative effects of stress on the dopaminergic system within the striatum.

Social Play and the Striatum

A recent paper by Kerrie Lewis Graham (2010) found a robust correlation between the relative size of the striatum and the amount of social (but not non-social) play that juvenile primate species have been observed to engage in, as indicated from data from both wild and captive studies. The author suggests that striatum size may have co-evolved with social play, and that the importance of the striatum in both regulating procedural memory and rewarding prosocial interaction encourages expansion of the striatum in species that engage in larger amounts of social play. The study is correlative and relies on previously published data from the Stephan (1981) set. These data were collected from a small primate collection which in many cases represents only a single individual from each species. Thus, it is impossible to account for features including intraspecific variation and sexual dimorphism. However, the notion that social play may be related to size differences in the striatum remains compelling.

DISCUSSION

It is clear that the striatum serves a critical role in a host of social behaviors, and its chemical neuroanatomy underlies major facets of social organization. The primate order is characterized by an amazing diversity of reproductive strategies, and this diversity is likely supported by variability in the patterning and distribution of receptors for neuromodulators, including dopamine, oxytocin, and vasopressin. At present, the methods for highlighting the distribution of oxytocin and vasopressin receptors do not allow for the use of preserved tissue, so it is currently too difficult to determine the distribution of these receptors in apes and humans. Studying the evolutionary history of

mating and social systems using this comparative approach remains, at present, impossible.

Humans are characterized by substantial variation in culturally-reinforced mating systems, ranging from strict monogamy to polygamy, with polygyny more common than polyandry (Buss & Schmitt 1993). Indeed, there is no human universal in terms of mating and family systems, though to some, a shift away from the sexual dimorphism exhibited in the hominin fossil record strongly suggests a trend toward reduced intrasexual competition and the potential for monogamy. However, as Plavcan (2002) indicates, this reduction in sexual dimorphism is far from conclusive in determining the ancestral mating condition, as a case can be made to associate it with a variety of mating systems.

How differences in reproductive strategies are reflected in brain chemistry and morphology in humans remains to be studied, though evidence for genetic differences that may underlie human mating behavior have been asserted. The finding of a popularly-dubbed “gene for infidelity” has generated interest in the gene that codes for vasopressin receptors. Presence of the polymorphic allele 334 on the 5’ flanking region of the AVPR1a gene has been shown to correlate negatively with scores on a pair-bonding scale, and men with at least one copy of this allele tended to report lesser degrees of relationship satisfaction and higher rates of infidelity. A tendency toward monogamous behavior may thus be, to some extent, genetically encoded in males (Walum et al. 2008). An exploration of the genetics and neurobiology underlying women’s reproductive strategies and parental attachment would be an interesting complement to this research, and it is likely that striatal oxytocin is implicated in these aspects of social bonding.

It is always important to remain mindful of the clinical implications of research in evolutionary neurobiology. Autism spectrum disorders are characterized in part by the dysfunction of the mechanisms of social attachment, and as such, may be informed by the study of the evolution of peptide hormones involved in social interaction. Oxytocin in particular has been a target of study for contributions to social dysfunction in autism, and genes that code for oxytocin and vasopressin are of further interest for determining the evolutionary etiology of variation in patterning of neuropeptides influencing social behavior (Hammock & Young 2006). As such, deficits in social behavior mediated by neuropeptides may point to a critical role for the striatum in autism that at present remains largely underexplored.

CHAPTER IV. THE EVOLUTION OF THE STRIATUM

The striatum in its basic components including the caudate, putamen, and nucleus accumbens is present in all mammals and in most vertebrates, leading to the often dogmatically-held view that it is highly conserved. However, evidence for modification of the chemical anatomy, morphology, and connectivity can be observed across vertebrate phylogeny, and particularly with reference to the reciprocal connections with the mammalian neocortex, these anatomical differences yield important functional specializations that merit further investigation. Here, I will review what is known about the comparative neuranatomy of the striatum, with specific reference to functional specializations unique in mammals and in primates.

COMPARATIVE ANATOMY OF THE STRIATUM: GROSS STRUCTURE, MORPHOLOGY, AND CONNECTIVITY

General Morphological Evolution of the Primate Striatum

The striatum is the site of some major morphological modifications that have changed the shape of the corpus striatum in particular in the course of primate evolution. Whereas rodents have a conjoined caudate nucleus and putamen, this area is subdivided by the internal capsule in primates. The internal capsule is a white matter fiber tract that further separates the caudate from the thalamus and the thalamus from the putamen, and it is comprised of direct connections from the cortex to the medulla. The physical segregation of the caudate and putamen in these areas necessarily corresponds to differences in connectivity between the caudate and putamen (Jenkins 1978). Figure 6 shows the divisions of the striatum in humans, chimpanzees, macaques, and rats.

Volumetric Considerations

Often when comparing the evolution of structures within the brain, volumetric measures are utilized to attempt to discern the relative importance of brain structures for cognitive function. Jerison's (1973) principle of proper mass holds that the amount of neural tissue devoted to a brain region is a determinant of that region's relative importance for brain function. This follows logically from the notion that the brain has evolved mosaically—areas with greater functional significance have become disproportionately enlarged as the brain has expanded in size across primate phylogeny (Striedter 2005).

Allometric scaling principles have been historically applied to brain structures to compare the rate of expansion of structures as the brain has expanded across primate evolution (Striedter 2005). Volumetric comparisons have been undertaken which may unnecessarily downplay the significance of the striatum. The striatum seems to scale directly with the size of the neocortex, unsurprising given extensive corticostriatal connectivity, but the neocortex expands at a rate fivefold greater than the striatum (Stephan & Andy 1969).

Indeed, the limited volumetric comparisons that have been attempted show that the human striatum is smaller than would be expected for an anthropoid primate of human brain size, and this pattern holds true in chimpanzees and gorillas as well. Table 1 shows comparative volumes of the striatum for primate species measured by Stephan, Frahm, and Baron (1981). Methodologically, this data set presents certain issues: sample size is extremely small, and many species are represented by only a single individual of unreported sex. Still, this data set remains the most comprehensive comparison of

volumes of the primate striatum, and some general trends can be observed. Figure 7 shows progression indices of the striatum regressed against the progression indices of the neocortex, excerpted from the work of Stephan and Andy (1969). Progression indices follow the evolution of a trait from a *scala naturae* perspective, placing humans as "most evolved" and thus predicting values on an ordinal scale relative to humans and "lower" animals. Though this approach follows an outdated, hierarchical model of predictive values for the size of the striatum, it is still of interest that gorillas, chimpanzees, and humans fall below predicted values for size of the striatum relative to that of the neocortex.

Despite the fact that the striatum does not appear to be disproportionately enlarged in hominoid phylogeny, and even seems to scale smaller than would be expected, it would be premature to draw functional conclusions based on these limited data. A larger dataset more representative of intraspecific variation may help to clarify the phylogenetic history of the size of the striatum. Sherwood et al. (2004) have compared the size of the dorsal striatum in a sample of great ape species. Table 2 summarizes average volumes of the striatum, measured as the volume of the caudate and putamen, in two species of gorilla, orangutans, and chimpanzees. Gorilla species stand out among the sample as having the smallest volume of the dorsal striatum.

It is reasonable to suspect that interspecific variation may be a factor worth consideration, and closely-related species of gorilla showed significant variation in the size of the striatum as measured in this study, with eastern mountain gorillas *(Gorilla beringei beringei)* having significantly lower dorsal striatal volumes than western lowland gorillas *(Gorilla gorilla gorilla).* The authors attribute this difference to

variations in ecology and locomotion. Given the important role of the caudate and putamen in social behavior, such as mating systems, these differences might also reflect cognitive and social differences between groups.

It may be that substantial reorganization has occurred within the primate striatum, but so far, no investigations have attempted to examine this possibility. A comparative examination of the microanatomical organization of the striatum is absent from the literature. If and how the microanatomical organization of the striatum varies across primate species remains, at present, a mystery. However, the substantial departure in the relative location of the striatum in primate and rodent brains is highly suggestive of major modifications in brain structure.

A recent study of the gross morphology of human and extant ape brains (Aldridge 2011) has shown that the spatial position of the basal ganglia relative to the cortex varies dramatically. Humans show a pattern of the relative position of the basal ganglia that reflects a derived specialization, with the basal ganglia shifted anterolaterally, closer to cortical areas involved in language and higher cognition, including language areas and the prefrontal cortex. Aldridge asserts that this difference likely follows from differences in the expression of the FOXP2 gene, which plays a role in the development of the basal ganglia and language function.

Briefly, the FOXP2 gene is found in all mammals and regulates development in areas of the brain, including the basal ganglia, through the formation of FOXP2 proteins and related transcription factors. It is best known as a “language gene,” since mutations of this gene cause severe impairments in speech and language function (Lai et al. 2001). However, FOXP2 has a wide range of effects on the development of the basal ganglia

and cortico-striatal circuitry. Enard and colleagues (2009) created transgenic mice with the human-specific variant of FOXP2, finding major differences in basal ganglia function and behavior in affected mice. Physiologically, mice with the human FOXP2 variant developed longer dendritic arborizations, and experienced stronger long-term synaptic depression, indicating greater responses to stimulation in cortico-striatal neurons. This indicates enhanced synaptic plasticity in cortico-striatal neurons in mice with the human-specific FOXP2 variant.

The major divergence in spatial patterning of the basal ganglia in humans when compared to extant apes also further hints at differences that can likely be investigated on a microanatomical level, and may result from major differences in connectivity. Further examinations of corticostriatal connectivity in primates and other animals help to clarify how natural selection, in conjunction with the activity of human-specific FOXP2 variants, have resulted in divergent patterns of function and connectivity in the evolution of the striatum.

Differences in Connectivity Between Primates and Other Mammals

A key feature that distinguishes connectivity in the mammalian striatum from that of other vertebrates is the existence of major connections with the neocortex. Further, these patterns of corticostriatal connectivity show evidence of modification in primate evolution. In particular, modification of medial- and orbito-prefrontal circuitry has allowed for projections from novel cortical areas to innervate areas of the ventral striatum, including projections from Brodmann's areas (BAs) 13a and 13b (particularly in layers V and VI) to the medial ventral striatum, and projections from BAs 25 and 32 of the medial prefrontal cortex to the core of the nucleus accumbens. Projections from the

nucleus accumbens and medial ventral striatum in turn innervate discrete sections of the globus pallidus and extensive areas of the substantia nigra. The circuit that is formed indicates an executive control of the prefrontal cortex over dopaminergic neurons via the striatum in primates, which is of particular interest for primate behavior, since primate social life places high demands on behavioral regulation for appropriate social interaction with conspecifics living in social groups (Haber et al. 1995).

Figure 8 schematizes the connectivity of the striatum in primates, with projections from cortical areas forming a circuit through the nucleus accumbens and dorsal striatum. Major cortical inputs carrying diverse sensory and cognitive information travel in discrete fiber bundles to very specific targets in the striatum. Projections travelling from associative areas of the cortex, including the orbitofrontal, ventromedial prefrontal, and dorsal anterior cingulate cortices converge in more rostral areas of the nucleus accumbens of primates. This may provide evidence for integration of cognitive processing from these highly specialized cortical areas, such that these areas may exert some “top-down” control over the reward system as a whole in incentive-based, decision-making tasks (Haber & Knutson 2009).

Strikingly, a recent comparison of cortico-striatal connectivity between humans and macaque monkeys using diffusion-tensor imaging (DTI) fiber tracking has shown that the human prefrontal cortex, particularly orbitofrontal regions, sends significantly more dense projections to the anterior striatum than was observed in monkeys. A different pattern was observed in the macaques, with denser fibers projecting from the temporal and parietal cortices to the anterior striatum. Temporo-parietal projections to the basal ganglia in humans, by contrast, were relatively sparse and inconsistent in their

terminal locations (Lehéricy et al. 2004). This may suggest a major shift in connectivity during primate evolution, such that prefrontal cortical connectivity came to exert greater control over the function of the basal ganglia in the hominoid lineage.

EVOLUTION OF THE CHEMICAL ANATOMY OF THE STRIATUM

Because of its close association with the reward system and social and cognitive processing, the story of the evolution of the mammalian striatum is one in which chemical anatomy plays an important role. Given the importance of neuropeptide systems and receptors in the striatum in modulating social behavior, the evolution of neuropeptide systems merits further discussion. Since this paper has focused primarily on dopamine and oxytocin as neuromodulators central to the striatum's role in social behavior, the evolution of these neuropeptides will here be discussed.

Novel Mammalian Neuropeptide Receptors & Forms

Dopaminergic Receptor Subtypes. Two distinct classes of dopamine receptor subtypes exist in the vertebrate striatum: D1 receptors, which activate adenylyl cyclase activity, and D2 receptors, which decrease adenylyl cyclase activity and modulate the activity of calcium and potassium channels in the cell. Analyses of the molecular phylogeny of receptor subtypes have shown great diversity in the evolution of receptor subtypes in various vertebrate classes. Among mammals, two subtypes of D1 receptors (D1A and D1B/5) have been isolated, that are distinct from other subtypes isolated in other jawed vertebrates (D1C and D1D), which have disappeared in placental mammals. D2 receptor subtypes have yet to be analyzed due to practical difficulties in the sequencing of receptor phylogeny. At present, the exact significance of differences in

dopaminergic receptor subtypes and their function remains largely unknown (Callier et al. 1995).

Interestingly, when transgenic mice were created with the human FOXP2 varaiant, differences in dopamine levels were observed. A decrease in tissue concentrations of dopamine, corresponding to higher extracellular dopamine levels, also correlates with an increase in exploratory behavior. How exactly the human FOXP2 variant influences tissue and extracellular dopamine levels remains unknown, as FOXP2 is not expressed in dopaminergic medium spiny neurons. Further study may help to elucidate the mechanisms by which FOXP2 influences dopaminergic receptor development in the brain (Enard et al. 2009).

Oxytocin. As previously mentioned, the novel mammalian neuropeptide oxytocin, with important implications for social behavior, is chemically distinct from its nonmammalian analogue in other vertebrates. However, isotocin in fish and mesotocin in amphibians, reptiles, and birds seem to serves some similar functions in regulating sociosexual behavior, though the mechanisms are somewhat dissimilar owing to anatomical divergences in these species. The exact significance and implications of the gene duplication giving rise to oxytocin in the mammalian lineage remain, at present, somewhat poorly understood, and seem to involve differences in receptor binding potential that likely plays an important role in the formation of uniquely mammalian social and reproductive behavior (Insel & Young 2000).

DISCUSSION

Clearly, the striatum is the site of some major derived specializations in terms of morphology, connectivity, and chemical anatomy. The primary site of reorganization in

connectivity in mammalian lineages corresponds to the formation of connections with the neocortex, and novel projections from the striatum to neocortical areas connect to areas involved in higher cognitive function. Interestingly, area 13 of the orbitofrontal cortex, which projects to the medial ventral striatum, has been shown to be relatively smaller in humans and bonobos as compared to other apes. This area in humans and bonobos has been shown to appear less limbic in its organization, important for inferring the nature of socioemotional behavior (Semendeferi et al. 1998). Greater top-down control of behavior and emotional regulation likely contributes to the ability of primates to live in complex social groups.

Area 32, implicated in complex social behavior including mental self-projection and theory-of-mind (Raghanti 2008), projects to the striatum at the core of the nucleus accumbens. The functional significance of this connectivity is unknown, but it may be possible that a relationship exists between inferring the mental states of others and the experience of pleasure at this important reward center.

Cortico-striatal connectivity further seems to be a major site of reorganization of connectivity in the primate brain. Denser fiber tracts connecting prefrontal associative cognition areas to the striatum appear to converge in the anterior striatum, making this an important site of cognitive integration in reward-based tasks. In humans, this seems to correspond to greater cognitive control over the reward system and its function.

With regard to the evolution of neuromodulatory systems, differences in receptor type and function may be an important it seems that more research will be necessary to determine the nature of phylogenetic differences in receptor subtypes and the chemistry of oxytocin. Given the important role of oxytocin in lactation, the genetic point mutation

in the gene for oxytocin may be a crucial turning point in the evolution of the very specialization that defines the mammalian clade.

CHAPTER V. CONCLUSIONS & FUTURE RESEARCH DIRECTIONS

Though classically best understood with regard to their functional contributions to motor control, the basal ganglia clearly serve important roles in cognition and social behavior as well. The striatum is an important part of the brain that participates in many aspects of its intrinsic function important for social cognition, and discussions of the social brain ought to take into account its role in mediating social behavior.

The striatum participates in the integration of cortical input and reward circuitry with other structures of the basal ganglia and limbic system through associative and limbic loops, and serves as an important relay center in all of these systems. Its additional extensive innervation by neuromodulators and their receptors, such as dopamine and oxytocin, indicates a crucial role of the striatum in these systems throughout the brain as well. In primates, the striatum also serves as the primary site of input and integration of information from the medial and orbital prefrontal cortices. These areas and their homologues are recently evolved and represent derived specializations in primates and other cognitively-complex taxa, so emphasizing the role of the striatum and its connectivity with frontocortical regions will give us a more holistic view of the evolution of advanced cognitive specializations.

Models of functional connectivity in the striatum are far from complete, however, as anterograde and retrograde tracing studies, a major source of information regarding specific targets of axonal termination, require invasive procedures in live subjects, and thus, cannot be carried out in humans or apes. However, as imaging technology is refined and its methods applied to the study of the functional connectivity of postmortem samples, further comparative study of the afferent and efferent connections of the

hominoid striatum may reveal interesting data regarding the density and extent of extrinsic connections. Recent advances in diffusion tensor imaging (DTI) technology have allowed for the postmortem study of fiber tracts in the brain. This non-invasive, non-destructive method enables researchers to visualize and quantify white matter fiber bundles in the brain and highlight the directionality of their origins and terminations. Spatial resolution has already allowed for one comparative study of connectivity between humans and macaques (Lehéricy et al. 2004), and the addition of ape-human comparisons will help to clarify the natural history of increasingly dense prefrontal cortico-basal ganglia circuitry.

Conspicuously absent from the data are studies of the development of the striatum from a comparative perspective. This is unsurprising at the level of ape-human comparisons given the extreme rarity of subadult ape specimens, but even comparisons of non-human primates and other mammals are also lacking. This may be due to the notion that the basal ganglia are highly conserved, though this assertion is not warranted in light of the phylogenetic modifications detailed in this thesis. Given the highly plastic nature of the reward system, developmental study of cortico-striatal connectivity in humans, as well as from a comparative approach, may help to elucidate why primates and humans especially seem to be especially sensitive to reward and reinforcement in social situations.

Studies of function from the perspective of pathology have been informative in illuminating the role of the striatum in learning and cognition. Though the cognitive deficits associated with damage to the basal ganglia tend to take a back seat to the pervasive motor and somatic impairments characteristic of diseases like Parkinson’s and

Huntington's diseases, neuropsychological symptomatology in these conditions offers an interesting opportunity to model striatal function in human subjects. Further, other neuropsychological disorders affecting the striatum, such as schizophrenia and autism, indicate its important role in social cognition, emotional regulation, and attachment.

With respect to autism, the striatum in particular seems to be largely overlooked as a site of probable anatomical differences contributing to socioemotional dysfunction. This is surprising, given that oxytocin has been a major target of investigation, and its distribution in the caudate seems to correlate with differences in the formation of social attachment. Studies that have addressed the differential enlargement of the caudate generally (Sears et al. 1999) and developmentally (Langen et al. 2009) seem to miss the connection between oxytocin and the caudate, choosing instead to focus on the role of the caudate in routine formation and behavioral deficits involved in the disorder. This seems to reflect the misguided trend toward emphasizing non-social functions of the striatum. In general, it seems that the striatum is not often considered a major player in the evolution of the social brain, but it is likely that further examination of the role of the striatum in social cognition from an evolutionary perspective may challenge that view.

Currently, a paucity of data focuses on the comparative anatomy of the striatum, particularly at a microstructural level. It is likely that further investigation of the morphology, cytoarchitecture, and connectivity of the striatum from a comparative and evolutionary perspective, taken together with our knowledge of the involvement of the striatum in cognitive processes and social behavior, will point to a critical role for derived specializations in the striatum in regulating processes underlying defining features of primate social life. We must target the evolution of connectivity and chemical anatomy in

the striatum as a means of better understanding complex cognitive function and social behavior across phylogeny.

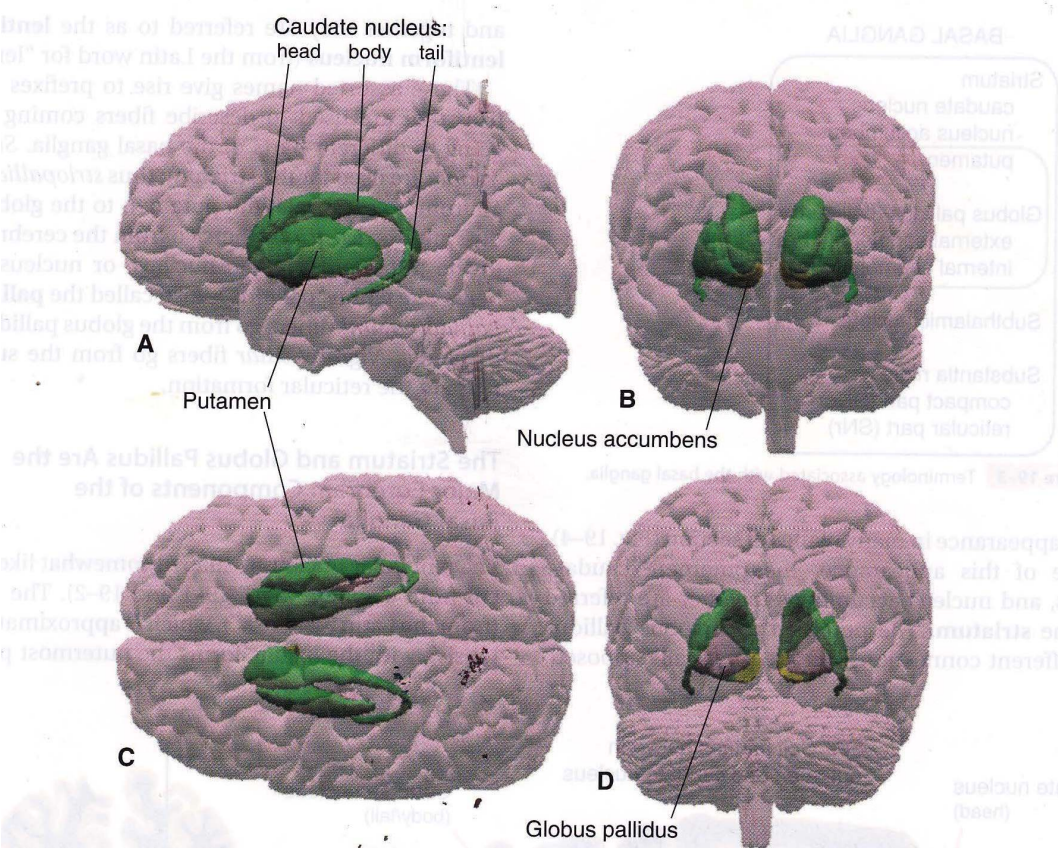
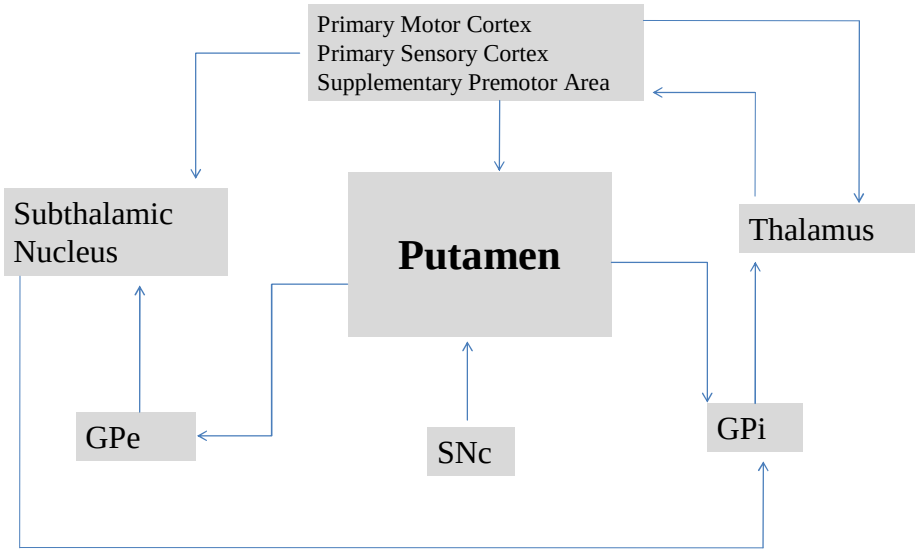


Figure 1. Some major structures of the basal ganglia in their anatomical orientation. Adapted from Nolte (2009).

A. Motor Loop



B. Oculomotor Loop

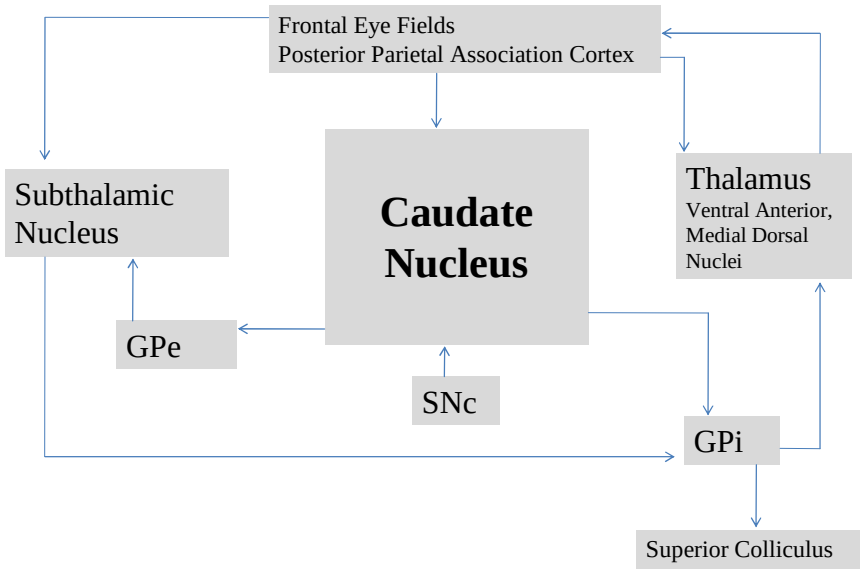
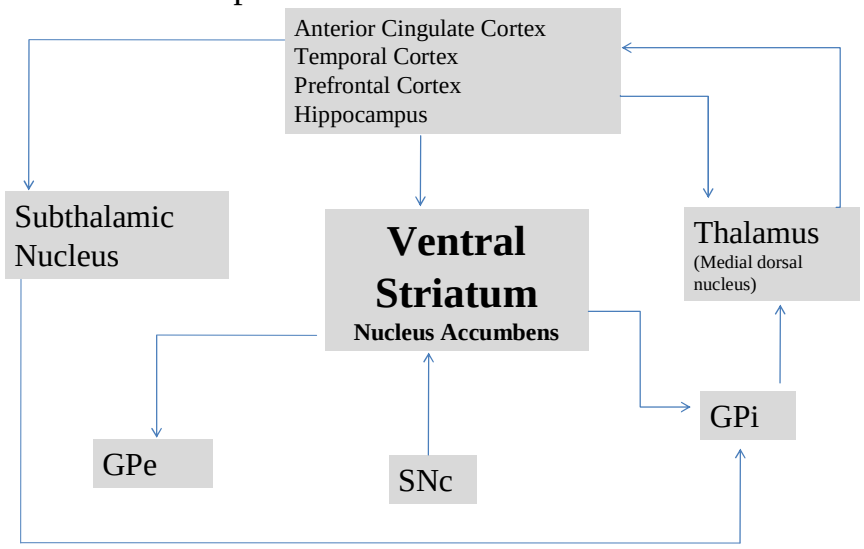


Figure 2. Functional Loops of the Basal Ganglia. Cortical inputs to basal ganglia structures in the human brain are shown. GPe: globus pallidus (external portion), GPi: globus pallidus (internal portion), SNc: substantia nigra pars compacta

C. Limbic Loop



D. Cognitive Loop

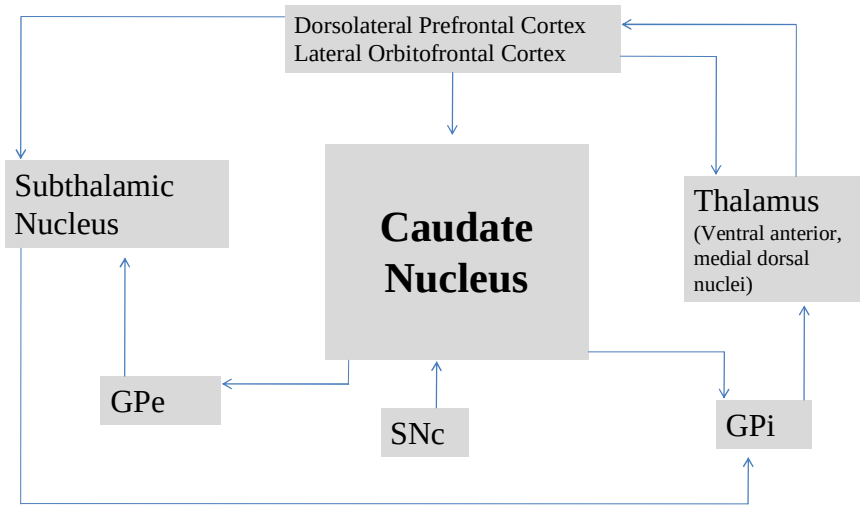


Figure 2. Functional Loops of the Basal Ganglia (Continued).

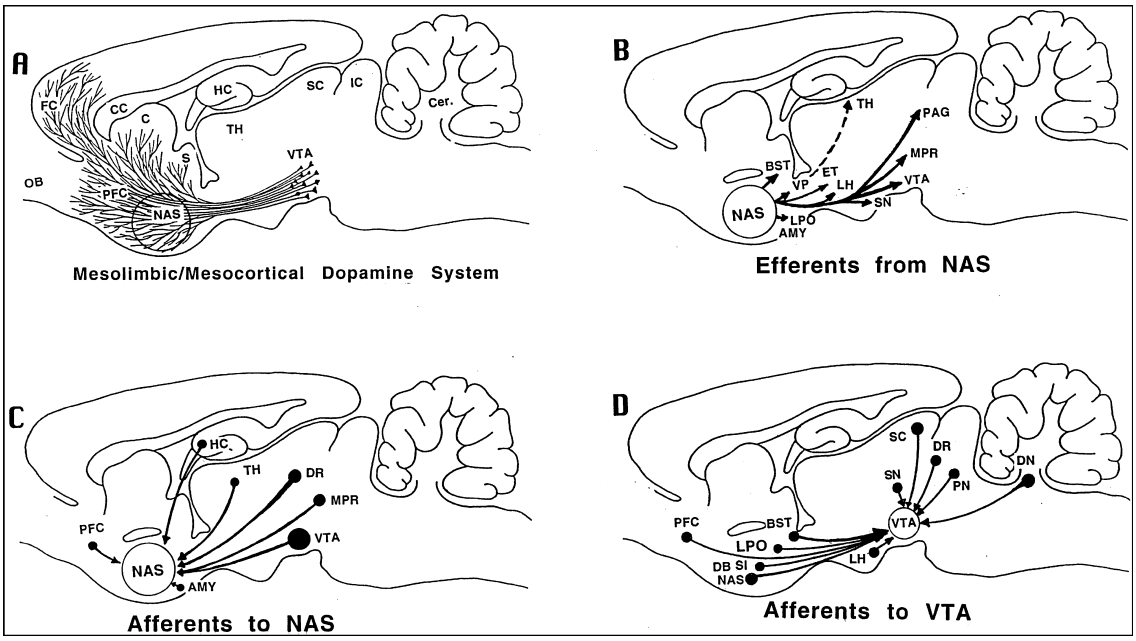


Figure 3. The Reward Circuit. As indicated on a model rat brain, arrows show the direction of projections. Abbreviations — AMY, amygdala; BST, bed nucleus of stria terminalis; C, caudate–putamen; CC, corpus callosum; DB, diagonal band of Broca; DN, dentate nucleus; DR, dorsal raphe; ET, entopeduncular nucleus; FC, frontal cortex; HC, hippocampus; IC, inferior colliculus; LH, lateral hypothalamus; LPO, lateral preoptic area; MPR, mesopontine reticular nuclei; OB, olfactory bulb; PAG, periaqueductal gray; PFC, prefrontal cortex; PN, parabrachial nucleus; SC, superior colliculus; SI, substantia innominata; SN, substantia nigra; TH, thalamus; VP, ventral pallidum. Adapted from Ikemoto & Panksepp (1999).

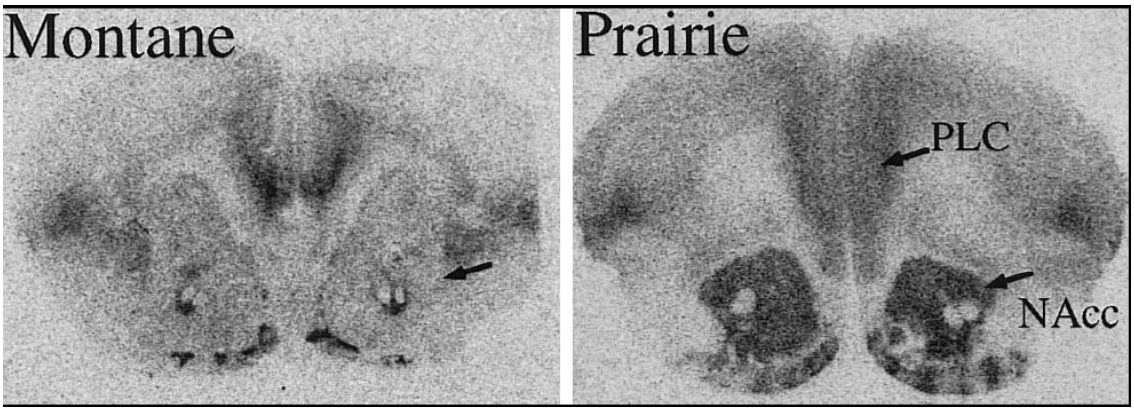


Figure 4. Distribution of Oxytocin Receptors in the Vole Brain. Density of oxytocin binding sites was measured and compared in non-monogamous montane voles (left) and monogamous prairie voles (right). The darkness of staining in the nucleus accumbens (NAcc) and prelimbic cortex (PLC) of the prairie voles shows a markedly higher density of oxytocin receptor binding. Adapted from Young et al. (2001).

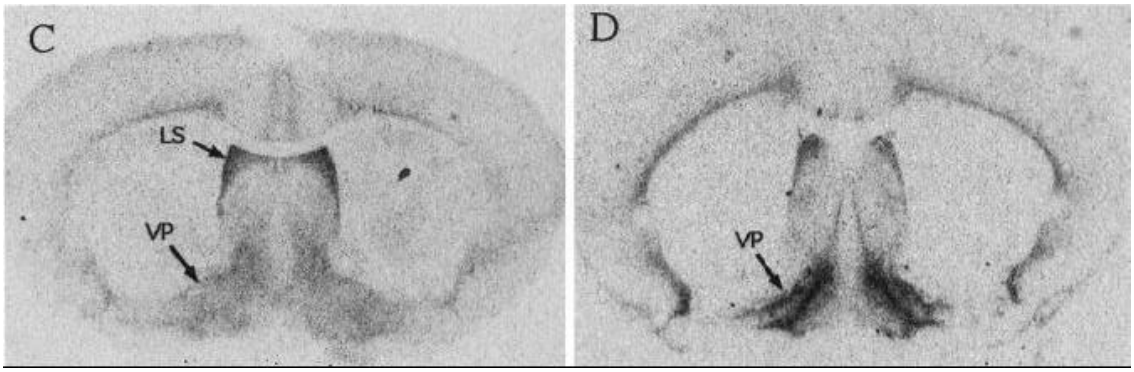
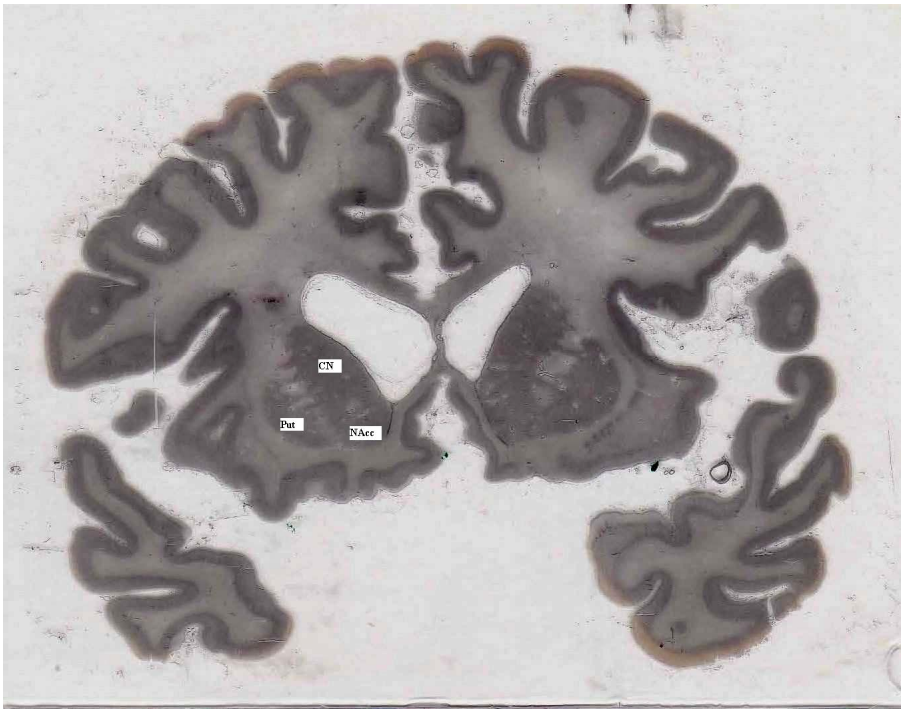


Figure 5. Distribution of Vasopressin Receptors in the Vole Brain. Density of AVPR1a receptors in the ventral pallidum and lateral septum of non-monogamous (left) and monogamous (right) voles. Darker staining of the ventral pallidum in prairie voles and of the lateral septum in the montane voles indicates greater density of AVPR1a receptors in these areas. Adapted from Young et al. (2001).

A. Human



B. Chimpanzee

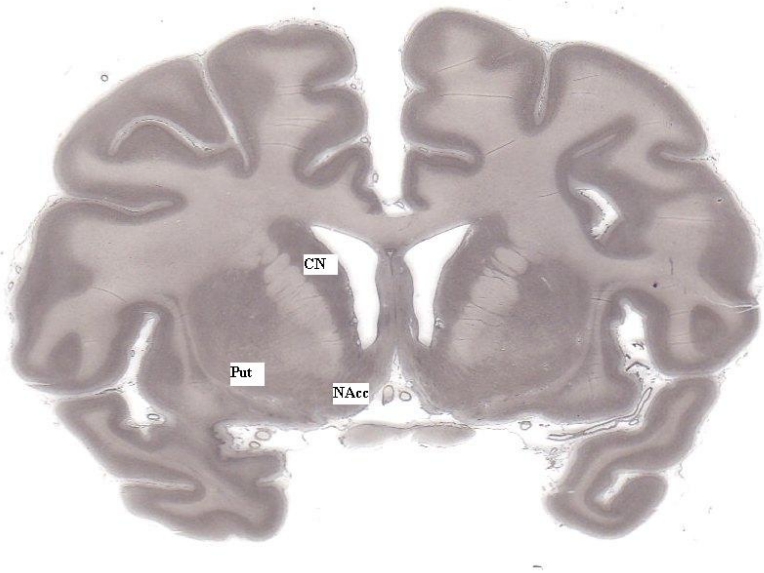
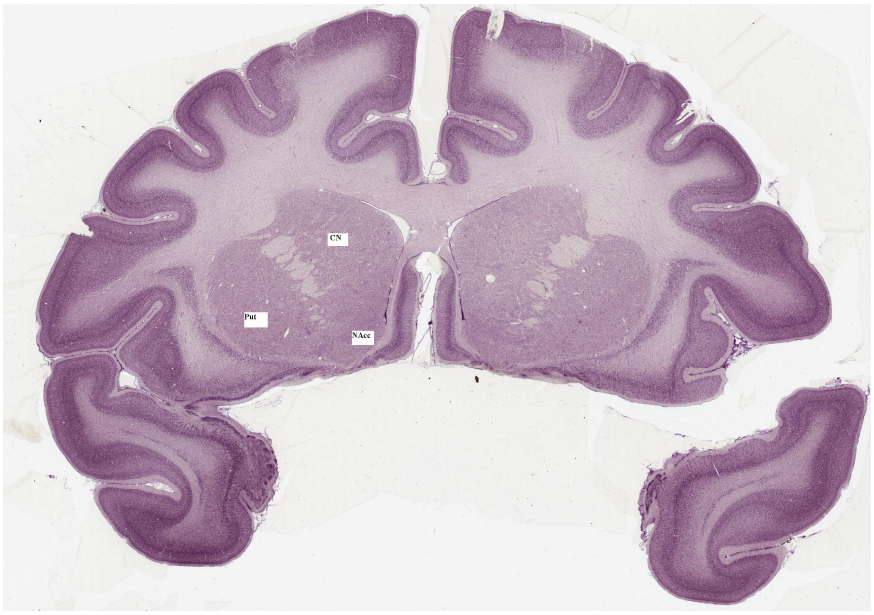


Figure 6. The Mammalian Striatum. Structures indicated in the human (A), chimpanzee (B), macaque monkey (*Macaca mulatta*, C) and rat (*Rattus norvegicus*, D). Images not to scale but enlarged to show detail. CN = Caudate Nucleus, Put = Putamen, NAcc = Nucleus Accumbens, CaPut = Caudate-Putamen, conjoined in rats. Human and chimpanzee images from the Semendeferi collection at UCSD. Macaque and rat images adapted from public domain collection at Brainmaps.org.

C. Macaque



D. Rat

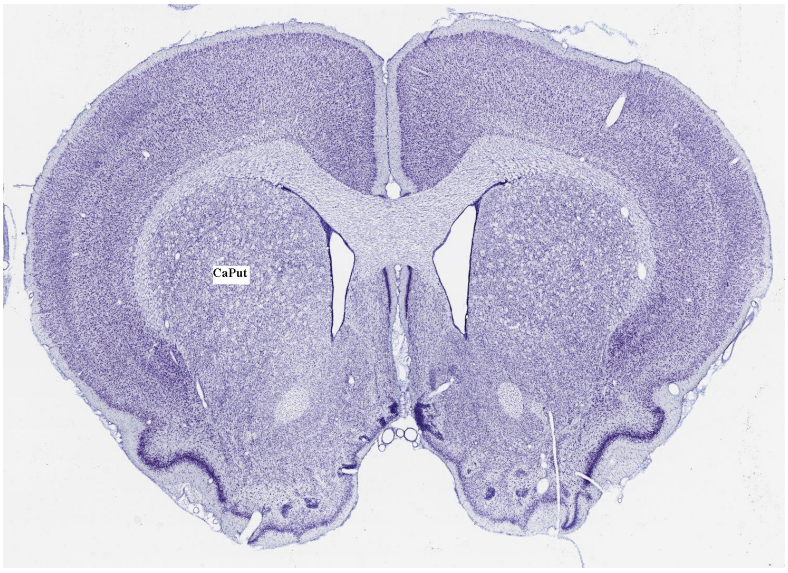


Figure 6. The Mammalian Striatum (Continued)..

Table 1. Volumes of Brain Components in Anthropoid Primates. Striatum data: fourth column from right. Adapted from Stephan, Frahm, & Baron (1969).

Code number	Species	Number of individuals	Telencephalon	Bulbus olfactorius	Bulbus olfactorius accessorius	Lobus piriformis	Septum	Striatum	Schizocortex	Hippocampus	Neocortex
			10 (= 11–18)	11	12	13	14	15	16	17	18
0151	*Callithrix jacchus*	4	5,318	22.8	0.326	191	49.8	372	90.0	221	4,371
0156	*Cebuella pygmaea*	2	3,099	12.3	0.386	133	29.2	174	81.8	133	2,535
0164	*Saguinus oedipus*	3	7,052	19.1	0.406	256	60.5	453	107	262	5,894
0165	*Saguinus tamarin*	2	7,055	17.3	0.290	243	40.9	471	120	280	5,883
0166	*Callimico goeldii*	1	7,733	27.0	0.512	253	63.5	493	138	281	6,476
0171	*Aotus trivirgatus*	5	12,128	56.0	0.222	394	83.8	862	243	539	9,950
0172	*Callicebus moloch*	2	13,465	19.2	0.325	454	86.4	920	234	588	11,163
0174	*Pithecia monacha*	2	24,920	34.8	0.846	675	140	1,918	289	834	21,028
0179	*Alouatta* sp.	2	37,388	41.4	0.595	827	200	2,829	510	1,320	31,660
0184	*Ateles geoffroyi*	1	79,946	90.4	2.19	1,625	324	4,950	732	1,366	70,856
0186	*Lagothrix lagotricha*	3	74,822	73.4	1.43	1,395	266	4,947	680	1,586	65,873
0191	*Cebus* sp.	2	52,113	39.9	0.667	931	174	3,258	390	890	46,429
0192	*Saimiri sciureus*	1	17,635	26.8	0.985	413	90.6	1,042	168	352	15,541
0202	*Macaca mulatta*	1	71,080	84.3	0	1,220	271	4,032	639	1,353	63,482
0209	*Cercocebus albigena*	1	77,049	121	0	1,639	294	4,146	630	1,485	68,733
0212	*Papio anubis*	2	154,987	287	0	2,111	559	7,182	1,309	3,398	140,142
0227	*Cercopithecus mitis*	1	56,277	117	0	1,265	246	2,733	617	1,366	49,933
0231	*Cercopithecus ascan.*	1	51,279	99.5	0	1,052	251	2,827	694	1,189	45,166
0232	*Cercopithecus talap.*	2	30,166	27.8	0	706	133	1,908	259	705	26,427
0234	*Erythrocebus patas*	2	84,770	51.8	0	1,339	330	3,624	693	1,591	77,141
0242	*Pygathrix nemaeus*	1	56,189	10.7	0	942	290	3,166	723	2,295	48,763
0243	*Nasalis larvatus*	1	70,873	30.3	0	1,268	333	3,735	855	1,966	62,685
0246	*Colobus badius*	2	57,885	51.3	0	937	288	3,217	814	1,671	50,906
0271	*Hylobates lar*	1	76,001	43.9	0	1,264	302	4,784	1,136	2,673	65,800
0277	*Pan troglodytes*	1	313,493	257	0	2,750	851	12,246	2,018	3,779	291,592
0279	*Gorilla gorilla*	1	369,878	316	0	4,871	1,173	14,567	2,729	4,781	341,444
0280	*Homo sapiens sapiens*	1	1,063,399	114	0	9,032	2,610	28,689	6,142	10,287	1,006,525

0 = Structure is not present in the species under consideration.

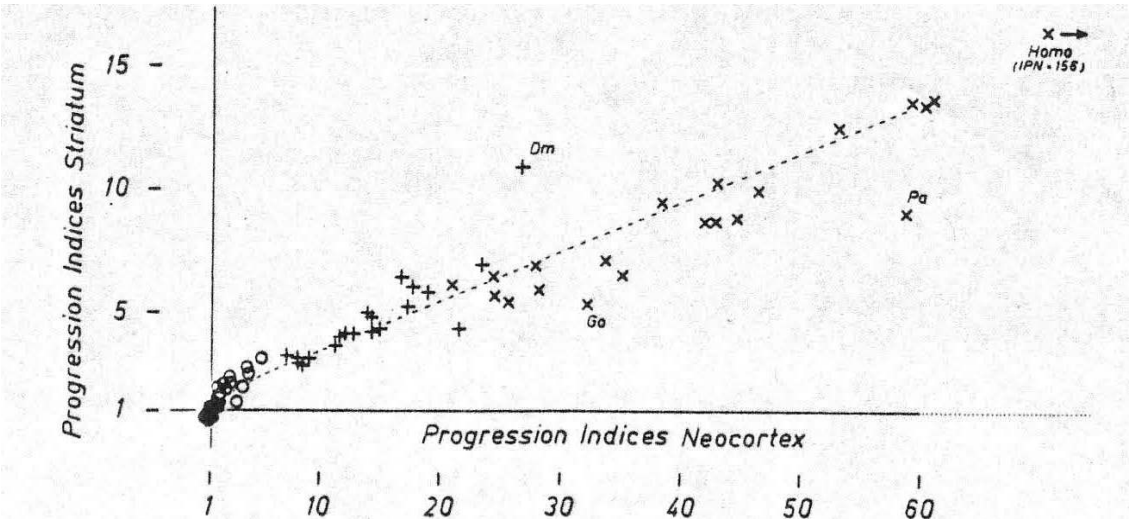


Figure 7. Progression Indices for the Neocortex and Striatum. Apes and humans fall below the line for expected relative size of the striatum as compared to the neocortex, indicating that the growth of the neocortex outpaces the growth of the striatum. Adapted from Stephan, Frahm, & Baron (1969).

Table 2. Volume of the Striatum in Two Gorilla Species, Orangutans, and Chimpanzees (in cm^3)

Species	Sex	Whole Brain	Striatum	Species Avg.
Gorilla beringei beringei	F	401.6	9.0	
	M	460.6	8.2	
	M	486.7	8.0	
				8.4
Gorilla gorilla gorilla	F	490.2	6.3	
	M	459.4	8.6	
	M	564.3	7.3	
				7.4
Pongo pygmaeus	F	311.2	5.5	
	F	394.1	9.6	
	F	298.6	5.6	
	M	374.1	9.0	
	M	344.7	7.0	
	M	370.3	6.8	
				7.25
Pan troglodytes	F	299.0	6.8	
	F	262.0	5.8	
	F	343.9	6.3	
	F	229.2	4.6	
	F	354.3	7.9	
	F	314.3	6.4	
	F	373.5	7.9	
	F	348.1	6.2	
	F	355.9	6.6	
	F	297.7	5.5	
	F	370.7	6.7	
	F	345.3	7.5	
	F	327.8	6.8	
	F	324.2	5.8	
	F	332.9	6.4	
	F	312.9	5.2	
	F	344.6	6.5	
	M	353.5	7.7	
	M	384.0	7.5	
	M	364.6	6.5	
	M	414.3	9.6	
	M	345.4	6.4	
	M	341.2	7.2	
	M	377.2	7.6	7.3

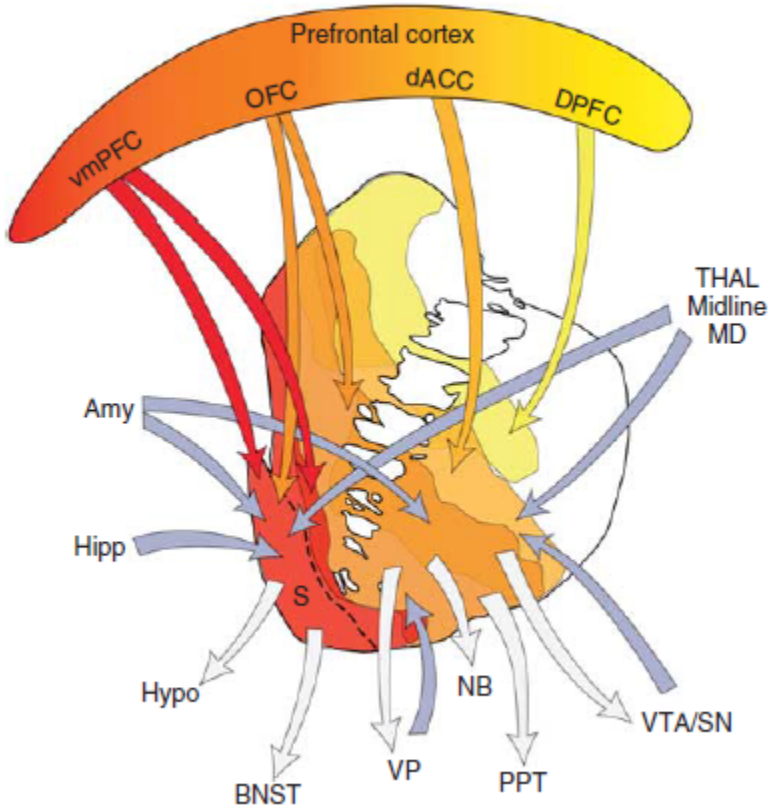


Figure 8. Projections from the cortex to the striatum in humans. OFC = orbitofrontal cortex, vmPFC = ventromedial prefrontal cortex, dACC = dorsal anterior cingulate, DPFC = dorsal prefrontal cortex, Amy = amygdala, Hipp = hippocampus, Hypo = hypothalamus, BNST = bed nucleus of the stria terminalis, VP = ventral pallidum, NB = nucleus basalis of Meynert, PPT = pedunculopontine nucleus, VTA/SN = ventral tegmental area/substantia nigra, THAL = thalamus, medial dorsal nucleus. Red/orange/yellow arrows show cortical inputs color-coordinated with termination sites. Blue arrows indicate inputs from subcortical structures.

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