

Basal ganglia neural mechanisms of natural movement sequences¹

J. Wayne Aldridge, Kent C. Berridge, and Alyssa R. Rosen

Abstract: Natural rodent grooming and other instinctive behavior serves as a natural model of complex movement sequences. Rodent grooming has syntactic (rule-driven) sequences and more random movement patterns. Both incorporate the same movements—only the serial structure differs. Recordings of neural activity in the dorsolateral striatum and the substantia nigra pars reticulata indicate preferential activation during syntactic sequences over more random sequences. Neurons that are responsive during syntactic grooming sequences are often unresponsive or have reverse activation profiles during kinematically similar movements that occur in flexible or random grooming sequences. Few neurons could be categorized as strictly movement related—instead they were activated only in the context of particular sequential patterns of movements. Particular sequential patterns included “syntactic chain” grooming sequences of paw, head, and body movements and also “warm-up” sequences, which consist of head and body/limb movements that precede locomotion after a period of quiet resting (Golani 1992). Activation during warm-up was less intense and less frequent than during grooming sequences, but both sequences activated neurons above baseline levels, and the same neurons sometimes responded to both sequences. The fact that striatal neurons code 2 natural sequences which are made up of different constituent movements suggests that the basal ganglia may have a generalized role in sequence control. The basal ganglia are modulated by the context of the sequence and may play an executive function in the complex natural patterns of sequenced behaviour.

Key words: movement, basal ganglia, striatum, movement sequences, sensorimotor behaviour.

Résumé : La toilette qu'effectuent naturellement les rongeurs ainsi que d'autres comportements instinctifs servent de modèle naturel de séquences de mouvement complexes. La toilette des rongeurs comporte des séquences syntaxiques (dérivant de règles) et des mouvements effectués au hasard. Il s'agit dans les 2 cas des mêmes mouvements : seule la structure sérielle diffère. Les enregistrements de l'activité neurale dans le striatum dorsolatéral et la substance noire pars reticulata indiquent une activation préférentielle pendant les séquences syntaxiques plutôt que pendant les séquences aléatoires. Les neurones qui réagissent pendant les séquences syntaxiques souvent ne réagissent pas ou ont des profils d'activation inversés pendant des mouvements cinématiquement similaires qui se produisent au cours de séquences flexibles ou aléatoires. Peu de neurones ont pu être associés strictement au mouvement; ils ne sont plutôt activés que dans le contexte de séries séquentielles particulières de mouvements. Les séries séquentielles particulières incluent la « chaîne syntaxique » de la toilette des pattes, de la tête et du corps ainsi que les séquences de « réchauffement », formées des mouvements de la tête et du corps et des membres qui précèdent la locomotion après une période de repos (Golani 1992). L'activation pendant le réchauffement était moins intense et moins fréquente que pendant les séquences de toilette, mais la quantité de neurones activés pour les 2 séquences dépassait les niveaux de base, et ces mêmes neurones réagissaient parfois aux 2 séquences. Le fait que les neurones striataux codent 2 séquences naturelles, composées de mouvements différents, semble indiquer que les noyaux gris centraux jouent un rôle généralisé dans le contrôle de la séquence. Les noyaux gris centraux sont modulés par le contexte de la séquence et remplissent peut-être une

Received 27 January 2004. Accepted 24 June 2004. Published on the NRC Research Press Web site at <http://cjpp.nrc.ca> on 22 October 2004.

J.W. Aldridge^{2,3} Department of Neurology and Department of Psychology, University of Michigan, 1150 West Medical Center Drive, Medical Science Bldg. I, Room 3317, Ann Arbor, MI 49109-0607, USA.

K.C. Berridge Department of Psychology, University of Michigan, 1150 West Medical Center Drive, Medical Science Bldg. I, Room 3317, Ann Arbor, MI 49109-0607, USA.

A.R. Rosen Department of Neurology, University of Michigan, 1150 West Medical Center Drive, Medical Science Bldg. I, Room 3317, Ann Arbor, MI 49109-0607, USA.

¹This paper is one of a selection of papers published in this Special Issue, entitled Nerve, muscle, and beyond: the R.B. Stein Symposium.

²Corresponding author (email: jwayne@umich.edu).

³Present address: Harvard Medical School, 260 Longwood Ave., Boston, MA 02115, USA.

fonction exécutive dans les schémas naturels complexes des comportements séquentiels.

Mots clés : mouvement, noyaux gris centraux, striatum, séquences de mouvement, comportement sensorimoteur.

[Traduit par la Rédaction]

Introduction

Natural movements of humans and animals flow seamlessly and fluently from action to action. Indeed, the unitary gestures or actions we study in the laboratory may be less frequent than the complex arrangements and patterns of movements that occur spontaneously in natural life. Even simple sequences that we execute every day automatically and skillfully with what seems to be little effort present daunting sensorimotor control problems. How the brain organizes and controls movement sequences is an important question for motor physiology, neuroscience, and psychology. In this paper we focus on a possible role for the basal ganglia in the execution of motor sequences.

The idea that the basal ganglia have a role in motor control is well accepted, but what the basal ganglia do for movement is less clear. Disorders of the basal ganglia in humans (e.g., Parkinson's disease), suggest that organizational aspects of movement may be more affected than the elemental properties of movement. Parkinson's patients can control kinematic and dynamic features such as force and direction even while their ability to perform sequences of movements is impaired (Harrington and Haaland 1991). Alterations of the temporal organization of speech in basal ganglia disorders suggest that higher order aspects of complex movement patterns may be managed in part by the basal ganglia (Lieberman 2001; Volkman et al. 1992). The role of the basal ganglia in movement sequences may even extend to sequential processes, in general, as Marsden suggested: "The sequencing of motor action and the sequencing of thought could be a uniform function carried out by the basal ganglia" (Marsden 1984). The pathological repetitions of spoken words in Tourette's syndrome (Cummings and Frankel 1985) and tormenting habits and thoughts of obsessive-compulsive disorder (Rapoport and Wise 1988) are associated with disorders of the basal ganglia, further supporting the idea that the basal ganglia may participate in the organization of the sequential aspects of "cognitive" behaviour. Thus, an understanding of the executive functions of the basal ganglia in motor sequences may contribute to understanding behavioural sequences in general.

In our laboratory, we have exploited rodent grooming as a model to study the organization and neural mechanisms of movement sequences. Grooming is natural and ubiquitous. It consists of complex strings of movements to clean and maintain the fur and skin of the body. Rats spend a substantial proportion of their waking hours engaged in grooming (Bolles 1960). Most grooming bouts are initiated by paw-licking or face-washing movements that proceed to grooming of the fur around the head, neck, and body in a cephalocaudal stepwise pattern (Richmond and Sachs 1978). Unitary grooming actions such as scratching or direct contact with the trunk are emitted on their own in some instances, but the cephalocaudal progression is the most frequent order

of actions. One particular type of cephalocaudal ordering is the "syntactic chain" sequence described below.

Grooming patterns have lawful relationships among the individual components, and the basal ganglia play a key role in sequence implementation (Berridge et al. 1987). Evaluations of the timing and serial order of individual movements, the statistical predictability of sequence elements, and the probabilities of sequential patterns reveal the predictable organizational features and temporal structure of grooming actions (Berridge and Fentress 1987) (Berridge et al. 1987). Grooming is not random; rather, it exhibits a marked serial dependence (Berridge et al. 1987; Berridge 1990).

Most grooming sequences consist of flexibly ordered mixtures of strokes, licking, scratches, etc.; however, occasionally rats emit a fixed pattern or "chain" of grooming actions. These occasional chain sequences are composed of the same movements as flexible grooming patterns, but the serial structure of chains is relatively fixed in order and time. The temporal structure is "syntactic", that is, like language, it is rule-based with a "syntax" pattern (Lashley 1951). In contrast to "nonchain" grooming patterns, which are more flexible in their sequential composition and serial structure, chains are consistent and repeatable in pattern.

The syntactic grooming chain has approximately 25 contiguous movements and each chain lasts approximately 5 s. This chain has a stable serial order of 4 phases (Berridge et al. 1987; Berridge 1990) (Fig. 1). Phase 1 consists of 5–9 rapid elliptical strokes over the nose and mystacial vibrissae lasting for about 1 second. Phase 2 is short (0.25 s) and consists of small asymmetrical strokes of increasing amplitude. Phase 3 consists of large bilateral strokes that take 2–3 s for the animal to complete. The chain concludes with Phase 4, which consists of postural and head turning movements followed by a period (1–3 s) of body licking directed to the flank. The last phase of body licking varies more in length than other phases and often ends by blending into subsequent nonchain grooming in which chains are embedded. For practical purposes, the signature rapid elliptical strokes of Phase 1 provide a reliable marker for the stereotyped syntactic chain. In contrast, elliptical strokes are usually unitary in flexible nonchain grooming.

Thus, rodent grooming has 2 notable sequential types: (i) a fixed chain sequence (emitted at rates of 2 to 15 times per hour) and, (ii) nonchain sequences in more variable and flexible patterns (up to 20 times more frequent than fixed syntactic chains). Both grooming types are composed of the same actions—only the pattern and rigidity of the sequence structure differs.

Neuronal mechanisms

A particular advantage of rodent grooming as a model system for evaluating the functional organization of behaviour sequences and underlying neural mechanisms is the fact the grooming actions of the syntactical chain sequence occur in unpredictable order and flexible combinations outside of

Fig. 1. Syntactic and nonchain grooming. The 4 phases of syntactic chain grooming, elliptical strokes, unilateral strokes, bilateral strokes, and body licking are illustrated at the top. Each column represents activity from a single neuron and compares activation during the syntactic chain (middle row) and kinematically similar nonchain strokes (bottom row). Vertical dashes represent spikes in the rasters, which are aligned with the onset of the grooming action at time 0. The raster has 2 s before and 8 s after the movement onset. In the syntactic chain rasters, grooming actions that precede and follow the alignment event are marked (filled triangles and circles). Phase 1 has no preceding event; Phases 2 and 3 are marked. The perievent histogram averages spike activity in 200 ms bins. The left column is a neuron from the substantia nigra pars reticulata; others are striatal neurons. Note the excitation preceding the Phase 4 in the syntactic chain (top right) could be associated with the head-turning movement that precedes flank licking onset, which is the action that defines time 0 in this phase. The bottom left diagram summarizes regional differences in striatal neural responses. Dorsolateral striatum has slightly more responses throughout the entire course of the syntactic chain and it is more likely to have neurons with 2 or more responses. Bottom right: Chain vs. nonchain responses in the nigra. Chain responses dominate in the early phases of the chain sequence. Phase 3 has more nonchain responses.

the syntactical chain sequence. Thus, the same movements can be studied in 2 different sequence contexts: (i) the syntactical chain and (ii) flexible combinations of nonchain grooming. The similarity of individual grooming actions and sequences of actions among individuals facilitates comparisons of kinematically similar movements in syntactic and nonsyntactic, flexible sequences. Additionally, grooming sequences do not depend on learning and memory. Learned sensorimotor sequences, which are commonly used in behavioural neuroscience, are valuable and productive tools for complex cognitive testing; however, in some instances it may be difficult to dissociate coding for a sequence function from a memory function. Innate grooming sequences (Colonnese et al. 1996), in contrast, do not depend upon explicit training and thus provide a window on behavioural organization and neuronal mechanisms independent of memory and explicit training.

We tested basal ganglia participation in coding sequential processes directly by recording neuronal activity in neostriatum (dorsolateral or ventromedial) and substantia nigra pars reticulata with indwelling multisite recording electrodes in freely behaving rats. The electrodes were connected by a flexible cable to a commutator that allowed animals to move and groom freely (Aldridge and Berridge 1998; Meyer-Luehmann et al. 2002). Spontaneous behaviour for 1 or more hours of normal grooming and free movement was recorded on time-synchronized videotape from below through a glass floor while simultaneously recording neuronal spike activity on a computer. A frame-by-frame analysis of the videotaped grooming sequences was done off-line (Aldridge and Berridge 1998; Meyer-Luehmann et al. 2002) to demarcate syntactic chain groom and flexible nonchain grooming and to determine the onset and end times of syntactic grooming phases and individual grooming movements within phases. Changes in neuronal activity in relation to grooming actions were assessed by perievent time histograms to average neural spike activity over 5 to 10 repetitions of each movement. Recording sites were verified histologically after the completion of recording.

Forty-one percent of striatal cells were preferentially related to the sequential pattern of syntactic chains (Fig. 1), that is, neurons were activated during movements in the context of syntactic chain grooming but not during equivalent movements emitted in flexible nonchain grooming (Aldridge and Berridge 1998). Only 14% of neurons had a pattern of activation, suggesting they could code simple motor properties of grooming movements. These broadly tuned neurons

were activated during movement in both contexts, inside and outside of sequential chains.

Regional specializations of the striatum (Aldridge and Berridge 1998) supported the idea that the dorsolateral quadrant is crucial for syntactic chain grooming (Cromwell and Berridge 1996). The firing rates of neurons in the dorsolateral striatum increased over baseline by 116% during syntactic chains. A smaller (30%) change was observed for neurons in the ventromedial striatum, suggesting that dorsolateral neurons might be more specialized for a role in sequential processes. In addition, the dorsolateral striatum exhibited a more inclusive involvement throughout the syntactic chain sequence in contrast to ventromedial striatum. This was evidenced by the fact that more dorsolateral neurons responded to multiple phases of the sequence compared with the ventromedial region (Fig. 1, 18% of dorsolateral neurons, 5% of ventromedial neurons).

We exploited the fact that kinematically similar movements occur in both syntactic chains and nonchain grooming to test the idea that the basal ganglia are involved in controlling sequences specifically—and not merely movements within them. Most striatal neurons (84%) that responded during syntactic chain sequences did not respond in the same manner to similar movements made during nonchain grooming (Fig. 1). Only 16% exhibited a fixed relationship to movement in which activation occurred during the same movements in both syntactic chain and nonchain movements. A comparison of neuronal firing rates affirmed the importance of sequence context for dorsolateral striatum neurons. Rates were significantly higher during syntactic chain grooming than during nonchain grooming (17%; paired t-test, $p < 0.001$).

We recorded neuronal activity in the substantia nigra pars reticulata (SNpr), an important output structure (Deniau et al. 1996), and confirmed the significance of syntactic grooming sequences beyond the striatal basal ganglia component (Meyer-Luehmann et al. 2002). Fifty-five percent ($n = 26$) of SNpr neurons were active during grooming behaviour with most activation (73%, 19 of 26 responsive neurons) during the first 2 phases of the syntactic sequence (Fig. 1). The onset of the syntactic grooming sequence was the dominant feature in SNpr with vigorous activation during Phase 1 (96%, 25 of 26 responsive neurons). The importance of sequential context was evident in SNpr as in the striatum with many neurons (36%) responsive during Phase 1, and not responsive at all during similar paw movements in nonchain random grooming. Even neurons that were active during el-

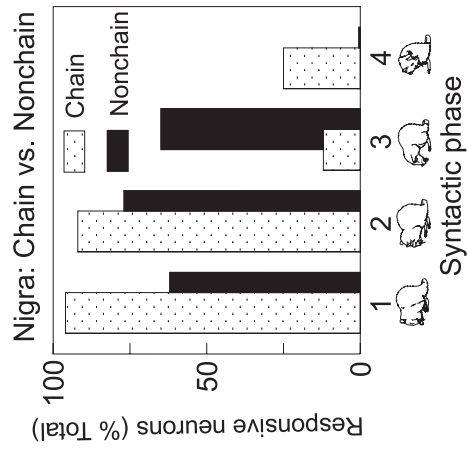
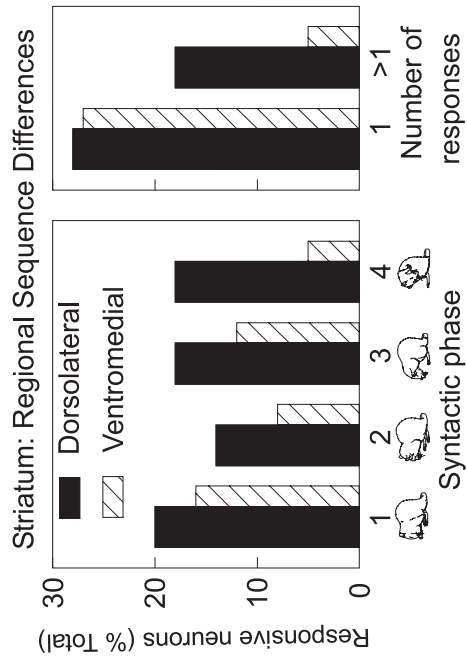
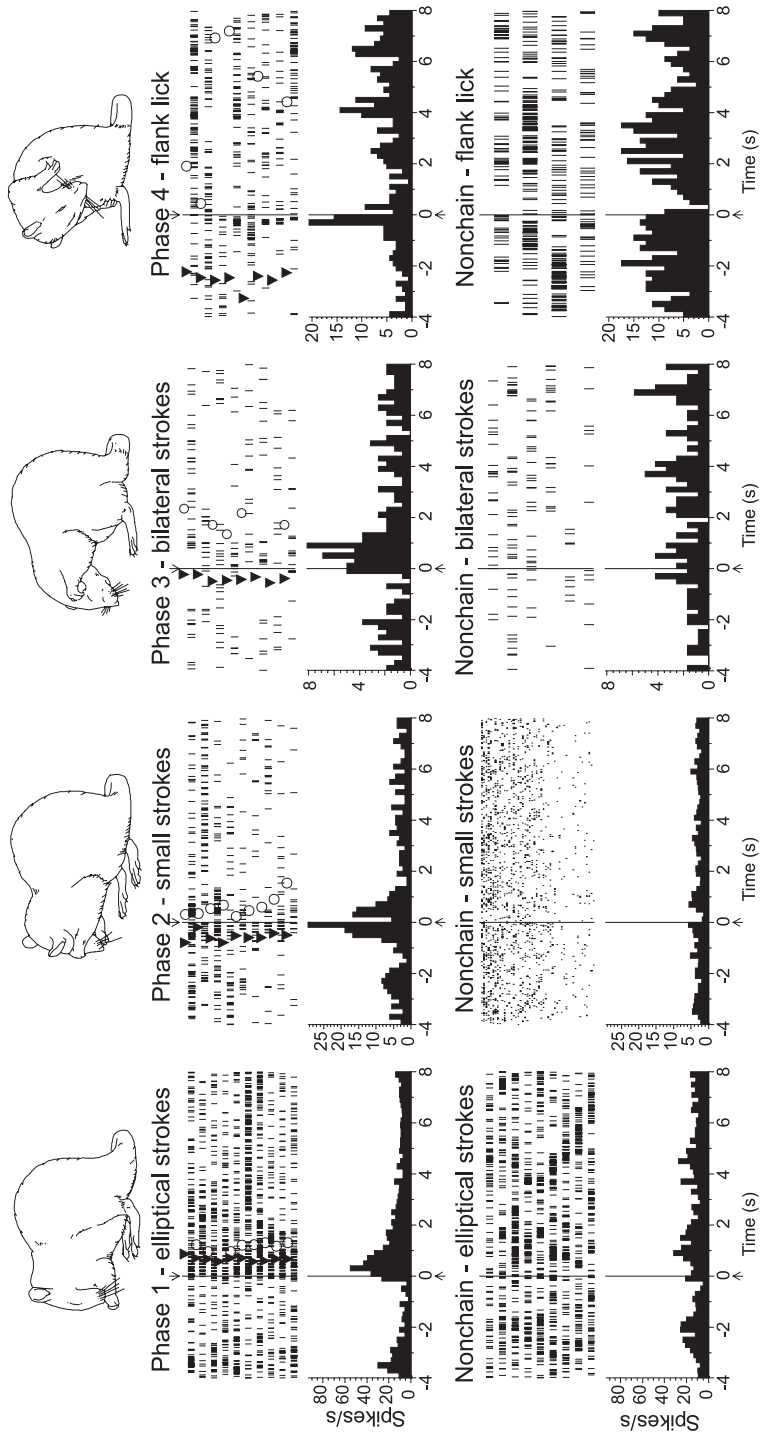
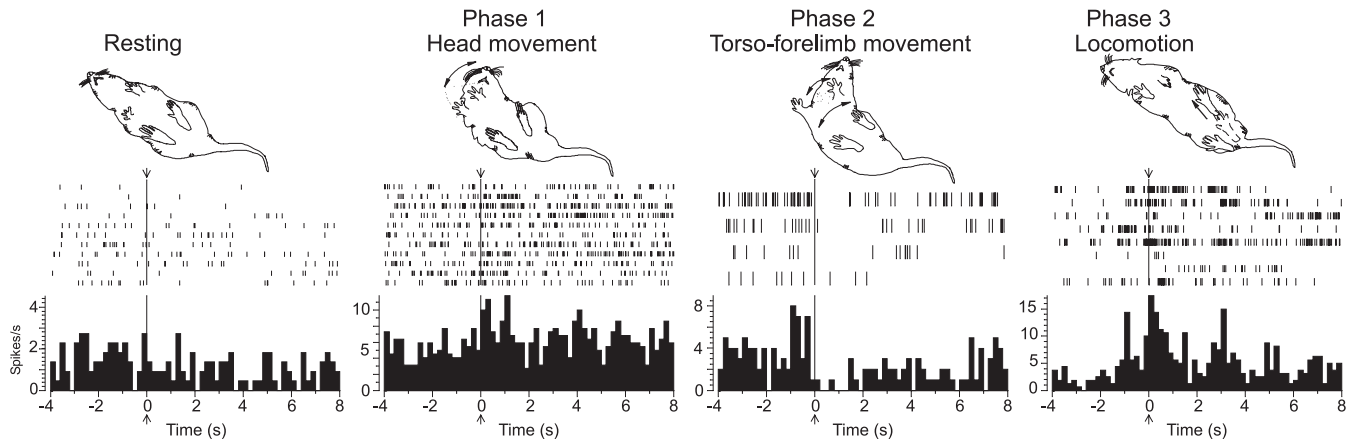


Fig. 2. Neural activation during warm-up. The 3 phases of warm-ups that occur with movement onset following a period of quiet resting are illustrated in the top row. Striatal neuron activity associated with the onset of each action is shown in the perievent time histogram and raster beneath each drawing. Weak inhibitions occur at the onset of resting and Phase 2 and excitations occur in examples of Phases 1 and 3.



liptical strokes of nonchain grooming had significantly faster firing rates when the strokes occurred in the context of syntactic grooming than during random grooming (50 vs. 28 spikes/s).

In addition to Phase 1, SNpr neurons exhibited sequence-dependent activation patterns during subsequent grooming phases. In contrast to the striatum where neuronal activation remained strong throughout the entire syntactic grooming chain, SNpr activation during the late phases of the grooming chain was less vigorous than during kinematically similar actions during flexible nonchain grooming (Fig. 1). For example, the proportion of activated neurons was higher during bilateral strokes of nonchain (65% of neurons) and firing rates were faster during Phases 2 and 3 than during similar strokes of syntactic chain grooming. Thus, SNpr neurons preferentially coded 2 types of patterns by excitation: the initiation (but not maintenance) of syntactic chains, and the maintenance (but possibly not initiation) of more random grooming. In a syntactic chain, SNpr neurons fired to the onset of the syntactic sequence (Phase 1), and then seemed to diminish or inhibit activation related to later components of Phase 2 and Phase 3. In terms of mechanism, the specificity of SNpr-activation to the onset of the syntactic chain pattern (and then relatively diminished in later phases of the chain) may reflect a sequence-dependent balance between excitatory STN and inhibitory striatal inputs.

Thus, overall, the neuronal activation in the SNpr codes the onset of syntactic chains, whereas striatal neurons preferentially code the maintenance of syntactic chains. Also, SNpr neurons are generally more excited during random sequences than syntactic chains (at least for late phases), whereas dorsolateral striatal neurons are typically more excited during all phases of syntactic chains than during random grooming. But all of these results demonstrate that neurons at the SNpr output of the basal ganglia, like the striatal input region, are modulated by the sequence context in which grooming movements occurred.

“Warm-up”: a natural movement sequence following quiet resting

Do striatal neurons code sequential processes more gener-

ally for other types of natural movement sequences beyond grooming? To answer this question, we examined neural activation during “warm-up” sequences. Warm-up is the pattern of actions that characterizes the transition from a period of quiet resting to forward locomotion, as described by Golani and his students (Golani 1992). Each warm-up sequence (Fig. 2) lasts a few seconds and consists of (i) behavioral resting, then (ii) side-to-side head movements, followed by (iii) side-to-side movements of the torso and pelvis, and finally (iv) forward locomotion using walking movements of limbs and body. Like grooming, warm-up has a cephalocaudal progression, and also like syntactic grooming (Berridge and Aldridge 2000a, 2000b), shows evidence of dopaminergic involvement (Golani 1992). Do striatal neurons that code grooming syntactic chains also code this naturally stereotyped pattern of warm-up movements?

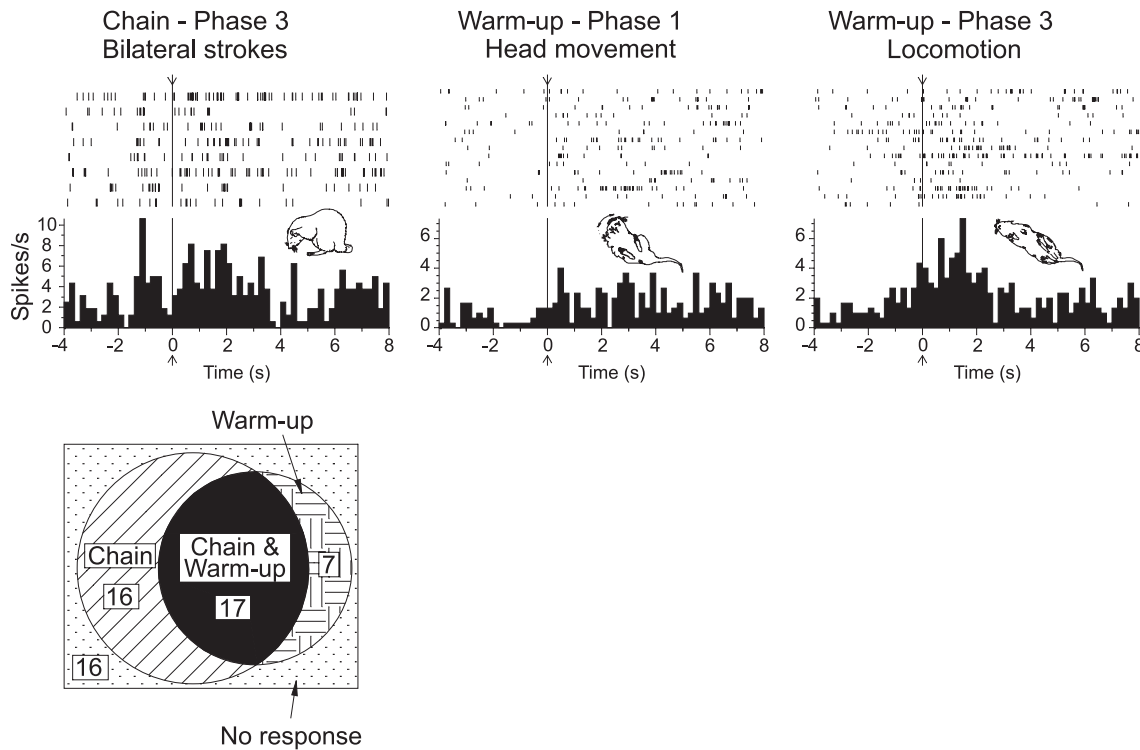
Methods

Warm-up-related neural activity was evaluated from the same striatal recordings acquired previously for grooming studies (Aldridge and Berridge 1998). Each recording session typically lasted 2 hours to obtain several minutes of grooming behavior and warm-up behavior. Warm-up sequences from unanalyzed sections of the recordings were located and evaluated.

Animals and surgical preparation

Experimental preparation, equipment, recording, and analysis procedures for grooming sequences analyzed from this data are detailed elsewhere (Aldridge and Berridge 1998; Meyer-Luehmann et al. 2002). Briefly, animals were prepared for single neuron recording with permanent multisite recording multielectrodes in dorsolateral or ventromedial neostriatum. A flexible cable from the electrode to a commutator allowed unrestrained movement during sessions typically lasting 2 hours. All spontaneous behaviour during the entire session was recorded on time-coded videotape synchronized to the time stamp clock on the computer that simultaneously recorded neuronal data. The Unit for Laboratory Animal Medicine at the University of Michigan

Fig. 3. Chain and warm-up activity in a single neuron. This neuron was activated with onset of Phase 3 of the syntactic chain (left) but not bilateral strokes in nonchain grooming (not shown). This same neuron was activated during Phases 1 and 3 (middle and right histogram) during the warm-up sequence. The Venn diagram on the bottom illustrates the overlap between chain and warm-up responsive populations. The area of the diagram is proportional to the number of responsive neurons. There were more chain responsive neurons and most warm-up responsive neurons had chain responses.



oversaw animal use procedures in accordance with the NIH Guide for the Care and Use of Laboratory Animals, revised 1985.

Warm-up

The warm-up sequence analysis, after the methods of Goliani and his colleagues (Golani et al. 1981; Golani 1992), consisted of a frame-by-frame inspection of videotapes to locate episodes in which animals made the transition from quiet resting to locomotion. Three movement phases characterize the warm-up sequence (Fig. 2). Phase 1 begins with side-to-side head movement after a period of quiet resting lasting 15 s or more. The first video frame with detectable head movement was defined as the onset of Phase 1. In Phase 2, the animal recruited the front paws and made a lateral head and torso movement while hind paws remained fixed in place. The onset of Phase 2 was marked by the video frame in which front paw was lifted. Phase 3 onset was scored at the first frame in which the hind paw was lifted for the forward step. If forward steps were not made, the warm-up was classified as incomplete. The onset and end times of warm-up phases were recorded from the identified video frames. These times and descriptive information about them were stored in a database for the neural analysis.

Neural analysis

Neural spikes were discriminated from each other and background noise, digitized, and stored in a database. Peri-event time histograms of averaged neural spike activity over

5 to 10 repetitions were constructed with Stranger (Biographics, Winston-Salem, N.C.) and NeuroExplorer (Nex Technologies, Littleton, Mass.) to evaluate changes in neuronal activity with respect to the onset of warm-up phases.

Results

Warm-up sequences were analyzed in 17 animals. The median duration of Phase 1 (first head movement to first torso/forelimb movement) was 3.9 s. The median length of the total warm-up sequence (end of resting to locomotion onset) was 7.9 s. These durations were in the same overall range as the syntactic grooming sequence duration, although individual phases in grooming sequences were shorter with a more rigid temporal structure. Forty-one percent (23/56) of neurons tested were responsive during warm-up (Fig. 2). In comparison, 59% (33/56) were responsive to syntactic grooming sequences. In many instances, the same striatal neurons responsive to syntactic grooming were also responsive during warm-up (Fig. 3). Indeed, neuronal activation in the 2 sequences exhibited a significant degree of overlap (Fig. 3) and statistical dependence (Chi squared test of independent samples, $\chi^2 = 3.88$, $p < 0.05$) (Siegel 1956). That close relationship in activation suggests that warm-up neurons and grooming neurons may be drawn from the same striatal population, and are sometimes identical. In terms of functional localization of warm-up neurons, however, there was no significant difference between the proportion of neu-

rons in the dorsolateral vs. ventromedial neostriatum (38% vs. 42% for VM and DL respectively, $\chi^2 = 3.88$, $p > 0.9$). That contrasts with our previous findings that dorsolateral neurons are most active during grooming sequences, and deserves further investigation.

Warm-up sequences were weaker in both behavioral and neural dimensions compared with grooming syntactic chains. Behaviorally, warm-up sequences were completed less often than syntactic grooming chains (49% warm-up vs. 60% syntactic chains), suggesting that the relative "syntactic strength" of warm-up sequential patterning was less than the syntactic grooming chains. Neural firing rates were also slower for warm-up patterns than for syntactic chains (matched pair t-test, $p = 0.015$; syntactic chain = 3.6 ± 0.8 spikes/s vs. warm-up = 2.1 ± 0.5 spikes/s during 4 s after sequence onset). Although more remains to be done, it appears that some of the same neurons code both grooming syntactic chains and pre-locomotion warm-up patterns, and that their strength of activation corresponds to the sequential strength of these patterns. This suggests basal ganglia neurons may have a general role in controlling sequential processes that cause natural action syntax.

Discussion

Neurons in the neostriatum and substantia nigra reticulata (SNpr) appear to code and implement natural serial action patterns, such as grooming syntax and possibly also warm-up movements during the transition from resting to walking (Aldridge and Berridge 1998; Meyer-Luehmann et al. 2002). This is evident given the fact that neuronal activation in these basal ganglia structures is often strongly dependent on the sequential context in which a movement occurred (i.e., syntactic chain versus nonchain flexible grooming sequences; warm-up sequences of head movements and locomotion). Differential firing properties further support this idea of sequential pattern coding. The dorsolateral striatum contains neurons that especially code all phases of syntactic grooming (Aldridge and Berridge 1998). The substantia nigra pars reticulata also codes syntactic grooming, especially the initiation of the pattern's early phases. Interestingly, in the nigra's biphasic coding of grooming sequence, movements early in the chain sequence activated neurons more than the same movements activated outside of the chain, whereas later movements of the sequence evoked more activity when they occurred in unpredictable strings outside of the chain.

These results support the idea that striatal neurons are involved in controlling the underlying syntax of sequential motor behaviour (action syntax). Finally, as currently described, striatal neurons activated during chain grooming are also more likely to be activated during the warm-up sequence of rest-to-locomotion. This finding, along with the fact that neurons responsive to syntactic grooming chains are also responsive to learned movements sequences (Matell et al. 2003), provides some evidence for a generalized role in action syntax control. Neural activity in warm-up was weaker in general than chain-grooming related activity, however, and was less concentrated in dorsolateral striatum. Future work will be needed to assess if these differences are robust or related to movement in general (Trytek et al. 1996)

or specific movements such as head-turning and locomotion, for example (West et al. 1990).

Conclusion

Rodent grooming behaviour and other natural behavioral patterns are particularly useful model systems to study the organization and neuronal mechanisms of behavioural sequences, due to the spontaneity and sequential richness of their natural behavioral structure. Because they have both syntactical and nonsyntactical modes and each contained essentially the same component actions to control for motor parameters, natural sequences such as rodent grooming and warm-up were ideal for dissociating motor-control from sequence-control properties. It was possible with these naturally occurring movement sequences to compare how the individual neurons code movements in stereotyped, syntactical sequences with how they code movements in flexible, less rigidly structured sequences. When neurons respond preferentially to specific stereotyped patterns, it suggests they code the distinctive sequential structure of those syntactic patterns. The clinical importance of these findings on brain sequential processes for pathological sequence control should not be underestimated because of their potential to shed light on sequential coordination aspects of basal ganglia pathology, which almost always extends beyond simple movement deficits. Parkinson's disease, Huntington's disease, and Tourette syndrome all have basal ganglia disturbances associated with abnormal movement sequences. A better understanding of the neural mechanisms related to sequence control might lead to new therapeutic tactics for neurological treatments.

Acknowledgments

Jonathan Lee and other students in the Undergraduate Research Opportunities Program at the University of Michigan assisted with data analysis. The authors would like to acknowledge the technical assistance of Jeff Thompson, Nadia Sidiqui and Rick Kindt. The research was supported by NIH grants NS31650 (J.W.A.).

References

- Aldridge, J.W., and Berridge, K.C. 1998. Coding of serial order by neostriatal neurons: a "natural action" approach to movement sequence. *J. Neurosci.* **18**: 2777–2787.
- Berridge, K.C. 1990. Comparative fine structure of action: rules of form and sequence in the grooming patterns of six rodent species. *Behaviour*, **113**: 21–56.
- Berridge, K.C., and Aldridge, J.W. 2000a. Super-stereotypy I: Enhancement of a complex movement sequence by systemic dopamine D1 agonists. *Synapse*, **37**: 194–204.
- Berridge, K.C., and Aldridge, J.W. 2000b. Super-stereotypy II: Enhancement of a complex movement sequence by intraventricular dopamine D1 agonists. *Synapse*, **37**: 205–215.
- Berridge, K.C., and Fentress, J.C. 1987. Deafferentation does not disrupt natural rules of action syntax. *Behav. Brain Res.* **23**: 69–76.
- Berridge, K.C., Fentress, J.C., and Parr, H. 1987. Natural syntax rules control action sequence of rats. *Behav. Brain Res.* **23**: 59–68.

- Bolles, R.C. 1960. Grooming behavior in the rat. *J. Comp. Physiol. Psychol.* **53**: 306–310.
- Colonnese, M.T., Stallman, E.L., and Berridge, K.C. 1996. Ontogeny of action syntax in altricial and precocial rodents: grooming sequences by rat and guinea pig pups. *Behaviour*, **113**: 1165–1195.
- Cromwell, H.C., and Berridge, K.C. 1996. Implementation of action sequences by a neostriatal site: A lesion mapping study of grooming syntax. *J. Neurosci.* **16**: 3444–3458.
- Cummings, J.L., and Frankel, M. 1985. Gilles de la Tourette syndrome and the neurological basis of obsessions and compulsions. *Biol. Psychiatry* **20**: 117–126.
- Deniau, J.M., Menetrey, A., and Charpier, S. 1996. The lamellar organization of the rat substantia nigra pars reticulata: Segregated patterns of striatal afferents and relationship to the topography of corticostriatal projections. *Neuroscience*, **73**: 761–781.
- Golani, I. 1992. A mobility gradient in the organization of vertebrate movement: The perception of movement through symbolic language. *Behav. Brain Sci.* **15**: 249–308.
- Golani, I., Bronchti, G., Moualem, D., and Teitelbaum, P. 1981. “Warm-up” along dimensions of movement in the ontogeny of exploration in rats and other infant mammals. *Proc. Natl. Acad. Sci. USA* **78**: 7226–7229.
- Harrington, D.L., and Haaland, K.Y. 1991. Sequencing in Parkinson’s disease—abnormalities in programming and controlling movement. *Brain*, **114**: 99–115.
- Lashley, K.S. 1951. The problem of serial order in behavior. *In Cerebral Mechanisms in Behavior. Edited by L.A. Jeffress.* Wiley, New York. pp. 112–146.
- Lieberman, P. 2001. Human language and our reptilian brain. The subcortical bases of speech, syntax, and thought. *Perspect. Biol. Med.* **44**: 32–51.
- Marsden, C.D. 1984. Which motor disorder in Parkinson’s disease indicates the true motor function of the basal ganglia? *In Functions of the Basal Ganglia. Ciba Foundation Symposium 107,* Pitman, London. pp. 225–241.
- Matell, M.S., Berridge, K.C., and Aldridge, J.W. 2003. Striatal firing patterns code multiple types of behavioral sequences. Society for Neuroscience, Washington, DC, Online Abstract Viewer Prog. # 704.14.
- Meyer-Luehmann, M., Thompson, J.F., Berridge, K.C., and Aldridge, J.W. 2002. Substantia nigra pars reticulata neurons code initiation of a serial pattern: implications for natural action sequences and sequential disorders. *Eur. J. Neurosci.* **16**: 1599–1608.
- Rapoport, J.L., and Wise, S.P. 1988. Obsessive-compulsive disorder: evidence for basal ganglia dysfunction. *Psychopharmacol. Bull.* **24**: 380–384.
- Richmond, G., and Sachs, B.D. 1978. Grooming in Norway rats: the development and adult expression of a complex motor pattern. *Behaviour*, **75**: 82–96.
- Siegel, S. 1956. *Nonparametric Statistics for the Behavioral Sciences.* McGraw-Hill, New York.
- Trytek, E.S., White, I.M., Schroeder, D.M., Heidenreich, B.A., and Rebec, G.V. 1996. Localization of motor- and nonmotor-related neurons within the matrix-striosome organization of rat striatum. *Brain Res.* **707**: 221–227.
- Volkman, J., Hefter, H., Lange, H.W., and Freund, H.J. 1992. Impairment of temporal organization of speech in basal ganglia diseases. *Brain. Lang.* **43**: 386–399.
- West, M.O., Carelli, R.M., Pomerantz, M., Cohen, S.M., Gardner, J.P., Chapin, J.K., and Woodward, D.J. 1990. A region in the dorsolateral striatum of the rat exhibiting single-unit correlations with specific locomotor limb movements. *J. Neurophysiol.* **64**: 1233–1246.