

## Research Report

### NEURONAL CODING OF SERIAL ORDER: Syntax of Grooming in the Neostriatum

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**Abstract**—*How does the brain create rule-governed sequences of behavior? An answer to this question may come from a surprising source: the neostriatum (caudate nucleus and putamen). Traditionally, the neostriatum has been considered part of the brain's motor system, but its contribution to the preparation or execution of movement is recognized generally to concern high-level motor functions. Recent work implicates the neostriatum in disorders of sequential action and thought, as in the repetition of thoughts or habits in human obsessive-compulsive disorder and movements or speech in Tourette's syndrome. Yet there is no direct evidence to support the idea that the neostriatum controls sequences of behavior. Using ethological and neurophysiological techniques to study neural activity in the rat neostriatum during syntactic grooming sequences, we found that neuronal activity in the anterolateral neostriatum depended on the execution of syntactic sequences of grooming actions. The individual grooming movements themselves did not activate the neostriatum; activation was determined by the syntactic sequence in which grooming movements were performed. These data provide the first direct evidence that the neostriatum coordinates the control of rule-governed behavioral sequences.*

A child's first spoken sentence, the tying of one's shoelace, and the opening of a nut by a squirrel all share something in common. Each of these tasks requires the activation of a set of skilled behavioral elements. In order to be effective, each element must be activated at the proper time and in the proper serial order: These tasks are sequential. In so many tasks in human and animal life, it is

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not enough to know what to do: One must also know when and in which order to do it. Nearly every action, word, and thought produced by a brain relies on its serial relation to other actions, words, and thoughts for part of its significance. Even movements must be arranged serially according to rules of "action syntax" in order to form meaningful acts, just as words must be arranged syntactically to form meaningful sentences (Lashley, 1951).

Patterns of serial order in behavior are old and phylogenetically pervasive. Early in the evolution of the brain, natural selection must have produced a solution in the form of neural systems to generate rule-governed sequences of behavior. These neural systems might first have evolved to sequence simple patterns of behavior, such as particular sequences of grooming, feeding, and social actions, and later have been extended to control the serial order of human language and thought.

We have capitalized on the primacy of simple behavioral sequences in mammalian evolution by using simple sequences to reveal brain systems that control the serial pattern of behavior. Our strategy has been to study the role of neural circuits within the neostriatum. Recent work indicates that the neostriatum participates in high-level aspects of motor control (Aldridge, Anderson, & Murphy, 1980a; Alexander & Crutcher, 1990; Berridge, Gilman, & Aldridge, 1993; Marsden, 1982, 1984; Oberg & Divac, 1979). In addition, there is mounting evidence that neostriatal circuits are uniquely crucial to the serial coordination of some behavioral sequences (Berridge & Whishaw, 1992).

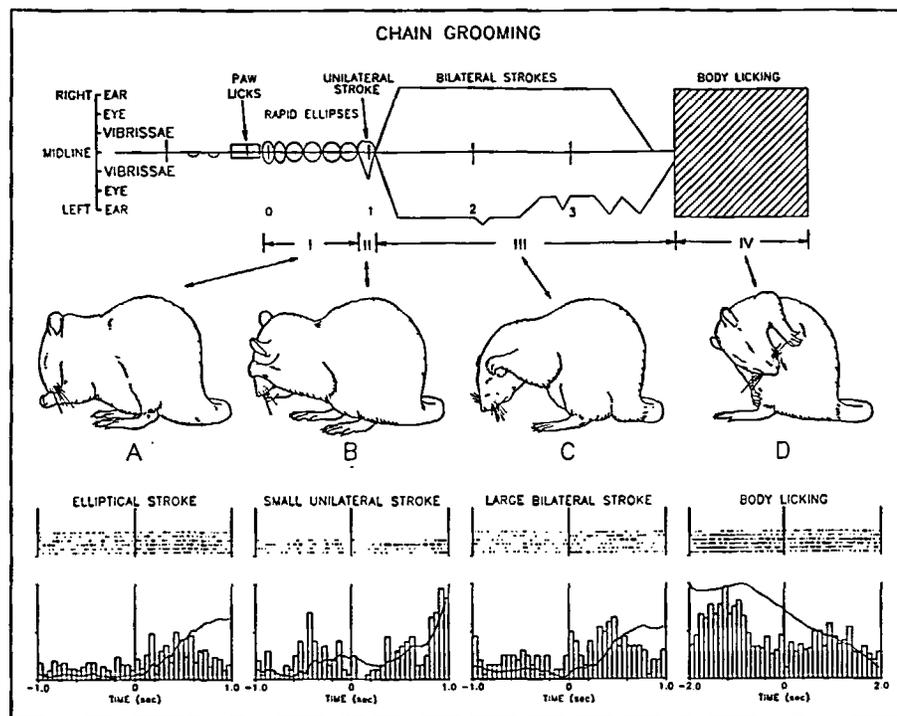
Two types of evidence are required to assert that a neural system controls the serial order of behavioral sequences. First, lesions of the neural system should disrupt the sequential organization of a behavior event but spare the behavioral elements. Second, neurons within the neural system must show activation pat-

terns that are correlated specifically with the sequence of such behavioral patterns rather than with their elemental constituents. Regarding the first type of evidence for the neostriatum, it is becoming clear that a variety of human disorders, such as Parkinson's, Huntington's, and Tourette's syndromes, can produce special deficits in the sequential organization of movement and language (Agostino, Berardelli, Formica, Accornero, & Manfredi, 1992; Benecke, Rothwell, Dick, Day, & Marsden, 1987; Frankel et al., 1986; Harrington & Haaland, 1991; Lieberman et al., 1992; Stelmach, Worringham, & Strand, 1987; Trimble, 1989). But human neurological disease disrupts many aspects of behavior besides sequential organization. More precise correlations between serial order and neural systems can be obtained by studies of animal behavior.

The neostriatum is crucial for the sequential pattern of rule-governed chains of rodent grooming behavior (Berridge & Fentress, 1988; Berridge & Whishaw, 1992; Cromwell & Berridge, 1990). For example, in one grooming sequence, up to 25 forelimb and body movements are linked in a "syntactic" chain that comprises four sequential phases. This syntactic chain of grooming actions occurs with a probability that is vastly higher than would be expected by a chance combination of the individual movements (Fig. 1). Conveniently for the analysis of whether brain systems contribute to the sequence or the individual movements of this syntactic grooming chain, the same movements that make up the syntactic chain occur frequently in other nonchain sequences that do not exhibit a rigid syntax.

Providing the first type of evidence for sequential control, damage to the anterolateral neostriatum disrupts the integrity of syntactic grooming chains, but does not disrupt the occurrence of constituent grooming movements outside the chain (Berridge & Fentress, 1988; Cromwell & Berridge, 1990). This con-

Neuronal Coding of Sequence



**Fig. 1. Syntactic grooming chain.** The four phases (elliptical strokes, unilateral strokes, bilateral strokes, and body licking, respectively) of the syntactic chain are schematized in the drawings in the central row (columns A, B, C, and D). All grooming sequences were elicited by moistening the fur. The serial pattern of grooming, syntactic or nonchain (i.e., sequences in which the serial order of actions does not follow the syntactic chain pattern), was determined solely by the rat. A typical syntactic chain is depicted by the top graph, which expresses in choreographic notation forepaw movement as distance from the nose's midline (y-axis) as a function of time (x-axis, tics = 1 s). The boundary definitions of the four phases are indicated by the dimension lines under the timing diagram. The bottom row shows activity of four neurons during syntactic grooming phases in four perievent time histograms and rasters. The central line (time = 0 s) in each raster and histogram is the time at which the defining event for that phase began. For example, in A, the spike trains of that neuron were aligned to the onset of the first Phase I stroke in each of six chains. Each dot in a raster line represents one neuronal spike or action potential. The spikes are averaged in 50-ms bins and displayed in the histograms. The solid curve overlying each histogram is a cumulative sum of the differences between histogram bins and the average bin height of the first 25% of the bins. An increasing rate of discharge is indicated by a rising cumulative-sum line. In A, for example, there is an increase of discharge associated with the onset of Phase I (the elliptical strokes), and in C, Phase III has an increase of discharge by a different neuron. In B and D, discharge decreases with the onset of Phases II and IV, respectively. The histogram duration and bin width are doubled in D.

tribution to serial order is uniquely neostriatal in origin and does not derive from cortical projections to the neostriatum: Damage to prefrontal cortex, primary or secondary motor cortices, or the cerebellum does not produce an enduring disruption of grooming syntax (Berridge & Whishaw, 1992).

Although lesion studies have established that the neostriatum is uniquely necessary to the sequential organization of these behavioral patterns, the second

type of evidence for neural control of serial order has remained lacking. In order to conclude that neostriatal circuits control the serial order of behavioral sequences, it is necessary to show that neurons within them code the sequential organization of serial patterns. In this study, we provide the first demonstration that neostriatal neurons code the serial order—not the component elements—of behavioral sequences.

Eleven rats (Sprague-Dawley, 250-

400 g) were anesthetized with ketamine-xylazine and implanted with a permanent, vertically movable electrode in the rostral lateral neostriatum. The electrode was designed for painless extracellular recording from multiple individual neurons during free spontaneous behavior (Aldridge, Berridge, & Herman, 1990). An amplifier mounted near the electrode was connected to the recording computer by a commutator that permitted free movement in a circular recording chamber. The electrode implant did not cause discomfort and did not interfere with normal behavior in the rat's home cage. The entire behavioral testing procedure was free of distress for the rats.

Beginning a week after implantation, behavior was videotaped and neuronal discharge activity was recorded for 1 or more hours while the animals groomed and moved about freely. A frame-by-frame analysis of the videotaped grooming sequences was conducted subsequently (Berridge, 1990; Berridge & Fentress, 1986) to find the onset and offset times of movements. Twenty-three different behavioral events were evaluated, including the component movements of syntactic chain grooming (Phase I = synchronous rapid strokes by both paws over the nose; Phase II = strokes by a single paw along the side of the face; Phase III = synchronous large strokes by both paws over the eyes or ears; Phase IV = licking of the body flank) and their nonchain equivalents, and of a visual stimulus (a 1-cm-square flag that moved toward the eye), and tactile stimulation (brushing and light touching) of four body regions. Each of these behavioral events occurred spontaneously, except sensory stimuli, which were presented several times per hour. Individual neurons were identified and discriminated from each other by the computer after recording on the basis of spike waveform shape.

The onset and offset times of more than 6,000 behavioral events were entered into the computer and used to construct 683 perievent time histograms for 34 neurons at 21 recording sites. Each perievent time histogram (Figs. 1 and 2) representing several repetitions of the same behavioral event was analyzed quantitatively (Macpherson & Aldridge, 1979). Most neurons (94%, 32/34) responded to at least one of the 23 behav-

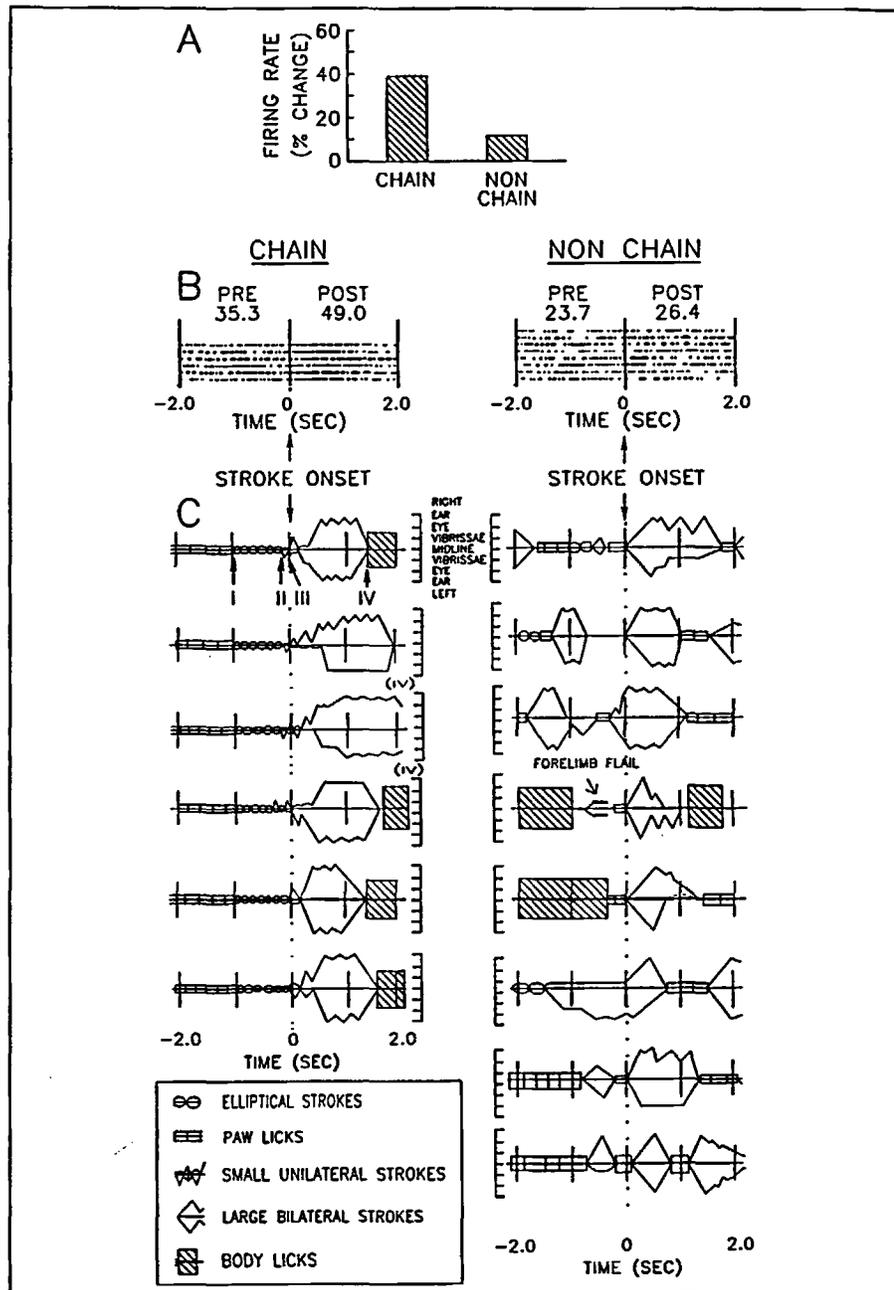


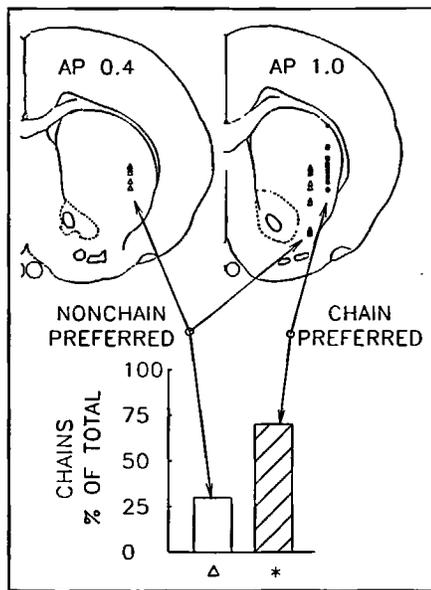
Fig. 2. Sequential specificity: Comparison of bilateral stroke movements and neuronal discharge made during a syntactic chain (left column) with movements and discharge activity from the same neuron made outside of a chain (right column). The change in discharge activity with respect to the prestroke phases during these grooming actions is indicated by the bar graph (a). The increase during chain grooming is nearly four times higher. In addition to this relative difference, the absolute discharge rate is higher both before and after the bilateral grooming stroke in sequential chain grooming. The average firing rates (in spikes per second) are indicated above each period on the rasters (b). Each row in a raster corresponds to one of the behavioral sequences in the choreographic diagrams (c) below the raster (ordering in raster and choreographic diagram is the same from top to bottom). Both the rasters and the choreographic displays are aligned such that the onset of the bilateral stroke movement is centered at time = 0.

ioral events. Additionally, most neurons had changes in discharge activity associated with more than one behavioral event. Grooming was the most potent elicitor of neostriatal activity of all behavioral events studied: During grooming, 88% of the neurons were activated. In comparison, 62% of neurons responded during locomotion or orientation movements, and only 41% responded to sensory stimulation. The majority of neurons that exhibited a change in activity correlated to a specific behavioral event tended to show increased rates of firing during the event, although some decreases were observed.

Sequential syntax of grooming was the main determinant of neuronal responses: Of the neurons that responded to a grooming movement, 85% (29/34) responded differentially to that movement depending on whether the movement was made inside or outside of a syntactic chain (Fig. 2). At least some neurons responded (with either increased or decreased activity) to each type of grooming movement, although individual neurons showed preferences for particular grooming movements (forelimb strokes vs. body licks). For 47% of neurons, the sequential context in which a movement occurred determined the neuronal response properties in an all-or-none way. For example, many of these neurons altered their firing during a grooming stroke by the forelimb only when the stroke was emitted within a syntactic chain. When the same stroke was emitted outside the syntactic sequence during nonchain grooming, discharge activity was unchanged. Some neurons responded in different directions (increase vs. decrease in the rate of neuronal discharge) to the same movement depending on whether the movement occurred inside versus outside of the syntactic chain pattern. The coding of sequence was especially noticeable for neurons in the most rostral and anterolateral region of the neostriatum. This is the only region in which lesions disrupt sequential performance of the grooming chain studied here (Cromwell & Berridge, 1990). Neurons in this region also had the highest degree of chain-specific coding of grooming sequence compared with medial and posterior locations (Fig. 3).

The power of behavioral sequence to predict whether or not a neuron altered

## Neuronal Coding of Sequence



**Fig. 3.** Anatomical location of sequence-coding neurons. The recording tracks were in the anterior-posterior (AP) planes lying 1.0 and 0.4 mm anterior to Bregma. The anterolateral region of the neostriatum contained most of the neurons that responded preferentially to syntactic chains (marked by \*) compared with similar movements outside of syntactic chains. The open triangles mark the location of units that did not encode syntactic grooming chains preferentially. The relative strength of chain coding by the two groups is illustrated in the bar graph below the maps.

its activity when a movement was performed provides the strongest evidence yet that the neostriatum coordinates the rule-governed serial order of behavioral sequences. The activity of neostriatal neurons is known to be correlated to learned movements (Aldridge, Anderson, & Murphy, 1980b; Aldridge et al., 1980a; Alexander & Crutcher, 1990; DeLong & Georgopoulos, 1981; Kimura, 1990). The instinctive nature of the sequential pattern studied here allows confidence that this neuronal activity is not an artifact due to training or to unnatural task constraints, but instead reflects a fundamental property of sequencing in neostriatal function. One can safely conclude that sequential coding by neostriatal neurons arises intrinsically and is not imposed by inputs from the cerebral cortex since lesions of the precentral cortical areas or of other cortical areas do not impair the performance of this

behavioral sequence; only neostriatal lesions do (Berridge & Whishaw, 1992).

It is perhaps surprising that the neostriatum should be uniquely important to the serial order of behavior given its traditional classification as a "motor" structure. Why should neostriatal contributions to serial order be especially evident in the syntactic grooming sequences of rodents? The answer may be that natural sequences of grooming are precisely the sort of behavior that neural substrates for action syntax originally evolved to control. This original function may be more easily detected in the rat neostriatum than in the highly encephalized brain of primates.

The neostriatum as a whole also receives massive sensory projections from the cerebral cortex (Kunzle, 1975, 1977; Selemon & Goldman-Rakic, 1985), and sensory processing in the neostriatum may be vital to understanding how the neostriatum coordinates grooming syntax (Aldridge et al., 1980a; Cools, 1985; Cromwell & Berridge, 1990; DeLong, Alexander, Mitchell, & Richardson, 1986; Lidsky, Manetto, & Schneider, 1985; Schallert, 1991). A hypothesis for neostriatal sequential control suggests that hierarchic neostriatal circuits temporarily switch motor control toward central pattern generators and away from sensory-guided systems at the beginning of a syntactic grooming chain (Berridge & Fentress, 1988; Berridge & Whishaw, 1992). If true, this hypothesis of syntax through hierarchical modulation might be extended to understand how pathological perseveration of action and thought seen in human Tourette's syndrome, obsessive-compulsive disorder, and Huntington's disease might result from neostriatal dysfunction (Cummings & Cunningham, 1992; Frankel et al., 1986; Rapoport, 1989a, 1989b; Rapoport & Wise, 1988). Hierarchical modulation of sequential elements by the neostriatum may operate in essentially similar ways for grooming actions and for thoughts, but upon very different classes of modulated elements in the two cases (Berridge & Whishaw, 1992).

Our argument that very different behavioral or mental elements might be sequenced by essentially similar neural processes echoes a suggestion made four decades ago by Lashley (1951). In a paper that defined the issue of action syn-

tax, Lashley noted the continuity between serial order at different levels of psychological complexity, and the continuity this may imply for the underlying neural substrates of syntax. He noted that "language presents in a most striking form the integrative functions [of syntactic coordination by the brain]"; however, "temporal integration is not found exclusively in language; the coordination of leg movements in insects, the song of birds, the control of trotting and pacing in a gaited horse, the rat running the maze, the architect designing a house, and the carpenter sawing a board present a problem of sequences of action [each of which similarly requires syntactic organization]" (p. 113). Circuitry within the neostriatum might provide a common sequencing link between phenomena as diverse as actions, words, and thoughts.

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