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Adaptive Functions of the Corpus Striatum: The Past and Future of the R-Complex

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ABSTRACT

The basal ganglia is emerging from the shadow cast by the most conspicuous clinical expression of its dysfunction: motor disorders. What is revealed is the nexus of a widely distributed system which functions in integrating action with cognition, motivation, and affect. Prominent among non-motor functions are striatal involvement in building up of sequences of behavior into meaningful, goal-directed patterns and repertoires and the selection of appropriate learned or innate sequences in concert with their possible predictive control. Further, striatum seems involved in declarative and strategic memory (involving intentional recollection and the management of retrieved memories, respectively). Findings from reptile experiments indicate striatal control over specific assemblies of innate units of behavior that involve autonomic modulation. Its involvement in the appropriate expression of species-typical action patterns in reptiles and primates provides an interesting vantage point from which to interpret its involvement in the assembly of units of behavior into specific adaptive behavioral patterns.

THE BASAL FOREBRAIN AND STRIATAL COMPLEX

Anatomy and Connections

"Basal ganglia" is the term most favored by clinicians for the striatal complex -- an array of structures collectively called the R-complex by Paul D. MacLean (“R” for “reptilian”). It includes the *corpus striatum* (*caudate* and *putamen*). The putamen is so intermeshed with an afferent projection (the *globus pallidus*) that the two structures are occasionally regarded together as the *lenticular nucleus*. The *nucleus accumbens* –once regarded as part of the septum or olfactory system is, along with the *olfactory tubercle*, sometimes called the “*olfactostriatum*” in higher primates, and it is now viewed as a medial extension of caudate-putamen in mammals. Caudate, putamen,

and globus pallidus are sometimes referred to collectively as “neostriatum” while nucleus accumbens, olfactory tubercle and ventral pallidum are called “paleostriatum.” These terms suggest relative phylogenetic antiquity that **Butler and Hodos (1996)**. find unwarranted, and so they term these aggregates dorsal and ventral “striatopallidal complex,” respectively, in their recent textbook of comparative vertebrate neuroanatomy. The collection of structures includes adjacent gray matter termed *substantia innominata* which encompasses *nucleus basalis* (=the *basal nucleus of Meynert*) which is well interdigitated with the overlying lenticular nucleus.

Although often included in the basal ganglia because of topology, MacLean did not include *amygdala* and *claustrum.*

> [Claustrum has enjoyed several interpretations, but judgement about affinities with striatal complex can be rejected on the basis of a fundamentally different neurochemistry –lacking indications of either cholinesterase or dopamine, characteristic chemicals of the corpus striatum) Claustrum does, however, have connections with the neocortex much like those of thalamus and include “discrete visual and somatosensory subdivisions . . . interconnected with the corresponding primary sensory areas of the neocortex,” according to Olson and Graybiel (1980). These authors conclude “that loops connecting sensory areas of the neocortex with satellite zones in the claustrum contribute to the early processing of exteroceptive information by the forebrain.”]

Amygdala has multiple connections with the hypothalamus and is regarded as part of the limbic system although it may well function as the major mediator of interactions between limbic and striatal functions. Claustrum has no known major connections with core striatal structures. Neither did MacLean define *substantia nigra* as part of the striatal complex but he discussed its outputs in concert with those of the striatum because of the similarities of its *pars reticulata* to *globus pallidus*. **André Parent (1986)** proposed as core structures, dorsal striatum (caudate nucleus, putamen), ventral striatum (nucleus accumbens and part of the olfactory tubercle), and pallidum. As associated structures, he identified the substantia nigra, ventral tegmental area, and subthalamic nucleus (see Table 1). The core structures, striatum and pallidum, which originate in the lateral and medial parts of the developing telencephalon along with the associated structures are now often regarded as a basal ganglia system. The structural plan is very conservative and manifest from amphibians through reptiles, birds, and mammals **(Marín, Smeets, and González 1998)**. In the dorsal striatum, chemo-specific stains reveal that two classes of chemically (and probably functionally) specific cells are present. Strands of cells called “striosomes” are embedded in a larger “matrix” and appear to possess reciprocal connections with the dopaminergic cells of the substantia nigra. They thus have the potential to regulate dopaminergic activity, and indeed, stimulation in or near a striosome is more likely to evoke self-stimulation by an animal that can control its own electrode (references in **Milner 1999**). The matrix consists of neurons that participate in paths between cortical areas and lower centers.

TABLE 1. Structures of the mammalian Basal Ganglia*

CORE STRUCTURES

STRIATUM

caudate and putamen (sometimes "dorsal" or "non-limbic striatum")

ventral striatum (sometimes, "limbic striatum") n accumbens and part of olfactory

tubercle; =olfactostriatum)

PALLIDUM (globus pallidus)

external segment

internal segment (entopeduncular n in nonprimates)

ventral pallidum (comprising part of the substantia innominata)

ASSOCIATED STRUCTURES

SUBSTANTIA NIGRA (reciprocal connections with caudate and putamen)

VENTRAL TEGMENTAL AREA (reciprocal connections with ventral striatum)

SUBTHALAMIC NUCLEUS (reciprocal connections with pallidum)

*adapted from Parent (1986)

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Parent and Hazrati (for example, **1995a, 1995b**) incorporate striatum, pallidum, and substantia nigra along with the subthalamic nucleus as basal ganglia. While the first three are regarded as "main axis," subthalamic nucleus, along with pars compacta of substantia nigra the centromedian/parafascicular thalamic complex, dorsal raphe and pedunculopontine tegmental nucleus are regarded as "control structures" that provide various neurochemical modulation. (1995b). They reviewed the anatomical details of cortico-striatal projections, the intrinsic organization of striatum, the striatofugal system, and the output structures of the striatum and posit a cortico-basal ganglia-thalamo-cortical loop. The unexpected complexity of intrinsic organization and the orderliness of its highly structured repetitive units makes it ideal for selective control of psychomotor functions.

To clarify the basal ganglia's potential for information processing, **Parent and Hazrati (1995a)** analyze the anatomy (see above) and considered the evidence they provide for two views of information processing, the "**parallel processing**" and the "**information funneling**" hypotheses. As Parent and Hazrati characterize these, parallel processing involves processing different kinds of cortical information through well segregated cortico-basal-ganglia-thalamo-cortical loops. Information funneling, on the other hand, is informed by the fact that striatal axons from distinct functional areas are received by widely arborizing dendrites of pallidum and substantia nigra. Parent and colleagues (references in **Parent & Hazrati 1995a**) have used new and highly sensitive anterograde tract-tracing and determined that there are extensive dendritic arborization of pallidal and nigral neurons that could in principle lead to convergent "funneling." But such an apparent convergence does not mean that functional specificity is thereby lost – they acknowledge that they have yet to ascertain if specificity is retained in the loops from cortex to basal ganglia to thalamus to cortex.

Striatal Connections with the cerebral cortex and their possibilities

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The rich connections the striatum receives from the cortex feed forward into other parts of basal ganglia such as internal and external pallidum, and from the internal pallidum to the thalamus and thence back to the cortex. This one-way traffic involving inhibitory as well as excitatory synapses consists of fairly well separated parallel pattern. In Edelman's view, this pattern is ideally suited to effect independent neural routines. But further, because of the way these isolated parallel loops are connected to the thalamocortical system with its dynamic reciprocities, these routines would remain, in **Edelman & Tononi's (2000)** view, unconscious for cognitive routines much like those of motor programs. These routines within the basal ganglia or between the basal ganglia and cortex might then compete for representation in the cortex in a way that maintains the seeming "unity of behavior and thought," and explains why we tend to have or implement one conscious activity at a time (**Edelman & Tononi 2000:186**).

The basal ganglia seem as important as the prefrontal cortex in the analysis of serial order in which events or perceptions are detected and the control of behavior based on such information. **Beiser and Houk (1998).** noted that frontal lobe patients and those with Huntington's or Parkinson's disease can manifest strikingly similar deficits. This led them to propose a model to gain insight into the ways prefrontal cortex and basal ganglia work to transform sequences of input into patterns of neural activity. The model involves an encoding process whereby the serial order of stimuli are represented as a spatial pattern of neural activity, utilizing topographically specific circuits that loop from prefrontal cortex through basal ganglia and thalamus and then back. Recurrent corticostriatal projections and collateral inhibition between striatal spiny units were able, then, to sustain representations of contextual events in working memory. A decoding process would then transform spatial patterns of neural activity to sequences of actions.

The Interface: Nucleus Accumbens. Nucleus accumbens, a dominant part of the ventral striatum, is the leading candidate for the interface between sites that integrate affective, motivational, and cognitive functions with action. As MacLean (1990) points out, as the recipient of limbic (hippocampal and amygdalar) inputs and by virtue of its projections to ventral pallidum and substantia nigra, accumbens is often regarded as the key limbic-motor interface (**Mogenson et al. 1980**). "An important link between the motivational-emotional parts of the brain and certain effector regions," as **Groenewegen et al. (1996)**, put it. **Graybiel (1997)** goes further in speculating that "this limbic basal ganglia system has a key function in translating action plans related to drive states and homeostatic control into action repertoires" (p. 460) or stereotyped responses (such as "fixed action patterns") in general.

> [The "fixed action pattern" implies a degree of fixity that is not intended by the original term. Erbkoordination originally meant "inherited movement coordination" and was presumed, like a morphological feature, to be genetically fixed. It is stereotyped in the sense that once elicited, it is relatively fixed in performance. Stereotyped behavior also refers to responses that have become functionally autonomous. They are especially noted in deprived environments where their exteroceptive and proprioceptive stimulation may be rewarding or in instances of overstimulation where they may function to modulate or mask stress-evoking stimuli (Hinde, Robert A. 1970. Animal Behavior: A Synthesis of Ethology and Comparative Psychology. McGraw Hill N.Y. 876 pp. And 1977. The relevance of animal studies to human neurotic disorders. In: Ethological Psychiatry" (NF White, ed.) Grune & Stratton, NY]

For example, accumbens has been linked to the highly stereotyped behavior of laughing, whether in response to a joke or contagious laughter, by means of MRI (**Shibata et al. 2000**). Different causes of laughter were interpreted at other sites (ventromedial frontal lobe for "getting it" or anterior supplemental motor area for contagious laughter), but all scans also showed activity in the nucleus accumbens.

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While the accumbens is also often associated with appetitive motivation (for example, Paradiso et al. 1999) and reward (**Wise & Bozarth 1984;** other references in Paradiso et al. 1999), various stressful situations evoke dopamine release in accumbens (Salamone 1994); but not the nigrostriatal system (**Herve et al., 1982; Thierry et al., 1976. In: Bowers et al., 1987**)

> ["...sought neural circuits associated with the evaluation of visual stimuli for emotional valence. . . Results: pleasant stimuli -- increased blood flow in the dorsal-lateral, orbital, and medial frontal cortex (relative to the unpleasant condition) and in the cingulate, precuneus, and visual cortex (relative to the neutral condition).; unpleasant stimuli activated amygdala, visual cortex, and cerebellum (relative to the pleasant condition) and the nucleus accumbens, precuneus, and visual cortex (relative to the neutral condition). They concluded that observing and assigning emotional value to unpleasant stimuli activates subcortical limbic regions, pleasant stimuli activate cortical limbic areas. "These findings are consistent with the notion of a subcortical and archaic danger recognition system and a system detecting pleasantness in events and situations that is phylogenetically younger, involving primarily the prefrontal cortex"] --- [recall theclassic view of accumbens is that it plays a role in appetitive motivation and positive reinforcement . . . but a variety of aversive and stressful situations (e.g., active avoidance behavior) increase dopamine release within the accumbens & recently, the function of the accumbens has been conceptualized as linking motor and motivational processes that characterize goal-directed behavior]

Accumbens is also prominently associated with negative emotional valence in adult humans shown pictures designed to evoke affect. Subjects whose brains were being scanned by positron emission tomography (PET) while being shown neutral, negative, or positive affect-evoking pictures manifested different patterns of activity depending on the stimulus. Negative valence would reasonably dominate an aversive or avoidance situation while positive valence implies a pleasant or approach situation. When compared to the effects of a neutral stimulus, viewing unpleasant pictures stimulated increased blood flow primarily in limbic striatum, including nucleus accumbens. Pleasant pictures, on the other hand evoked increased activity in the phylogenetically newer cortical limbic areas including prefrontal cortex (Paradiso et al. 1999) system and a system detecting pleasantness in events and situations that is phylogenetically younger, involving primarily the prefrontal cortex. The authors suggest that detection and rapid stereotyped response to avoidance situations is reasonably coordinated with older, conserved mechanisms, but the basal ganglia may in **Graybiel's (1995)** view may also be a critical part of a distributed forebrain system that helps assemble and express learned as well as innate sequences of behavior. Indeed, Graybiel feels evidence is accumulating that basal ganglia may participate significantly in planning and cognition **(1997).**

Neurochemistry, neuroendocrinology

The known and growing understanding of basal ganglia connections is converging with findings about regional histochemistry. As **Graybiel (1990)**. [This complexity suggests, in Graybiel's view, "that dynamic regulation of transmitter expression may be a key to extrapyramidal function."] has pointed out, basal ganglia contains "a remarkable diversity of neuroactive substances organized into functional subsystems that have unique developmental histories and vulnerabilities in neurodegenerative diseases." Although the neurotransmitter dopamine (DA) is prominently associated with the basal ganglia because of the famous clinical manifestations of an insufficiency or excess, the neurotransmitter of most striatal neurons is gamma aminobutyric acid (GABA). Serotonin is present in striatum (as in hypothalamus) in relatively high concentration as are the opiate-like endorphins, receptors for which were found in high concentration in the corpus striatum (Pert and Snyder). In fact, as **MacLean (1990)** emphasizes, endorphin

concentrations are several times higher in the external segment of the globus pallidus than in other cerebral structures [MacLean's cite 29]. Substance P, a vasodilating agent described in the 1930's was found about 20 years later to exist in high concentrations in the medial segment of the globus pallidus, as well as caudate nucleus and hypothalamus.

Dopamine (DA) is the neurotransmitter most prominently associated with the basal ganglia, and indeed, across taxa, it is one of its most conservative traits (see **Marín, Smeets, and González 1998)**. In mammals, different subclasses of dopaminergic receptors, D1 and D2 are associated with the so-called direct and indirect basal ganglia subsystems, respectively. These pathways represent the conceptual if not anatomical basis for understanding of motor control and their disorders. These systems are recently viewed in terms of an "opponent parallel pathway hypothesis" in which direct and indirect systems compete with each other to cause net inhibition or excitation of activity, respectively. This is similar to **Mink's (1996)**"focused selection and inhibition hypothesis," in which a specific motor program is activated while competing programs are broadly inhibited. In either event, motor activity is perceived as the outcome of a balance in activity of these pathways maintained in part by activation of D1 and D2 dopamine receptors. Thus if the direct pathway predominated, motor activity might be excessive (as in Huntington's disease) and if the indirect pathway was relatively more active, Parkinsonian poverty of movement might be seen (Graybiel 2000). Interestingly, D1 and D2 receptors can be seen in a laminar pattern in lizards (Clark et al 2000, see below).

In the mammalian brain, DA is found principally in the substantia nigra, from whence it is projected to caudate/putamen (dorsal striatum), and in the ventral tegmental area, the mesolimbic projection of which supplies forebrain sites (including nucleus accumbens, olfactory tubercle, amygdala, septal area, and the prefrontal cortex). There is also a dopaminergic projection from the hypothalamus to the median eminence (where it modulates reticular formation output), in a system around the fourth ventricle, and in local circuits intrinsic to the retina, olfactory bulb, and the optic tectum.

The functional specificity of alternative projections was underscored by the finding that a single gene (in the mutant mouse, weaver) could differentially cause severe dopamine depletion in the mesolimbic and nigrostriatal systems affecting the "non-limbic" dorsal (caudate/putamen) but not the "limbic" ventral (including n. accumbens) striatum (Roffler-Tarlov & Graybiel 1984)

> [". . . Ungerstedt observed that the dopamine-containing innervation of the forebrain can be divided into two parts: a nigrostriatal system, originating mainly in the pars compacta of the substantia nigra and innervating the caudoputamen; and a mesolimbic system arising mainly in the ventral tegmental area and innervating the nucleus accumbens and olfactory tubercle. This classification has since been modified and extended with the discovery of the mesocortical dopamine system. The original distinction between nigrostriatal and mesolimbic systems nevertheless was pivotal in suggesting that the basal ganglia are related to limbic as well as to sensorimotor functions, and remains of interest because dopaminergic mechanisms may be implicated not only in the aetiology of sensorimotor impairments such as those of Parkinson's disease, but also in neuropsychiatric disorders such as schizophrenia. The striatal targets of the mesolimbic and nigrostriatal systems are now known to be distinct also in terms of forebrain connections, despite some overlap of fibre projections. The nucleus accumbens-olfactory tubercle region and abutting caudoputamen (together called the 'ventral' or 'limbic' striatum) are characteristically related to limbic parts of the forebrain, whereas the large remainder of the caudoputamen (the 'dorsal' or 'non-limbic' striatum) is most closely related to sensorimotor regions. We report here evidence that the mesolimbic and nigrostriatal systems are differentially affected in the mutant mouse weaver, and in particular that dopamine is severely depleted in the dorsal striatum of weaver but relatively spared in the ventral striatum. We conclude that dopamine-containing fibre systems innervating the limbic and non-limbic striatum can be influenced separately in genetic disease and that genetic control, whether direct or indirect, may be exerted at the single gene level."]

may be exerted at the single-gene level.]

While diseases of the basal ganglia can impair learning of sensorimotor skills,. Tasks such as mirror tracing that improve with practice. the effects, according to Gabrieli (1998), are not uniform. Repetitive tasks appear basal ganglia-dependent while tasks requiring new associations apparently depend on the cerebellum. Alternatively, Gabrieli suggests that open-loop skill learning (depends on planning and delayed feedback about errors) is cerebellar, while closed-loop skill learning (continuous feedback about errors) is striatal.

Striatal Functions and Dysfunctions

The "R-Complex" is the basal "reptilian" structure in Paul MacLean's well-known heuristic model, the triune brain, reflecting the predominant behavioral functions believed to have been first integrated in its constituent neural structures in evolutionary time (**MacLean 1990**).

Of course neural structures and systems continue to evolve after the initial innovation that provided an advantage in its initializing "environment of evolutionary adaptiveness," and other structures can certainly come to coordinate comparable behavioral patterns. The idea of the triune brain remains controversial, in part because of its vulnerability to oversimplification, but the basic idea of a nested hierarchy of structures is attractive, but point-to-point continuity cannot be expected. For example, as MacLean points out, the newest (thalamocingulate) part of the limbic system has no representation in reptiles (1990:247).

The basal ganglia are prominently associated with motor control, probably because of the dramatic, often devastating effects of dysfunction on movement (see below). Although an array of corollary functions such as motor learning and automatization were long suspected, only recently are these structures coming to be understood as indispensably involved in many functions (and dysfunctions) beyond those traditionally ascribed to it (**Table 1**). Ann Graybiel's observations that the basal ganglia have learning and memory functions driven by cortically-derived information, identifies them as likely key components in an assortment of behavioral disorders not commonly associated with striatal dysfunctions (for example 1997, 2000).

The comparative approach has brought forth some of the best insights when unlikely constraints on behavior or an unexpected expression of an organism's potential are manifested. A sense of the evolutionary process is evoked when specific traits in various taxa are compared. When they are seen to be related through a possible common ancestor, we can posit a homology between them and explore the ways in which the function of a putative ancestral trait can be adapted by circumstances to the needs of the organism. When comparable functions are performed by fundamentally dissimilar structures, we suspect they are analogous and can speculate on the capacity of organisms to cope in different ways to similar selection pressures. There is a long history of looking to ethology to provide possible models for understanding dysfunctional behavior (White 1974).

TABLE 2. Putative Functions of the Basal Ganglia*

Motor Functions

initiates motor patterns of cognitive or motivational significance (Heimer et al. 1982)

initiates motor patterns of cognitive or motivational significance (Passingham et al. 1992)

motor sequence planning, coordination (Graybiel 1995)

inhibition of competing motor programs (Mink 1996)

Sensory functions

somatosensory motor control (Schneider & Lidsky 1981, other refs in Brown et al. 1997)

somatosensory discrimination; pain (see Brown et al. 1997);

visual discrimination (Pribram 1977) **including facial expression and hallucinations** (Middleton and Strick 1996, other refs in Brown et al. 1997)

auditory (see Brown et al. 1997)

Cognitive functions

cognitive sequence planning (". . . acquisition, retention, and expression of cognitive patterns" Graybiel 1997)

expectations, prediction (ventral striatum, Schultz et al. 1992, Schultz 1998)

attention (Schneider 1984, Parent 1986:247, Brown and Marsden 1998; Hayes et al. 1998)

categorizing (tactile stimuli, Merchant et al. 1997)

learning (Jueptner et al 1997); **procedural memory** (for habits and skills: Jog et al. 1999);

habit learning & acquisition of "non-motor dispositions and tendencies (Knowlton et al. 1996)

classify spatial patterns and serial ordering of sensory events (Beiser & Houk 1998)

executive function (". . . focused and sustained attention in concert with flexibility of thought . . . planning and regulation of adaptive and goal directed behavior . . . [utilizing] working memory . . ." Peigneux 2000; and see Brown et al. 1997)

creativity (ventral striatum becomes activated when predictions are violated by stimuli that appear in an unexpected context: references in Cotterill 2001)

*adapted from Brown et al. (1997), Parent (1986), and MacLean (1990) and others. These are exemplars of research reports and reviews that demonstrate

or suggest the diversity of functions in which the basal ganglia (see table 1) integrates or participates; no attempt has been made to be exhaustive.

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Another powerful way of envisioning the possibilities and constraints of neural structures is through is dysfunction, and the basal ganglia are significant participants in several disorders that provide interesting clues. The study of basal ganglia functions presents a wonderful exemplar of the “logic of the lamppost.” Employing this seductive mode of reasoning, traditionally treated by analogy with looking for lost keys in a dark parking lot where we can search only under the illumination of a solitary lamppost, we tend to forget that the keys may yet be discovered someplace in the darkness. Our illumination until recently has been the more easily discerned evidence of motor dysfunction as a consequence of striatal damage.

Motor functions.

Deficits in motor behavior correlated with basal ganglia damage or insufficiency have dominated perceptions of its function for generations, but among the symptoms of the "Shaking Palsy" described early in 1817 by James Parkinson was also an impairment of intellectual and cognitive processes ("bradyphrenia") with an associated depression sometimes preceding the more overt neurological symptoms. MacLean (1990) pointed out that despite a century of prominent textbooks of neurology expressing great caution if not reserve about regarding the basal ganglia as an organ of motor control, popular textbooks continued to make the point. Autonomic dysfunctions are also present and physical or psychological stress can alter the clinical profile in one of two ways: "freezing", an exacerbation or precipitation of neurological deficits, or "paradoxical kinesia", a sudden transient remission of bradykinesia when confronted with a life_threatening emergency (**Zigmond, Stricker, and Berger, 1987**). The extraordinary expression of motor effectiveness in otherwise dyskinetic Parkinson patients under conditions in which compelling stimuli are suddenly presented (see Brown & Marsden 1998, above), suggests the neurological components of the emergency stress response may be involved (see Greenberg 2001).

Another intriguing dimension of Parkinsonism is an apparently faulty internal model of movement –when an unimpaired person is following the trajectory of a moving target, he can extrapolate to fill in a brief gap in visual feedback, while the Parkinson’s patient cannot, and seems to lose track. This seems related to the fact that while initiation and execution of motor patterns are affected in Parkinson’s, accuracy is largely unimpaired as long as there is feedback from other senses. Indeed, other senses can seemingly ameliorate the disorder (see **Stein 1985**). **Mink (1996)** views motor dysfunctions less as a failure to generate the proper signals than as the result of a failure to successfully inhibit one of several possible competing motor programs that originated with the cerebral cortex or cerebellum.

The presumed dependence on dopaminergic function believed to be at the heart of certain movement disorders was however, being shadowed by other interesting observations. Dopaminergic synapses have been of interest since the 1960s when some anti_schizophrenic drugs were found to have their principal effect by binding to and blocking D2 receptors. This complemented the finding that DA agonists (such as amphetamine) cause

schizophrenic_like behavior. Dopamine, then, may be implicated in cognitive as well as motor functions of the basal ganglia (briefly reviewed by **Roffler-Tarlov & Graybiel 1984**). Even basic personality traits are associated with dopamine. More recently, genetic polymorphisms for a specific dopamine receptors were found to be associated with specific personality types such as “novelty seekers” or “reward-dependent” (Ebstein et al. 1996, 1997). [Novelty seeking, long thought to depend on the way the brain handles dopamine, is one of the variations in temperament suggested by C. Rbt Cloninger on the basis of decades of twin and adoption studies (the other three are harm avoidance, reward dependence, and persistence)(Wash Univ Sch Med, St. Louis, rptd in SN 3/5/94 p.152).]

Stereotyped behavior: Fixed action patterns, stereotypies, and obsessive-compulsive behavior:

Another significant class of motor-related basal ganglia functions are stereotypies and stereotyped “fixed action patterns,” which likely share more than mere etymology. Stereotyped behavior involves fixity of form. Social displays are among the most prominent of these and are excellent exemplars of the evolutionary process of ritualization –the progressive fixity in form that develops over evolutionary time (**Morris 1956, Huxley 1966**). The stereotypy of a display functions to reduce its ambiguity as a communicative signal and enhance the precision of stimulus control. These displays are often cobbled together from fragments of motor patterns and autonomic reflexes and can confer clear adaptive advantages. Unlike most learned or automatized motor patterns, they are presumed to be heavily influenced by genetics but subject to specific shaping during early development (Hailman 1969).

Highly aroused, energized individuals may repeat stereotyped patterns frequently, but such displays also resemble clinical stereotypies, typically expressed at levels of repetition that are clearly inappropriate or dysfunctional. While most dysfunctional stereotypies are manifest in abnormal contexts such as zoos or laboratories or as a result of trauma or extreme stress (discussed below), the stereotyped nature of adaptive expressions of behavior are observed to be spontaneously expressed in natural habitats. The form of such ethological stereotypies, often termed “fixed action patterns” by early ethologists (**Heymer 1977, Tinbergen 1951**) might involve complex motor sequences and were presumed to be under genetic control. Once triggered by an appropriate stimulus (a “sign stimulus” or “releaser”) the sequence was invariably completed.

Among the most interesting of fixed action patterns are those that serve communications. Most displays have evolved from motor patterns or autonomic reflexes with externally detectable expression, and they have evolved under a selection pressure to be unambiguous (**Morris 1956**) and are often used by animals to discriminate members of their own species. Such species_typical behavioral patterns, particularly social displays, have provided much robust data to illuminate neural corollaries of complex behavioral functions. **MacLean (1978)** demonstrated that lesions of the globus pallidus in the area where fibers converge to form the ansa lenticularis, or of the ansa itself, impaired a species_typical “greeting” display in the squirrel monkey, probably by interrupting the pallidal projection to the tegmental area.

The head-bobbing display of the green anole (described below) is such a stereotyped “greeting” display. Imposed upon the stereotyped bobbing pattern are slight variations such as number of bobs, forelimb contribution to the bobbing movement, erection of a slight nuchal crest, or erection of a hyoid bone that extends a conspicuous dewlap, can modify the message to indicate aggressive or reproductive motivation. The expression of these and related units of behavior are presumed to have become progressively more precise and stereotyped because of

an advantage that precision confers, such as the correct identification of the species or gender doing the display. For example, the anole's "signature" display, while precisely executed, is evoked by a broad spectrum of situations but units of behavior are added or deleted to modify the core display and send different messages (**Jenssen 1978, 1979**).

In a sense , stereotypies can be viewed as efforts to reduce stress or discharge high arousal levels channeled by circumstance. Inappropriate motor patterns or their expression in a dysfunctional context characterize dysfunctional stereotypies, and their possible function in reducing stress or arousal levels recalls Freud's famous idea that a neurosis is an attempt at self-therapy. Indeed, in addition to stereotypies, behavioral patterns such as eating, aggression, and sexual behavior in response to mild stress have been characterized as "chemotherapy without drugs" (**Antelman and Caggiula (1980).** Their expression may be significantly affected by progressive sensitization of underlying neural mechanisms attributable to positive feedback from the expression of the behavioral pattern. This possibility has informed the Jacksonian view that stereotypies are expressed when higher nervous functions fail to control motor patterns organized at a lower level (**Dantzer 1986**).

Dysfunctional stereotypies in humans are associated with schizophrenia and early autism where they appear in apparent independence of the environment, and in captive animals or those impaired by brain damage or dopamine-affecting drugs, where they appear more context dependent. Repetitive patterns as rocking movements, grooming patterns, vocalizations, pacing, although apparently rooted in adaptive behavioral patterns, can rapidly become dysfunctional. Clinicians associate them with frustration such as that when a selection cannot be made between incompatible alternatives. A stressfully barren stimulus environment or restrictive confinement and unavoidable stress are also prominently associated with the expression of stereotypies (see **Mason 1991** for a critical review).

Motor stereotypies were found by **Canales and Graybiel (2000)** to be related to an apparent imbalance of activation between the two neurochemically distinct elements of the striatum, striosomes and the extrastriosomal matrix in which they are embedded. When they induced different levels of stereotypy in rats by applying psychomotor stimulants in concert with dopamine receptor agonists, the degree of imbalance between activity of striosomes and the matrix predicated the degree of motor stereotypy.

Motor stereotypies (and possible comparable cognitive phenomena) are often fragments of more complex ensembles. The "chunking" of action repertoires within the striatum was proposed by **Graybiel (1998)** as a counterpart of the older idea of information chunking. As an adaptive mechanism, the assembly, adjustment, and reassembly of a relatively small number of behavioral patterns is much more efficient than the mastery of a huge collection of alternative programmed sequences. For example, the striatal coding of action sequences is apparently reorganized as the learning of new habits proceeds **(Jog et al. 1999)**.

Tom **Insel (1988)** correctly cautioned that the repetitive motor performance of obsessive compulsive disorder may not be homologous, but their common underlying neural circuitry in normal and inappropriate expression may yield important clues about potential sites for therapeutic intervention. Further clues may be expected from considering the selective modulation of circuits by specific elements of the stress response or other neurochemically distinctive mechanisms for maintaining balance between competing, opposing, or complementary systems. It is interesting that stereotyped motor patterns are seen in different but related contexts. Highly adaptive forms such as species-typical displays and clearly dysfunctional forms such as clinical stereotypies are related not only by the fixity of

expression but by a stress-evoking contexts. Indeed, attempts at stress-reduction have been implicated in the etiology of pathological expressions of repetitive motor patterns (**Cooper and Nicol 1991**)

Stereotypies beg comparison with obsessive-compulsive behavior, which has been associated with basal ganglia since at least the mid 1980's (**Cummings & Frankel 1985**). For example, OCD was specifically associated with lesions of the lenticular nuclei, especially the pallidum by Laplane (**1994**) Ranjit C. Chacko and colleagues observed five cases in which the symptoms presented by patients, associated with depression, could be mistaken for a delusional disorder, but more likely involved an impaired cortex-basal ganglia-thalamus-cortex circuit (**Chacko et al. 2000**). In **Baxter's (et al. 2000)** review, activity of the caudate was significantly correlated with that of orbital cortex and thalamus in untreated patients who subsequently responded well to treatment. In a smaller population that did not respond well, the correlation of activity in these brain regions was weaker.

Attention-deficit hyperactivity disorder is, along with Tourette's Syndrome and OCD (with which it is often co-morbid – **Sheppard et al 1999.**) often regarded as a dopamine based frontostriatal neurodevelopmental disorder (e.g., **Bradshaw and Sheppard 2000**). When striatal activity was determined by tomographic assessment of regional blood flow in children with ADHD, it was found to be low (**Lou et al. 1989**). This may be attributable to functional abnormalities of the putamen, as determined by a new type of fMRI used by **Anderson and colleagues (2000)** to look at steady-state rather than dynamic brain activity. Interestingly, students suffering from ADHD appear to have reduced sympathoadrenomedullary responses to cognitive challenge (**Anderson et al. 2000**)

["...correlations between epinephrine (EPI) excretion and classroom performance, the cognition-enhancing effects of EPI infusion, increased EPI excretion with stimulants, and reports of decreased EPI excretion in attention-deficit/hyperactivity disorder (ADHD) suggest that sympathoadrenomedullary function might be altered in ADHD. Correlational analysis of both parent- and teacher-rated behaviors revealed that inattention factors consistently negatively predicted urinary EPI excretion. CONCLUSIONS: The data extend findings of lower adrenomedullary activity during cognitive challenge in individuals with ADHD and suggest that the alteration is associated with inattentive behavior."]

Schizophrenia can also be regarded as a frontostriatal disorder. The dopaminergic systems have long been implicated in the etiology of psychosis and the successes of dopamine-blocking neuroleptic drugs was a major impetus to the so called dopamine hypothesis of schizophrenia. Projections from the ventral tegmental area to the ventral striatum (nucleus accumbens) were especially implicated. **Haber and Fudge (1997)** reviewed the dopamine system with particular attention to its amygdalar connections and hypothesized that overstimulated amygdalar projections to the substantia nigra stimulates excessive midbrain dopaminergic activity. In a review of the few studies that examined pathology of the basal ganglia associated with schizophrenia, **Heckers (1997)** found little support for neuropathies involving regional brain volume or cell density. Neuromodulation, on the other hand, remains an important potential variable. **Graybiel (1997)** suspected that the basal ganglia's potential function as a cognitive pattern generator that parallels its function as an organizer of motor patterns made it a candidate for a role in schizophrenia. Shortly thereafter, **Holt (et al 1999)** hypothesized that cholinergic interneurons of the striatum might be responsible for impaired output and tested the idea by measuring densities of neurons marked by their immunoreactivity to choline acetyltransferase. A patchy decrease in cell densities was identified in the ventral striatum (ventral caudate and nucleus accumbens) of schizophrenic versus control brains. Holt's tentative conclusion is that the reduced function of striatal interneurons disrupted the pathways from ventral striatum that end in the prefrontal cortex.

Stress.

It is significant that the physiological stress response is so intimately involved with the expression or exacerbation of behavioral disorders. The stress response is one of the organisms's most ancient adaptive mechanisms. While typically defined as a response to challenges to the maintenance of homeostasis (e.g., **Moberg 1999**), it also deals with many real or perceived challenges to the capacity of the organism to meet any of a variety of needs (reviewed in **Greenberg 2002**). **McEwen's (1999)** definition of a stressor is particularly useful because it implicitly acknowledges that homeostasis is only the most urgent of many possible needs: "Stress may be defined as a threat, real or implied, to the psychological or physiological integrity of an individual" (McEwen 1999a). Useful recent reviews of the neural and endocrine physiology of stress have been provided by **Axelrod and Reisine (1984)**, who summarized the multiple regulatory mechanisms and interactions of stress hormones, **Goldstein (1987)**, who provided a helpful collation of stress-induced actions of the sympathetic nervous system, and **Johnson and colleagues** (1992) who reviewed stress with an emphasis on the dynamism of endocrine and behavioral mechanisms. Neural pathways were recently reviewed by **Van de Kar and Blair (1999).** The literature on the effects of stress on stereotyped behavior and stereotypies implicates the basal ganglia. For example, **Scott et al. (1996)** bred 5 generations of rats that differed markedly in their susceptibility to showing decreased struggling activity in a swim test after being exposed to an uncontrollable stressor. Compared to susceptible rats, those rats that displayed no decrease in struggling after shock manifested an array of symptoms, including more home_cage activity, larger shock-induced depletions of norepinephrine (NE) and 3-methoxy-4-hydroxyphenylglycol (MHPG) in the locus coeruleus and much higher concentrations of dopamine (DA) and dihydroxyphenylacetic acid (DOPAC) in striatum and nucleus accumbens.

Perceptions of circumstances and their potential challenges to welfare are also important – the phrase "real or perceived" emphasizes the fact among the most potent stressors are expectations. Organisms apparently invoke adaptive responses that are most likely to be adaptive, even under adverse circumstances. A mirror image of the ecological concept of "maximizing" the effectiveness of a strategy relative to cost, the organism's anticipatory stress response can be viewed as "minimizing" the future adverse impact of a prospective challenge to meeting its needs. This is directly related an animal's perception of the "controllability" of the stressful situation, the attribute of a stressor at the heart of the "learned helplessness" paradigm postulated by Martin Seligman and colleagues (e.g., **Seligman 1975, Seligman et al. 1975**).

Interestingly, the effects of stressful experience on the basal ganglia system's mesoaccumbens dopaminergic system is highly dependent on an animal's perceived controllability of the stressor (**Cabib & Puglisi-Allegra 1996**) and the basal ganglia are demonstrably able to couple expectations to sensory input in support of developing new habits (**Schultz et al. 1992**, **Kawagoe et al. 1998**).

[C &P-A, studying animal models of depression, "effects of stressful experiences on behaviour and on mesoaccumbens DA functioning can be very different or even opposite depending on the behavioural controllability of the situation, the genetic background of the organism and its life history. Exposure to a single unavoidable/uncontrollable aversive experience leads to inhibition of DA release in the accumbens as well as to impaired responding to rewarding and aversive stimuli. Moreover, the data reviewed indicate a strong relationship between these neurochemical and behavioural effects and suggest that they could model stress-induced expression and exacerbation of some depressive symptoms such as anhedonia and feeling of helplessness caused by life events as well as syndromal depression provoked by traumatic experiences in humans. Repeated and chronic stressful experiences can reduce the ability of stressors to disrupt behaviour, induce behavioural sensitisation to psychostimulants and promote adaptive changes of mesolimbic DA functioning. Opposite neural and behavioural changes, however, can be promoted in specific environmental conditions

(repeated variable stressful experiences) or in genetically predisposed individuals. Thus, depressive symptoms may not represent the necessary outcome of stress experiences but be promoted by specific environmental conditions and by a genetically determined susceptibility].

Attention.

Teuber (1976) was convinced that, along with motor difficulties, the impairment of striatal structures resulted in characteristic perceptual and cognitive deficits. **Schneider (1984)** concluded from his psychiatric evidence that the basal ganglia play a profound role in attention structure and sensory gating (and see **Parent 1986** on nucleus basalis). The idea that attentional competition involves ventral striatum in a manner parallel to dorsal striatum's apparent involvement in competition between actions was found very attractive to **Dayan et al. (2000)**. They speculated that stimulus reliabilities could be stored in corticostriatal connections while stimulus predictability could be stored in the basolateral nuclei of the amygdala.

Attention has often been associated with human striatal dysfunctions because of the striking phenomenon of paradoxical kinesia. This phenomenon of transient release from akinesia inspired **Brown and Marsden (1998)** to hypothesize that the basal ganglia are integral to nonconscious attention (see below).

> [Brown and Marsden put another aspect of attention at their center of a hypothetical model of basal ganglia function, collating some intriguing observations about the power of synchronized neural processes to focus attention (typically at a nonconscious level) and thereby bind "input to output in the executive forebrain." In their view, basal ganglia facilitate the synchronization of cognitive and motor sequences in a manner much like the synchronization of distributed neuronal responses to various elements of a stimulus situation when one is asked to pay selective attention to it.

They envisioned that basal ganglia damage altered the flow of information from sensory input to motor output. In paradoxical kinesia, if heightened attention is demanded by a specific situation, the impairment may be over-ridden, often dramatically. For example, an akinetic Parkinson's patient might successfully avoid some sudden emergency such as an oncoming car. Brown and Marsden hypothesize that the basal ganglia facilitate the *synchronization* of distributed and perhaps competing neural responses related to action and bring them to focus on a specific motor act or thought sequence, that is, bring them to attention.

The basal ganglia may serve to sort and recombine information about current circumstances and predictions about future possibilities to serve adaptive ends. This view informs **Graybiel's (2000)** hypothesis that A dysfunction of excess (of activation) might lead to repetitive actions or thoughts while one of deficit would lead to a diminished competence of action or thought. **Graybiel and colleagues (1994**) related estimates of future possibilities ("predictive control") to relatively rare but distinctive dopamine-dependent striatal cells that are tonically active and which are recruited and change responsiveness when exposed to stimuli predictive of reward and then diminish during extinction.

> [Abstract The basal ganglia are neural structures within the motor and cognitive control circuits in the mammalian forebrain and are interconnected with the neocortex by multiple loops. Dysfunction in these parallel loops caused by damage to the striatum results in major defects in voluntary movement, exemplified in Parkinson's disease and Huntington's disease. These parallel loops have a distributed modular architecture resembling local expert architectures of computational learning models. During sensorimotor learning, such distributed networks may be coordinated by widely spaced striatal interneurons that acquire response properties on the basis of experienced reward.]

An organism's expectations are apparently reflected in the activity of ventral striatum (**Schultz et al 1992**) apparently as a result of error-signal detection by dopaminergic neurons (**Schultz, Dayan, Montague 1997**). **Schultz (1998)** has observed that the activity of dopamine neurons in the ventral striatum, once evoked by a rewarding stimulus, come to be controlled by reward-predicting stimuli over time. Considering the critical importance of an organism's capacity for making predictions to create associations between stimuli and responses and to help discriminate most favorable responses, ventral striatal neurons are apparently involved in the information processing that underlies motivation (as reviewed by **Schultz 1998).**

> ["Projections from cortical and subcortical limbic structures to the basal ganglia are predominantly directed to the ventral striatum. [Schultz 1998] investigated how the expectation of external events with behavioral significance is reflected in the activity of ventral striatal neurons. In macaque monkeys performing a delayed go-no-go task, "60 ventral striatal neurons showed sustained increases of activity before the occurrence of individual task events. In 43 of these neurons, activations specifically preceded the delivery of reward, independent of the movement or no-movement reaction. In a series of additional tests, these activations were time locked to the subsequent reward, disappeared within a few trials when reward was omitted, and were temporally unrelated to mouth movements. Changes in the appetitive value of the reward liquid modified the magnitude of activations, suggesting a possible relationship to the hedonic properties of the expected event. Activations also occurred when reward was delivered in a predictable manner outside of any behavioral task. These data suggest that neurons in the ventral striatum are activated during states of expectation of individual environmental events that are predictable to the subject through its past experience. The prevalence of activations related to the expectation of reward suggests that ventral striatal neurons have access to central representations of reward and thereby participate in the processing of information underlying the motivational control of goal-directed behavior

. In **Divac's (1977)** attempt to reconcile conflicting views of neostriatal function, he found that even though there was topographic evidence for independent functional units of neostriatal areas receiving specific neocortical afferents, the uniformity of neostriatal cytoarchitecture indicates that these units conducted neural processing of information in comparable ways. This view, in concert with the position of the neostriatum in the chain of neocortical control of motor mechanisms, converged on the idea that the neostriatum Caudate, putamen, and globus pallidus are sometimes referred to collectively as "neostriatum" while nucleus accumbens, olfactory tubercle and ventral pallidum are called "paleostriatum." intermediates between cognition and action. **Divac and Oberg (1979)**, impressed by the fact behavioral deficits subsequent to lesions of the striatum and their cortical projection targets were comparable, suggested that striatum was directly involved in cognition. In this regard it is interesting that **Cools and van der Bercken (1977)** regarded the neostriatum as the substrate of high_order information processing needed to link two or more behavioral acts to form an integrated behavioral program (**Cools 1985**).

The nucleus basalis varies greatly between taxa and is most distinctively differentiated in cetaceans and primates. Functional differences between its neurons and those of other basal ganglia (Parent 1986) and its significant projections to limbic and widespread neocortical sites (MacLean 1990:57) suggest it is likely involved in cognitive functions such as learning and attention, at least in primates (Parent 1986:247).

Among the diversity of significant problems that attend damage to basal ganglia, some resemble specific symptoms of schizophrenia. For example, damage to the substantia nigra in the area where the loop involving TE is likely to synapse (medial pars reticulata) can evoke hallucinations, probably by altering the normal balance of inhibitory and excitatory influences in a way that results in abnormal excitation of *Area TE*, known to be able to stimulate hallucinations. **Middleton and Strick (1996)** point out that the visual anomalies attributable to interfering with the TE striatal loop are much like those sometimes seen as a side effect of dopaminergic therapy for

with the TE-striatal loop are much like those sometimes seen as a side effect of dopaminergic therapy for parkinsonism, “Might this mechanism also underlie the hallucinations of schizophrenia?” they ask. There is supporting data, they note, indicative of significant changes in activation of areas that participate in the proposed loop during hallucinations of schizophrenics. A detailed and closely reasoned argument for the involvement of basal ganglia in the etiology of schizophrenia was advanced by **Graybiel (1997).**

The major output structures of the basal ganglia, **GPi and SNr,** report back to the ventral anterior and lateral thalamic nuclei, which then project back to the cerebral cortex. **Parent & Hazrati (1995a)** regard this as a source of redundancy which can make the same information available to different brain centers. Their analysis includes targets of the GPi and SNr, such as the *centromedian thalamic nucleus* (which receives information from cortical motor and sensory cortices as well as brainstem reticular information), the *habenula* (a major limbic relay which may constitute a functional limbic interface with basal ganglia), and the *pedunculopontine tegmental nucleus* (which may be a functional interface between cerebellum and basal ganglia). Other targets are functionally associated with memory, rewarded motor behavior, and various ways of combining cortical information at the striatal level.

Selective neurochemistry is the key to our fullest understanding of function. For example, there is a growing sense that the reward functions of dopamine are less significant –and may even be explained by– its role in underscoring the significance of stimuli that *predict* reward. This in part helps explain why non-rewarding behavior may be manifest if it is associated with a dopamine surge, as is often the case in addiction to cigarette smoking or cocaine use (See brief review by **Wickelgren 1998** and references therein). Another unexpected way dopamine affects behavior was shown by **Hayes (et al.1998)** on Parkinson’s patients asked to shift attentional set (the conditions that regulate responding, executive process) from (for example) the color of a stimulus to its shape as a cue for a response. These patients were significantly slower than control subjects and had difficulty filtering a competing but irrelevant set. When the deficit in switching was correlated with the amelioration of motor symptoms attributable to an l-dopa-based medication, it became apparent that deficit is based on dopamine insufficiency.

Memory and its disorders.

Participation of the corpus striatum in long-term memory systems, classically known from studies of patients with brain lesions has been more recently complemented by functional neuroimaging techniques. This information was reviewed recently by Gabrieli (1998), who observed that basal ganglia are significantly involved, particular in declarative memory (involving conscious or intentional recollection) and strategic memory (involving the evaluation, manipulation, and transformation of retrieved declarative memories). The pattern of memory impairment and reasoning in diseases of the basal ganglia such as Parkinson’s or Huntington’s led Gabrieli to hypothesize that strategic memory impairment is a result of limited reasoning ability attributable to reduced capacity for working memory. A decline in working memory, reasoning, and strategic memory seems to correspond to normal 5-10% per decade reduction in dopaminergic function across the life span, however Gabrieli is careful to point out that the extent to which these functions are causally related rather than merely correlative has not yet been determined (1998).

Basal ganglia are associated with human amnesia indirectly because that dysfunction is a core symptom of Alzheimer’s disease which also involves (among other things) a loss of cholinergic cells in the basal ganglia.

Hemorrhage-induced basal forebrain damage can also impair memory. But the role of the basal ganglia are generally regarded as uncertain because there is generally related damage to medial temporal (much more often associated with amnesia) or frontal lobes. This situation is reviewed briefly by Goldenberg (et al., 1999) who observed a patient with amnesia who suffered damage limited largely to the nucleus accumbens. By excluding the roles of structures that suffered collateral damage and because the n. accumbens is positioned to "integrate inputs from multiple cortical and subcortical areas including the hippocampus and the amygdalae, and to exert modulatory influences on widespread cortical function," the authors conclude the n. accumbens is an important candidate for direct involvement in memory processes (and see an editorial commentary by Mayes 1999).

Confabulation may be a related disorder of episodic memory generally in concert with faulty executive functions. Although associated with forebrain dysfunction, it has presented itself after focal basal forebrain damage in way suggesting that both circuits from striatum to both medial temporal and frontal lobes must be simultaneously impaired (Fisher et al. 1995, Hashimoto et al. 2000) When lesions were limited to the basal forebrain, a more transient expression of confabulation may result (Fisher et al. 1995).

Cognition.

The sensory and multimodal cortices of the forebrain receive information about the world, analyze it, and share it with the prefrontal association cortex where it may be incorporated into complex, often skilled, adaptive actions implemented by means of the premotor and motor cortices. Many theorists assume the function of cognition is to model reality by selective simplification of received information. In this, shared properties of stimuli are important in the economy of cognitive functions, and it is often assumed that the simplest generality possible that is not contradicted by experience is utilized. But modeling also involves potential responsive actions and in this the extrapyramidal and cerebellar control systems may provide essential support. The selection or execution of actions are then more or less energized by the perceived relevance of the situation, necessarily involving motivational and affective variables.

Nieuwenhuys' (1996) reviewed the "greater limbic system" and its constituent "emotional motor system, " which probably executes emotional and motivated behavioral patterns by means of fibers from the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and the lateral hypothalamic area. [the system also his monoaminergic fibers descending from medial hypothalamus and midbrain to modulate spinal sensory and motor neurons (Reviewed by Nieuwenhuys 1996]. The striatum is barely mentioned: ventral striatum is identified as a participant in a loop involved initiating locomotor activity (p. 575). The large association area of the frontal lobe, however, manifests a pattern of linkages in its outflow in which cascades of short association fibers connect successive structures, suggesting their participation in the planning and sequencing of complex motor tasks (Nieuwenhuys 1996 citing Fuster 1991).

Ann Graybiel (1995) gave important impetus to the view that the "basal ganglia . . . are critically involved in building up sequences of behavior into meaningful, goal-directed repertoires." Her review indicates, as she put it, ". . . that the basal ganglia act as part of a distributed forebrain system that helps to encode such repertoires through behavioral learning, and that is engaged in the expression of such repertoires once they have been internalized. The basal ganglia also may be critical to the expression of innate behavioral routines. Experimental findings on reward-based learning suggest that neural activity in the striatum and substantia nigra, pars compacta changes during behavioral learning. New evidence also suggests extreme specificity in the neural connections interrelating

the basal ganglia, cerebral cortex and thalamus. Adaptive control of behavior may centrally depend on these circuits and the evaluator-reinforcement circuits that modulate them."

Graybiel (1997) came to call the sequences "cognitive pattern generators" and she suggested that "by analogy with the central pattern generators of the motor system . . . these pattern generators operate to organize neural activity underlying aspects of action-oriented cognition. It is further proposed that the basal ganglia are involved in the control of cognitive as well as motor pattern generators. Disorders of the basal ganglia may thereby contribute to neural circuit dysfunctions that are expressed as positive and negative symptoms of schizophrenia." Further, they are likely important in initiating volitional activity (Graybiel 1990).["The positive and negative signs of basal ganglia disease provide strong clinical evidence that the basal ganglia and allied nuclei participate in the neural mechanisms underlying volitional activity. [Graybiel's chapter] reviews the range of neural subsystems in the basal ganglia that may contribute to these functions and their relationships with the dopamine-containing cell groups of the substantia nigra."]

Cotterill (2001) echoes Mink's (1996) idea that basal ganglia control activity mainly by the inhibition of competing motor programs (above) but goes further in his belief that modulation of sensory cerebrum signals to motor areas by the basal ganglia and cerebellum can lead to cognition and consciousness. Assuming the primacy of output over sensation for adaptive behavior, Cotterill considers that consciousness serves mainly to review probable outcomes of likely motor patterns in a given situation and hold those that have potentially adverse outcomes at a subthreshold level — thought but not actions.

Connections and loops between basal ganglia and other sites associated with cognitive function further underscores the adaptive potential of these structures. The cerebral frontal, parietal, and temporal cortices provide input to the basal ganglia, while only the frontal lobe was believed to be a major target of the striatum. The inferotemporal cerebral site known as Area TE is one of two specific visual areas associated with visual discrimination and recognition, and has recently been determined to also receive from as well as project to the basal ganglia. Using retrograde transneuronal tracers, **Middleton and Strick (1996)**. observed that the pars reticulata of the substantia nigra, a major striatal output nucleus, projects back to TE by means of the thalamus. In the authors' view, if a portion of these connections forms a closed loop, as seems likely, striatal structures could influence high order visual processing, which could explain some perceptual anomalies as well as movement disorders.

[The basal ganglia are known to receive inputs from widespread regions of the cerebral cortex, such as the frontal, parietal, and temporal lobes. Of these cortical areas, only the frontal lobe is thought to be the target of basal ganglia output. One of the cortical regions that is a source of input to the basal ganglia is area TE, in inferotemporal cortex. This cortical area is thought to be critically involved in the recognition and discrimination of visual objects. Using retrograde transneuronal transport of herpes simplex virus type 1, we have found that one of the output nuclei of the basal ganglia, the substantia nigra pars reticulata, projects via the thalamus to TE. Thus, TE is not only a source of input to the basal ganglia, but also is a target of basal ganglia output. This result implies that the output of the basal ganglia influences higher order aspects of visual processing. In addition, we propose that dysfunction of the basal ganglia loop with TE leads to alterations in visual perception, including visual hallucinations .]

A strict segregation of striatal output pathways, however, is less certain in light of findings by Parent and others (briefly reviewed in **Parent et al. 2000**) of striatal efferents with highly collateralized axons most of which reach two or three target structures. "It is now apparent," Parent et al. write, "that the basal ganglia system is a complex and widely distributed neuronal network" (2000:S23).

Creativity.

Creative behavior, despite its obvious significance in behavior is “one of psychology’s orphans” (**Sternberg and Lubart 1999**). Its neuropsychological causes and consequences are rarely approached by researchers, largely due to traditions of scholarship and academic parochialism. When carefully defined in terms of biological adaptation, however, creativity is accessible to the scrutiny of neuroethology.

[Creativity involves both the process and product of unprecedented or novel perception, thoughts, or actions by which an organism or group of organisms copes with present or potential changes in the composition and structure of its environment. In particular, it reflects an enhanced intensity of perception, cognition, and expression which occurs either spontaneously or is elicited by specific stimuli to relate and integrate variables not ordinarily associated with each other” --Greenberg 2001]

The capacity to generate innovative responses represents a behavioral trait of the highest importance, particularly when an organism confronts unique internal or environmental challenges to the its capacity to meet its needs. Indeed, the stresses evoked by environmental change can affect organisms in ways that require novel ways of coping which can change selection pressures in ways that feedback to affect their subsequent evolution (see eg, **Jablonski & Bottjer 1990, Hoffmann & Hercus 2000**). Adaptive behavior is the outcome of the assimilation of a continuing stream of experience into the structure and coordination of the brain. Coping with challenges to meeting adaptive needs almost constitutes a working definition of stress, and in light of recent ideas about the effects of coping on selective activation of specific pathways (for example **Huether 1996**, **Greenberg 2002**), specific neurophysiological components of the stress response may well be central to the expression of creativity as well as its continuing adaptive function. But deviation from the norm is a hazardous business and thus creativity and dysfunction are hazardously close, linked often at least in popular culture.

Among the hallmarks of creative behavior is the recombination of information from different sources in novel and potentially useful ways. The striatum may well be capable of combining information from different cortical areas as their respective terminal fields converge (see **Parent & Hazrati 1995a**). Adaptive and dysfunctional creativity both depend upon the selective expression of neural events that ultimately result in the creation and/or expression of novel neural constructs, typically known by their influence on behavior. These may represent familiar things seen in new ways, new things seen unhindered by their evocation of stereotypes, and various combinations of clarity of discrimination or categorizing. **Cotterill (2001)** reviews the idea that stimuli detected out of expected context likely activate ventral striatum, as it monitors the reliability of predictions made in the prefrontal cortex. Expectations may be cognitive as well as motor and the fact that the chemical signals of the stress response is evoked by even mild dissonance (**Hadley 1996**) such as discrepancies between perceptions and expectations (**Goldstein 1987**), it is reasonable that the basal ganglia, known to be sensitive to stress(**Zigmond, Stricker, and Berger 1987; Salamone 1994)**are deeply involved.

[Some models of creativity depend heavily upon pattern matching and completion (**Boden 1990**), however among the distinctive aspects of creativity is the breaking out of patterns, or the identification of previously unrecognized patterns, activities which likely involve the basal ganglia. The basal ganglia system is exquisitely sensitive to patterns as well as motor and cognitive sequences, the assembly and disassembly of which are responses to developmental or external needs.]

NEUROETHOLOGY OF STRIATAL FUNCTIONS IN A REPRESENTATIVE REPTILE

Reptiles and Reptile Neuroethology.

Can we penetrate appearances, misconceptions, and tangled nomenclature to the underlying common features that could link the rich mammalian literature with findings in reptiles? In their analysis of the paleostriatal system (PS) of Caiman and their comparison of this reptilian PS with both avian PS and mammalian basal ganglia, **Brauth and Kitt (1980)** concluded that overall design and possibly function is comparable in these three taxa and indicate a common function in spatial orientation and attention. (Paleostriatum is also termed ventral striatum by many authors while the overlying dorsal ventricular ridge (DVR) is also termed, dorsal striatum; the reptilian nucleus accumbens just medial to the PS is probably homologous with that of mammals (Parent 1986)). Unlike mammals which have comparably rich ascending and descending pathways from the basal ganglia, the corresponding structures in reptiles influence motor patterns only by descending pathways (**Parent 1986**). The dorsal ventricular ridge (DVR) has long been suspected to be related to the prominence of species-typical motor patterns in the life of reptiles (**Bellairs 1970: 336**).

When **Marín, Smeets, and González (1998)** integrated their work with the amphibian basal ganglia into a phylogenetic overview, they discerned dorsal and ventral striatopallidal systems in all tetrapods. Inputs from the thalamus and cortex ("pallium" in lower vertebrates) are always through the striatum and provide access to several classes of information. The cortex of mammals has excellent representation in the striatum, whereas the reptilian basal ganglia receives most of its projects from the dorsal ventricular ridge. This large distinctive subventricular structure is apparently derived from the pallium and often compared to isocortex of mammals. Further, the proposition that well organized projections of modulatory dopaminergic neurons from a substantia nigra/ventral tegmental complex to dorsal and ventral striatum in all tetrapods can be defended by new findings in amphibians. They concluded that although many functions of the basal ganglia system are unique to mammals, the conservatism of the system is remarkable. There is, however, an interesting difference detailed by **Clark & Baxter (2000).** They used a radio-tagged marker (125I-DOI) that is preferentially binds to specific classes of serotonergic receptors. While such staining highlights a patchy striosomal pattern in mammals, the lizard, *Anolis carolinensis* shows no such pattern.

The successes of the ethological method are grounded in close observation of behavioral patterns spontaneously performed in nature or in response to naturalistic stimuli. The heuristic power of a coordinated concern for the questions and methods of developmental biology, ecology, evolutionary biology, and physiology have informed ethological understanding ever since **Tinbergen (1951)** identified these perspectives. The ignorance of critical life history variables and the arbitrariness of stimuli for which organisms are unprepared had become progressively misleading to students of behavior even as they began to appreciate in principle the comparative method. Complementary detail from neurology, the growing clarity of neurotransmitter specificity and distribution, and even the promise of functional radiology, are converging on a newly invigorated understanding of adaptive constraints and possibilities as individuals as well as species endeavor to cope with a dynamic environment.

Species-typical Behavior of the Green Anole.

Research on the function of the reptilian corpus striatum is based on a detailed ethological study of social behavior of a lizard, the green anole, *Anolis carolinensis* (**Greenberg 1977**) in conjunction with an atlas of the

forebrain (**Greenberg 1982**). The fine-grained resolution of such ethological studies are important to a fuller understanding of behavior that are very likely amalgams of several units of behavior, each with their own respective evolutionary and developmental histories. Such ensembles of units of behavior often acquire communicative significance and their continuing evolution to become more precisely evoked and effective as a signal is termed "ritualization." In evolutionary terms, brains are conservative: most internal change is driven by environmental change and stresses they place on the organism. As the stimulus control of units of behavior and their orchestration shifts, proximate neural causation is affected and to the extent the change is adaptive, becomes a new selection pressure for evolutionary change in the brain.

When reproductively active male green anoles in a laboratory vivarium are confronted with an intruder, they respond with a characteristic sequence of displays. A typical first response is the "assertion" display. It is the definitive species-typical "signature" of many lizards, *Anolis carolinensis* included. In most lizards It is performed by highly alert animals, possibly patrolling their territories. It is often seen in the absence of any apparent specific stimuli or when an intruder of either sex becomes apparent to the focal animal. It is also commonly seen when a lizard is apparently startled by (for example) a sudden move by another lizard of another species or even by an insect too large to be regarded as prey. In other words, it is an indication of elevated non-specific arousal rather than a response to any specific evocative stimulus.

The "signature" display of a green anole also serves as an "advertisement." If a sexually responsive female conspecific intrudes into a displaying male's territory and observes his display, she may provide feedback indicative of status as a potential mating partner. Most commonly this is by responding to the assertion display with a species-typical head-nodding behavior. This response generally elicits a switch in the male's behavior to courtship: a series of rapid nods performed while approaching with a unique "strutting" gait. If an intruder is a male, on the other hand, and reacts with his own sequence of headnods coordinated with push-ups and extension of the dewlap, the resident will rapidly escalate its display into "challenge" (Fig. 2d).

By virtue of the display, with its species-typical sequence of headbobs and pushups, the resident apparently "recognizes" the intruder as a member of the same species. In this context, the display is complemented by postural changes: the animal expands the sagittal profile of his body and displays to the intruder in a manner that maximizes its apparent size. As aggressive encounters escalate, the male's behavior is accompanied by autonomic responses: After about 30 seconds, an erectile crest will appear along its neck and back and body color darkens. A black "eye-spot" appears just behind the eye. The intruder responds in kind as they stalk each other with slow, deliberate, apparently tense movements. In both lizards, the episode is often accompanied by changes between green and brown body color as the animals appear to assess their position relative to each other. In *Anolis carolinensis*, body color is dependent upon the flux and changing ratios of epinephrine and norepinephrine and relative autonomic tone may be important: the male that first manifests the eyespot invariably wins the contest (Summers & Greenberg 1994)

Forebrain Control of Species-typical Behavior in a Lizard.

Studies in which the brain was explored by electrical stimulation failed to reveal sites of influence on stereotyped responses In the brain of *Iguana iguana* **(Distel 1978).** Locomotion was occasionally elicited by stimulation [in several sites?], but tongue_flicking behavior was reliably elicited in the lateral striatal area, although the stimulation

of more medial sites resulted in the greatest number of such responses of any site investigated, possibly due to the proximity to olfactory structures. Work by **Sugerman and Demski (1978)** on another iguanid lizard species, *Crotaphytus collaris*, did elicit stereotyped agonistic behavior in response to electrical stimulation at several sites that roughly formed a column from the telencephalon to the rhombencephalon, but striatal sites were not tested. **Tarr (1982)** specifically stimulated striatal sites in the fence lizard, *Sceloporus occidentalis*, and observed stereotyped assertion displays at or near the tip of the lateral ventricle__nucleus accumbens. Points eliciting the more complex challenge displays were just anterior and dorsal to the nucleus sphericus in the posterior area of the dorsal ventricular ridge. Interpretation of stimulation experiments is always complicated, as **Distel (1978)** has indicated, by the difficulty in discriminating direct motor stimulation, sensory excitation, motivational changes, or general arousal. Much the same problems plague interpretation of lesion experiments, but still the techniques, in concert with further knowledge of striatal anatomy, will help point the way to progressively more specific hypotheses that can significantly inform future investigations of function.

Forebrain lesions. Many of the aforementioned attempts to identify a brain region with aggressiveness or stereotyped behavior were difficult to interpret because of the diversity and non-specificity of effects caused by the treatment. In a series of experiments devised in the MacLean lab, we hoped these difficulties could in part be circumvented by taking advantage of the natural spilt-brain preparation that lizards provide. The absence of a corpus callosum in this taxon **allows us** to experiment with unilateral lesions, which provides the advantage of each individual being his own progressive control. Responses of animals tested when visual input went to the lesioned hemisphere had as progressive, perfectly matched controls, tests with visual input directed to the intact side (**Greenberg et al, 1979**). Lizards were anaesthetized in crushed ice and small electrolytic lesions placed at specific coordinates determined with the aid of a stereotaxic atlas devised for the purpose (**Greenberg 1982**; animal care and research protocols in **Greenberg 1992**).

The behavior of lizards after surgery gave no evidence of any impairment of behavior until they were confronted with intruding conspecifics. Only then was it clear that lesions of the paleostriatum of male anoles profoundly alters their social dynamics. Where vigorous territorial combat might be expected when an individual views an intruding conspecific (**Greenberg 1977**), the brain-lesioned resident, while responsive to the presence of the intruder, is unresponsive to the species-typical releasers of territorial aggression it provides (**Greenberg et al., 1979**). This inability to recognize appropriate stimulus input might be characterized as "social agnosia." Interestingly, a striatal role in visual discrimination was already indicated by a lesion study of the forebrain of the turtle, *Chrysemys* (**Reiner and Powers 1980**). In other experiments, lizards with comparable lesions courted females quite normally (**Greenberg et al. 1984**).

An analysis of the forebrain activity of green anoles was undertaken by **Baxter** (**1999, Baxter and Ackerman, 1997**) who used the eye-patch technique to limit visual input to one hemisphere or the other and then used a radio-tagged glucose (2-deoxyglucose, 2-DG) to indicate areas that were metabolically active. After injecting 2-DG, they placed animals in habitats with a mirror that effectively evoked displays from isolated, dominant or subordinate males. Using this technique they determined that the hemisphere which received visual input was significantly more active than the contralateral, “eye-patched” hemisphere. The dorsolateral basal ganglia **(DL-BG)** was particularly active, and the number of aggressive pushup displays performed correlated with the activation in the “seeing” dorsolateral basal ganglia’s activation.

Subsequent analyses were performed on individuals who had established a dominance relationship and then isolated in a vivarium with a mirror. They each responded accordingly to their image with their “status-typical” display, and demonstrated that not only was activity increased in the “seeing” DL-BG of animals performing aggressive displays, but decreased in the “seeing” ventromedial basal ganglia (VM-BG). Further, the subjects that were submissive in the presence of the social dominant showed 2DG diminution in DL-BG and increased VM-BG activity. Interestingly, activity a lateral segment of the overlying anterior DVR was correlated with DL-BG activation while a medial portion of the aDVR showed 2-DG accumulation when VM-BG showed activity.

Social Dominance. If intact animals, fresh from the field and known to be reproductively active are allowed to cohabit a vivarium after a territorial confrontation, the winner typically goes about his business, alert to the cohabiting loser, but generally unperturbed as long as the loser responds with appropriate indications of deference when subjected to an occasional challenge display. A classic social dominance relationship has been established. The winner monopolizes the best sites to watch for predators, prey, or mating opportunities, while the loser, no less active in foraging or feeding acts with apparent indifference to the trappings of power. Observed for as long a month in this condition, such subordinate males were found to halve roughly half the normal circulating levels of the hormone testosterone (Greenberg and Crews 1990), indicating that the change in behavior subsequent to losing a fight is more likely a consequence of an altered hormone-mediated motivational state than a conditioned response to a more powerful cage-mate.

The significance of the famous bobbing display and its variations awaits the clarifying resolution of ethological analysis to more full appreciate the significance of their control by the basal forebrain. It seems relevant, however, that the ability to express the species typical action pattern is unaffected, but the capacity to recognize a conspecific and manifest the appropriate response to an intruding male’s species typical display is profoundly impaired. This is not a mere motor impairment. If the consequences of basal ganglia lesions can be construed as social agnosia, a defect of cognitive processing, is the process impaired in this lizard? It is interesting that in mammals, one of the several cerebral cortical inputs to basal ganglia is area TE in the inferotemporal area. This is interesting because this area, apparently essential to visual recognition and discrimination, also receives input from substantia nigra pars reticulata via the thalamus, creating a circuit that allows basal ganglia to “influence higher order aspects of visual processing” (**Middleton and Strick 1996**). Possibly related is the finding that rats which work for stimulation of their nucleus accumbens will reduce their responding under uncontrollable (but not controllable) stress in a way which indicated a loss of “reduction of the reinforcing or motivational value associated with the stimulation” (**Bowers et al. 1987**), recalling the social agnosia of paleostriatal lesioned lizards mentioned earlier.

> ["Cognition" refers to the mechanisms by which animals acquire, process, store, and act on information from the environment. These include perceptions, learning, memory, and decision making " (p5). Thus Sara J. Shettleworth (Cognition, Evolution, and Behavior; Oxford 1998) defines the term essentially as *information processing involving mental representations* –what Gallistel (1990 cited by Shettlesworth) calls *functioning isomorphisms between brain processes and events in the world.* Adaptive behavior arises because, in effect, brain processes perform computations on incoming information that transform it to appropriate behavior. "Cognitive Ethology" has been defined as "*the study of the mental experiences of animals, particularly in their natural environment, in the course of their daily lives*". . . . . Thus, broadly described, research in cognitive ethology includes any mental experiences and processes, including studies of habituation and sensitization, learning and memory, problem solving, perception, decision making, natural communication and the artificial languages taught to apes, dolphins and parrots. (Cognitive Ethology, Carolyn Ristau, MIT ECS (downloaded Oct 9, 2000). In Culture and Cognition (Ronald Schleifer,

Rbt Con Davis and Nancy Mergler 1992 Cornell Univ Press): "In other words, cognition itself, as a concept an object of scientific inquiry in the twentieth century, has been understood to be the simplification and generalization of experience" (P 38). . . . "a simplified representation of the operational environment." But more useful are Russell's comments recounted by Pat Duffy Hutcheon in her *Leaving the Cave* (Wilfrid Laurier UP 1996) "A belief, then, said Russell, 'is a certain state of the muscles, sense organs and emotions, together perhaps with certain visual images' (1948:155). Pre verbal experiences of relations in nature shared by all animals to some degree" (p302).]

Neurotransmitters in the behavior of anoles. When territorial lizards confront each other in an experimental vivarium in which they likely perceive each other as intruders. As observed in tests described above, losers of territorial fights invariably became socially subordinate, displayed darker color, selected lower perch sites, and maintained lower body posture than the winners. The subordination was unambiguous. When midbrain and hindbrain were analyzed for indolamines, catecholamines, and their metabolites by coulochem electrode array high pressure liquid chromatography, Cliff Summers and I learned that **central serotonin production and turnover is more rapidly activated in losers of fights** (destined to behave in a subordinate way) than in winners (Summers and Greenberg 1995).

A closer analysis revealed that serotonergic activity in dominants and subordinates had a distinctive time course as well as regional distribution in the brain (Summers et al 1998). Brain slices of dominant and subordinate males were micropunched to isolate specific areas and each then analyzed by high pressure liquid chromatography (HPLC). We found the greatest serotonergic changes were detected in the telencephalon of subordinate males. One hour after a fight, hippocampal cortex and nucleus accumbens showed increased ratios of 5-hydroxyindoleacetic acid/serotonin. Just as in earlier studies of the brainstems of these animals (**Summers and Greenberg 1995**), the ratio gradually decreased as the animal's social status became consolidated, and within one month, ratios had returned to normal. Measured in the brains of lizards sacrificed at an hour, day, week, and month following a fight, changes were seen to be more rapid in dominant males. The patterns of serotonergic activation are so similar in hippocampus, nucleus accumbens and brainstem that a co-ordinated response may be involved in mediating short-term social stress and aggression. Similarly, medial and lateral amygdala exhibit corresponding, but delayed patterns in subordinate males, suggesting a co-ordinated response in these regions mediating longer-term stress responses. (**Summers et al. 1998**).

Interestingly, low serotonin levels in the brains of a primate model have been associated with impulsiveness. [Higley, J.D. and M. Linnoila. 1997. Low central nervous system serotonergic activity is traitlike and correlates with impulsive behavior. A nonhuman primate model investigating genetic and environmental influences on neurotransmission. Ann. N.Y. Acad. Science. 836:39-56.] Recent work by Baxter (1999) has shown in the *Anolis* lizard model that beyond a sharp increase in forebrain serotonin during dominant displays and a decrease during subordinate displays, there was an activation of dorsolateral basal ganglia and deactivation of the ventromedial area. Clark and colleagues went further to analyze the subtypes of serotonin receptors and their distribution in *Anolis carolinensis,* confirming important commonalities with other taxa (**Clark and Baxter 2000**). In a series of analyses on dopamine receptors, the occurrence, distribution, and pharmacological specificity of dopamine D1 and D2 receptor sub-types were also seen to be similar to those of mammals. One interesting difference, however, is that neural tissue in the parts of basal ganglia outside the ventral striatum (see Table 1) characterized by D1 and D2 receptor subtypes is largely separated, rather than co-mingled as in mammalian basal ganglia (**Clark et al. 2000**).

[Clark et al. "used in situ autoradiographic ligand binding methods to determine the occurrence and distribution of dopamine D1 and D2 receptor sub-types in the anole lizard, *Anolis carolinensis*. Both were present and exhibited pharmacological specificity

and D2 receptor sub-types in the anole lizard, *Anolis carolinensis*. Both were present and exhibited pharmacological specificity characteristics similar to those described for mammals. However, unlike in mammals where in the neostriatum [outside the nucleus accumbens/olfactory tubercle complex (NA/OT)] these receptors exhibit only slight dorsolateral (D2 high, D1 low) to ventromedial (D1 high, D2 low) gradients that co mingle extensively, in the anole striatum outside the NA/OT there was a striking laminar pattern, with little if any overlap between D2 (high in a dorsal band) and D1 (high ventral to the D2 band) distributions. As D1 receptors are related to the direct and D2 to the indirect basal ganglia (BG) subsystems in mammals, we also determined anole striatal distributions of pre-proenkephalin mRNA, a marker for striatal efferents to the BG subsystem in mammals. Here, too, there was a striking laminar pattern, with pre-proenkephalin mRNA in a band similar to that seen for D2 receptors. The crisp neuroanatomical separation between these classic BG subsystem markers in *Anolis* striatum make this species attractive for the study of such systems' functions during behavior.

"From the cortex there is a direct and an indirect signal pathway through this conglomeration, maintained by circuits that use different neurotransmitters, such as GABA, glutamate, enkaphalin and substance P. There is a delicate balance between these two pathways that is partly maintained by dopamine release from the substantia nigra to the striatum. Dopamine release inhibits the indirect pathway by stimulating dopamine D2 receptors, and excites the direct pathway by stimulating the dopamine D1 receptor (recall the The Dopamine Theory of Parkinson's Disease: , Alexander P.M. van den Bosch November 22, 1996] [The motor circuit consists of direct connections between the putamen and internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr); and an indirect pathway from the putamen to the subthalamic nucleus (STN) via the external segment of the globus pallidus (GPe), and then back to the GPe, GPi, and SNr. GPi and SNr project to the thalamus and brainstem.–Brown & Marsden 1998][The subthalamic nucleus and the external pallidum (GPe) are classically viewed as part of the so-called indirect pathway, which acts in concert with the direct pathway. The direct and indirect pathways form the conceptual framework of the anatomical and functional organization of the basal ganglia. --Parent & Hazrati 1985]

Subsequent work on free-ranging lizards, *Sceloporus jarrovi*, provided consilient results: tissue samples from their telencephala and diencephala that were analyzed for monoamines, their precursors and metabolites, revealed significant differences according to social status. There was more serotonin activity and turnover in subordinates (satellite males without territories) compared to territorial males (Matter et al. 1998). Such findings also agree with findings in fish (Winberg and Nilsson 1993) and mammals (Yodyingyuad et al. 1985, in primates), suggesting a phylogenetically conserved mechanism of monoamine behavioral modulation.

Aggression is stressful in the short run whatever one's status and whatever the outcome –but the *experience* of that stressful episode apparently evokes different long-term consequences for winners and losers. Wins or losses, real or perceived, likely lead to significantly different endocrine tone. Serotonin elevation is associated with acute stress in all animals studied (e.g., **Winberg et al., 1992 a,b** among others) but only in losers of encounters does serotonin elevation persist.

Other data supportive of the idea of the relative *resilience* in dominants is apparent in color change data. In *Anolis carolinensis,* the circulating epinephrine-dependent eyespot appears earlier during an aggressive exchange in the future-dominant, and fades more quickly (Summers and Greenberg 1994).

The basal ganglia, the integrity of which is essential to an expression of a green anole's aggressive display, also mediates displays that characterize social status. Baxter and colleagues measured both activation of forebrain sites and changes in function in lizards displaying the pushup and profile change that characterize aggressive dominants and those that characterize subordinates. In dominant animals but not subordinates, increased 5-HT correlated well with dorsolateral basal ganglia activation. The complete decussation of optic tracts in anoles was exploited by Baxter in much the same manner as Greenberg, to direct visual stimuli to a hemisphere that can then be compared to the contralateral hemisphere for an effect. The glucose mimic, 2-DG (14C-2-deoxyglucose)

be compared to the contralateral hemisphere for an effect. The glucose mimic, 2-DG (14C-2-deoxyglucose) accumulates preferentially in more active cells. When eye-patched lizards were housed together, dominants and subordinates came to express their respective social displays repeatedly to mirrors, and accumulations of 2-DG were seen in the basal ganglia only of dominants and only in the hemisphere opposite the unpatched eye.(**Baxter et al. 2000**).

Connections. As mentioned earlier striatal structures in reptiles differ from those of mammals in that descending pathways predominate (**Parent 1986**). An alternative attempt to clarify the connections and role of paleostriatum involved the use of a neurotoxin that will selectively destroy dopaminergic cells. The meperidine analog, MPTP, was believed to be toxic to dopaminergic cells by its being selectively incorporated into neurons through their re_uptake systems. The procedure became popular because the symptoms produced can be similar to idiopathic Parkinson's disease (**Marsden and Jenner 1987**), presumably by means of toxic effects on the dopaminergic substantia nigra pars compacta, although some studies also report effects in locus caeruleus and the ventral tegmental area (reviewed by **Langston and Irwin 1986**). While the primary site of cell death is the pars compacta of the substantia nigra (SN), the adjacent ventral tegmental area and other sites are also often affected. The selectivity appears sensitive to both the age of the animal (less selective in older subjects, **Marsden and Jenner 1987**) and the amount of MPTP administered. In fact at low levels, many SN cells may survive while conspicuous mesostriatal axonopathies appear and tyrosine hydroxylase immunoreactivity in the striatum decreases (**Kitt et al. 1987**).

MPTP experiment. To help us confirm and extend our understanding of dopaminergic pathways and their possible influences on behavior, several *Anolis carolinensis* were injected intraperitoneally with varying doses MPTP. At high doses (100 mg/kg) the lizards showed postural rigidity, convulsions, stereotyped head and neck movements, and died within 24 hrs of injection. Lower doses resulted in a transient behavioral syndrome consisting of hypokinesia and signs of adrenal activation. Acute behavioral changes in MPTP_treated animals included indications of a physiological stress response and, in particular, color changes, including the formation of a post_orbital darkening (the "eyespot"), and nuchal crest erection, both indications of adrenal activation (see **Greenberg and Crews 1983**). These effects and a pronounced hypokinesia remitted in all but 8 individuals who received in excess of 50mg/kg of the drug and subsequently died. These individuals also developed akinesia, postural rigidity, episodic convulsions, and occasionally manifested stereotyped head and neck movements. Most individuals, however, survived and showed no further symptoms of physiological stress (**Font et al. 1988**). This survival is consistent with the idea of functional recovery of involved neural tissue; the individuals that did not survive may have suffered a crisis of adaptation due to massive and persevering adrenal activation (**Barbeau et al. 1985**). Most subjects that received smaller doses, while showing clear indications of neurological damage, displayed no significant behavioral deficits; several, however, showed episodic rigidity and diminished spontaneous behavior. In tests of species_typical aggressive behavior, such subjects performed appropriate stereotyped behavior, albeit at low intensities (Greenberg et al., unpublished data).

After behavioral observations, cytopathological effects were assessed using the cupric silver method of method of **de Olmos et al. (1981**). Degenerating axons were observed ascending in the lateral forebrain bundle from the midbrain tegmentum (substantia nigra and ventral tegmental area) to targets in the anterior dorsal ventricular ridge, ventral striatum, nucleus accumbens, anterior and posterior entopeduncular nuclei, dorsal nucleus of the posterior commissure, and tectum mesencephali. Two types of argyrophilic perikarya were observed:

degenerative and reactive. Cytopathological changes were apparent at several loci ranging from the forebrain to the cervical cord. Degenerative changes were also seen in striatal terminals in areas that also show catecholamine histofluorescence and AChE reactivity (**Greenberg, Font, and Switzer, 1988**), supporting the putative homology of the reptilian striatal afferents and the mammalian mesostriatal pathway.

The projections revealed by the MPTP treatment confirm and extend our knowledge of ascending midbrain projections in lizards. Parts of this projection system are similar to the mesostriatal dopaminergic pathway of mammals; however the distribution of argyrophilic perikarya found in lizards markedly differs from reports of cell damage in MPTP treated mammals. Dfficulty in interpretation is attributable to species variability (Langston & Irwin 1986, Kopin & Markey 1988) and the possibility that non-catecholaminergic neurons may be affected by MPTP (Switzer & Campbell 1987 with C57 mice).

When aggressive pairs of rats set up social dominance relationships, both are stressed, but subordination involves additional burdens. Such males manifest behavior much like chronic depression. They appear defensive, voluntary alcohol consumption increases, and life-spans are shortened. Corticosterone is elevated and testosterone is reduced in rats much as in lizards (above) and most vertebrates. Most relevant to understanding the neurochemistry of stress and stress-related dysfunction, subordinates also manifest changes in serotonin systems indicative of increased 5-HIAA/5-HT ratios in various brain areas and altered 5-HT(1A) receptor binding at some sites **(Blanchard et al. 1993).**

ENVOI AND NEED FOR FUTURE STUDY

The diverse assortment of phenomena in which the basal ganglia participates vividly conveys a sense of the nested priorities of organisms. The unique qualities of the basal ganglia from its most ancient expression in vertebrates through humankind is consistently involved with the allocation of resources and the attempt to respond to environmental stimuli with the optimal balance of responses. These responses include those firmly embedded in an organism's behavioral repertoire as well as more recent and innovative behavioral patterns.

Specialists approach the problems of structure and function each from their respective perspectives. Clinicians are appropriately preoccupied with expressions of pathology, most often negative symptoms such as functional deficits or losses, rather than positive signs such as excesses. And comparative neurologists are acutely sensitive to the fundamental promise of the more recently evolved structures to shape and control more "primitive" behavioral patterns organized at lower levels. Ethology, having been guided as an emerging field more by zoology than psychology, emphasizes the differences between organisms more than the commonalities. It is alert to the boundary conditions which reflect the limits of possibility. Neuroethology sought the best of both worlds: the necessarily evolutionary conservative nervous system and the incredible diversity of behavior manifest in diverse environments. As evolution cobbles together fragments of the organism's rich potential into new ways of coping with various selection pressures, only our broad experience of possibilities can prepare us to make the most of what natural or laboratory experiments show us. Striatal lesioned lizards, for example may appear unimpaired unless provided with an appropriate venue for expression –an expression one might never look for or find if ignorant of the details of their natural history.

In recent decades, research is famously becoming more collaborative. The isolation that results from great

disciplinary depth is being overcome by interdisciplinary research teams. But even in such an environment, ideas are born a single mind and then shared, and often the visionary idea is, as so often observed, the next generation's dogma. In an echo of the evolutionary process, ideas that lead to insights that successfully solve problems are retained and when the problems are solved they become available for some other use or are even allowed to disappear. Insights about the basal ganglia, which began as gross estimates based on major trauma or disease have become replaced by progressively more subtle understanding as more detail becomes available and particularly as the diversity of precisely described behavioral patterns associated with their function in a diversity of taxa and contexts is examined.

This is the essence of the ethological method, in which an appreciation of the expressions of comparable behavioral patterns in diverse taxa and in their natural environments instills a sense of the awesome richness of possibilities that nature fosters. An appreciation of this breadth of application by supreme masters of their fields such as Paul D. MacLean will continue to enrich us by virtue of their model of wide-ranging imagination grounded in deep disciplinary understanding.

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