CODING OF BEHAVIORAL SEQUENCES IN THE BASAL GANGLIA

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1. INTRODUCTION

The idea that the basal ganglia have a role in motor control is well accepted. Yet the fundamental question remains, what exactly do the basal ganglia do for movement?

One clue can be obtained from studies of Huntington's and Parkinson's diseases. The devastating impact on movement caused by these degenerative disorders of the basal ganglia strongly supports a motor function. However, close scrutiny suggests that basal ganglia pathology is not restricted to the elemental properties of motor control. Even more affected are higher-level organizational aspects of motor control. An important aspect of organization is sequential coordination. For example, Parkinson's patients can perform motor tasks that require them to control kinematic and dynamic features of movement such as force and direction; however, their difficulty in performing sequences of movements[1] suggests that a higher, organizational aspect of motor control is disturbed by this disorder. Huntington's patients also have deficits in related high-level "ideomotor" aspects of movement coordination.[2]

The neostriatum has even been suggested to be crucial to sequential aspects of human language.[3-5] Marsden[6] suggested "The sequencing of motor action and the sequencing of thought could be a uniform function carried out by the basal ganglia." Linguistic and cognitive evidence supports the idea that injury to the basal ganglia may produce an inability to control behavioral sequences in general. The pathological repetitions of spoken words in Tourette's syndrome[7] and the tormenting habits and thoughts of obsessive-compulsive disorder,[8] both of which are associated with pathology of the basal ganglia. These disorders suggest that the basal ganglia might even participate in the organization of the sequential aspects of "cognitive" behavior. Lieberman in particular has suggested that basal ganglia play a crucial role in controlling the syntax or serial generating rules of modern human language.[5]

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Four decades ago, Karl Lashley[9] noted the continuity between serial order at different levels of psychological complexity. He highlighted the continuity this may imply for the underlying neural substrates of syntax, which now especially appears to involve neostriatum. Several have suggested that neuronal sequencing might originally have evolved to coordinate sequences of instinctive behavior and later have been modified to control learned behavior.[10,11] We believe that Marsden and Lieberman may be right; circuitry within the neostriatum may provide a common link for sequencing phenomena as diverse as actions, words, or thoughts. Further, we propose that Lashley's idea of syntax can provide a profitable formulation of function for these structures. The central idea that has emerged from our studies is that the basal ganglia have a functional role in controlling syntactical sequences of motor behavior.

1.1. Syntactical Grooming Sequences in Rodents

All purposeful behavior is sequential, so what do we mean by syntactical sequence? In the simplest terms, a syntactic sequence is one that follows normative rules that determine the temporal progression of its elements. These rules impart a mathematical predictability to the sequence. Language has real syntax, complete with generative rules.[5] Given an arbitrary word, it is possible to predict with some level of probability what the next word in a language sequence will be. Other behaviors can be described as having properties of syntax if one can demonstrate lawful sequential dependencies. For example, the highly stereotyped sequence of grooming in rodents behavior that we will examine in this study has distinct syntactical properties (Figure 1). This sequence has approximately 25 movements that are linked in chain of motor actions that follows a rule-governed serial order of 4 phases.[12,13] Phase I consists of 5-9 rapid elliptical strokes over the nose and mystacial vibrissae lasting for about one second. Phase II is short (0.25 s) and consists of small asymmetrical strokes of increasing amplitude. Phase III consists of large bilateral strokes that take 2-3 s for the animal to complete. The chain concludes with Phase IV,
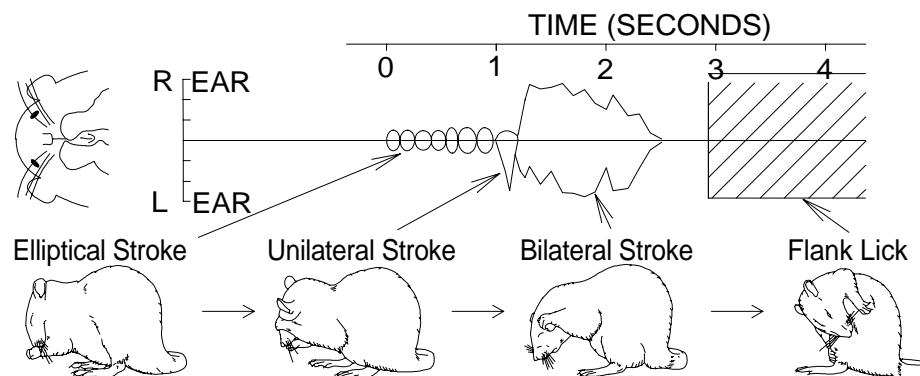

Figure 1. The 4 syntactic phases, elliptical strokes, unilateral strokes, bilateral strokes and body licking are schematized in the drawings. The choreography timeline has forepaw movement as distance from the midline (Right – up, Left - down) as a function of time (x-axis, tics=1 sec) for a typical syntactic chain (left paw represented by line below the axis, right paw represented by line above the axis).

which consists of a postural turn followed by a period (1-3 s) of body licking directed to the flank. Once the pattern begins, each remaining action can be predicted with over 90% accuracy. The four grooming actions that contribute to this sequence also occur in unpredictable order and combination outside of the syntactical chain sequence. The entire syntactical chain occurs with a frequency that is over 13,000 times greater than could be expected by chance (based upon the relative probabilities of the component 25 actions obtained from grooming outside of this syntactic chain.[12] Both Information Analysis and Transition Analysis[13] demonstrate that syntactical grooming sequences exhibit a high degree of predictability. Thus, grooming actions are not emitted in random order rather; they exhibit a marked serial dependence.[13]

1.2. Grooming Syntax is a 'Real' Trait.

It is reasonable to ask whether the syntactical grooming pattern described above truly represents a normative rule that is actively generated and imposed by the brain. We have shown that the patterns are not merely artifacts of the measures themselves, or idiosyncratic patterns of inbred lab rats, or trivial consequences of rodent anatomical structure that "forces" grooming to occur in these patterns. Instead, the syntactic pattern reflects a fundamental neurobehavioral function deeply embedded in rodent brain evolution. Comparative phylogenetic analysis of rat, mouse, hamster, gerbil, guinea pig, and ground squirrel grooming patterns[13] have confirmed that grooming syntax is a basic biological trait conserved across related species, rather than an artifact or idiosyncrasy of lab rats. Furthermore, the pattern of syntax variation across species corresponds more closely to their phylogenetic relations than to physical anatomical traits or evolutionary niches. In fact, phylogenetic relationships can be predicted based on grooming syntax patterns. This should not be surprising as syntactic patterns of action are the output of neural systems, which to a high degree are genetically determined. Grooming syntax is a "real' trait.

The ontogeny of action syntax further supports its real trait properties. Virtually every movement component of grooming in rat pups appears by postnatal Day 12, which precedes the appearance of syntactic chains by several days. [14] Interestingly, the time course of developing syntactic chains parallels the postnatal maturation of the neostriatum.[15] The density of connections to the striatum[16] and dopamine receptors properties[17,18] all occur during the period (Days 14 and 18) in which grooming syntactic completion evolve to their adult character. This is consistent, although not final proof, with our hypothesis that striatum is necessary for grooming syntax.

We do not mean to deny that the basal ganglia also have a role in simple aspects of movement too[19-22] Undoubtedly there are simple aspects of motor control as well as complex coordinating aspects in learned motor actions in the repertoire of the basal ganglia. However, such "simple movement" properties of neostriatal neurons are less evident than for neurons in other motor structures, and other "sensory" and complex "contextual" properties are relatively pronounced in the neostriatum.[23] It is likely that the basal ganglia may also participate in the performance of well learned tasks.[19,24-30] Basal ganglia neuronal activity is not related consistently to muscle activity[31,32] or to the kinematic and/or dynamic parameters of movement such as limb position, velocity and load.[33] Instead, one finds relationships dependent upon the behavioral context of

movements[22,34-36] and usually a temporal pattern in which neuronal activity changes begin at about the same time or just after the onset of muscle activity.[34] Timing patterns such as this would be especially advantageous to controlling the progress of a series of movements. A role in sequence control[5,37,38] and in coordinating a well-learned series of actions has been noted by other workers as well.[25,26,39,40]

1.3   Sequential Grooming Patterns: Brainstem Generation – Neostriatal Implementation

In a "levels-of-transection" study, rats decerebrated at either the midbrain, pontine, or medullary levels still generated the basic pattern of syntactic chains as long as the isolated pontine hindbrain was intact.[41] Syntactic chains with basic sequential phase structure were produced occasionally both by mesencephalic decerebrates that possessed a midbrain and hindbrain and by metencephalic decerebrates, which lacked a midbrain and had only a hindbrain.[41] By contrast, complete syntactic chains were never seen in myelencephalic decerebrates, which lacked a pons and cerebellum and had only a medulla remaining.[41] Nevertheless, the competence of the hindbrain is very limited: many abnormal sequential errors occurred. Unlike normal rats, even high-level decerebrates completed less than half the normal percentage of chains that they began. Most syntactic chains emitted by decerebrates were poorly structured in terms of serial order tending to "get lost" and to revert to nonsyntactic grooming. Although the hindbrain can generate the basic sequence, it is unable to implement it normally. The neostriatum is needed for implementation.

Supporting the notion the pattern is generated and implemented centrally by these brain systems, separate investigation demonstrated that sequential grooming patterns do not require somatosensory feedback from the face. Deafferentation of maxillary and mandibular branches of the trigeminal nerve do not disrupt the sequence of grooming patterns, even though individual movements of nonsyntactic grooming were deformed.[42,43] Deformation of grooming did not apply to syntactic chains.[42] In other words, tactile sensory feedback to guide movement appears to be suppressed during syntactic chains suggesting that the control of action form and sequence is generated and implemented centrally for the duration of syntactic chains and then returns afterwards to a more sensory-guided mode.[42,43] Together, these studies showed that basic grooming syntax patterns are generated by the pontine brainstem, but that the brainstem is not sufficient for the normal behavioral execution of syntactic patterns.

1.4. The Crucial Role of the Neostriatum: Evidence from Neostriatal, Cortical, and Cerebellar Lesions

The neostriatum and its dopamine inputs are uniquely necessary to normal implementation of grooming syntax. Excitotoxin or ablation lesions of the neostriatum, or 6-OHDA lesions of nigrostriatal dopamine projections disrupt grooming syntax as severely as decerebration.[43-45] In contrast, grooming syntax is not disrupted seriously by lesions of the primary or secondary motor cortex, by complete decortication, or by ablation of the entire cerebellum.[45] In a series of lesion studies,[43-46] the effects on grooming syntax of removing the neostriatum, and/or the primary motor neocortex (Fr1,

Fr3, and medial FL: agranular frontal cortex of rat where stimulation induces movement), the secondary motor cortex (Fr2: agranular frontal cortex where stimulation also induces movement but at higher currents than MI), other cortical areas (complete decortication of all neocortex including cingulate cortex dorsal to the level of the rhinal fissure, or complete aspiration of the cerebellum (all ansiform and simple lobules and most medial lobules) were compared. Only neostriatal lesions produced a permanent impairment of the serial organization of syntactic grooming chains. All other lesions (neocortical MI, MII, decortication, cerebellar ablation) produced only minor temporary disruption of sequential organization, related to nonsequential motor deficits, such as of fine coordination of forelimb trajectories, movement timing, or posture.[45]

The failure of primary and secondary motor cortex lesions to induce sequential deficits in grooming syntax is especially interesting; in light of certain views of neostriatal function as involving a set of "parallel loops" between cortex-striatum-thalamus-cortex. The cortical areas we destroyed project heavily to the dorsal neostriatum.[47] The fact that neostriatal syntactic deficits are not produced by a loss of cortical inputs indicates that neostriatal contributions to grooming syntax do not originate passively from cortical projections. The discrepancy between cortical and neostriatal damage highlights this intrinsic neostriatal function. Note that the fact that the function can operate independently of cortical inputs does not rule out the importance of other inputs in the integration of grooming and other behavior.

These studies demonstrate clearly that motor deficits per se are not sufficient to disrupt the sequence of grooming movements. In fact, a variety of forepaw coordination, timing, and postural deficits are produced by cortex and cerebellum lesions as detected in grooming movements by changes in the form and amplitude of grooming strokes, the duration of bouts, and in temporary pattern disruptions.[45] However, motor deficits were not sufficient to produce enduring degeneration of the sequential pattern of grooming actions. By analogy to language, these lesions might be said to disrupt the "words" but not the "sentences" of grooming bouts. The reverse effect of disrupting serial patterns but not component grooming actions can be produced by certain striatal lesions (below).

1.5. Neostriatum Lesions Disrupt Implementation

Berridge and Fentress[43] showed that neostriatal kainic acid lesions disrupt the fraction of syntactic chains completely by more than 50% even while the number of chains initiated was not reduced at all. In other words, the rats appeared unable to implement the syntactic rule despite their "attempts" to start the sequence. A follow up study found that an equivalent disruption of syntactic performance was produced by destruction of nigral dopaminergic afferents to the neostriatum.[44] Again, this disruption of grooming syntax was not due to a simple motor deficit. In fact, grooming overall was increased in lesioned rats, and did not have distortions of movement form (e.g., bout duration and number, individual stroke number and speed, body lick number and distribution over body parts, the amplitude and symmetry of stroke trajectories, the duration of syntactic phase bouts, etc.). This double dissociation between movement form and serial order patterns of action syntax indicates that the two types of deficit are independent.

Cromwell and Berridge[48] compared grooming syntax deficits produced by large lesions that destroyed more than 50% of the neostriatum to small lesions (1 mm or less) "mapping" crucial areas. They could produce syntax deficits comparable to large lesions when small lesions were placed bilaterally within the dorsolateral quadrant of the neostriatum. This crucial site in the dorsolateral quadrant is part of the dorsal "motor" circuit defined by Nauta and others.[47,49] Further, the fact that the deficit can be produced by lesions of less than 1 mm in diameter, together with the distribution pattern of effective lesions, suggests that the actual "syntax zone" may actually be much smaller than the entire motor zone or dorsolateral quadrant. A special role for this neostriatal syntax zone in coding sequence implementation has recently been confirmed by our electrophysiological studies of neurons during grooming behavior, as described below.

In summary, lesion and behavioral studies suggest that the basal ganglia have a role in coordinating serial patterns as well as a likely role in simple movement. By an examination of neuronal activity during syntactic grooming, we are exploiting brain mechanisms that evolved to control natural behavior as a window into the role of neural systems in sequential coordination. The more common approach of training animals to perform learned sequences provides very complex sequences, but depends heavily on learning and memory processes as well as sequence coordination. Natural behavioral sequences, such as grooming syntax on the other hand, do not depend upon explicit training. Natural behavioral sequences thus have a unique advantage regarding the neuroscience of action syntax: they alone provide a way to study neuronal mechanisms of behavioral sequencing independent of memory and explicit training.

2. NEURONAL CODING OF GROOMING SYNTAX

2.1 Methods and Results

These studies were based on neuronal recordings from freely moving rats, which had been implanted with a permanent multisite recording electrode in neostriatum (dorsolateral or ventromedial) or substantia nigra pars reticulata, connected to a preamplifier and a computer through a commutator, which permitted free movement throughout the chamber.[11,22] The lightweight implant did not interfere with normal behavior and caused no discomfort. Spontaneous behavior was videotaped and neuronal discharge activity was recorded for one or more hours while the animals groomed and moved about freely. A frame-by-frame analysis of the videotaped grooming sequences was conducted off-line[11,22] to find the onset and offset times of movements. Neuronal activity was analyzed in correlation to grooming actions by the construction of perievent time histograms. At the completion of recording the animals were killed by an overdose of anesthetic, brains were removed and prepared histologically for verification of recording sites.

2.2 Neostriatal Coding of Syntactic Chain Grooming

Neuronal activity in neostriatum during grooming suggests that the basal ganglia may code movement sequences more than movement elements.[11,22] Indeed, most striatal

activity appeared to code sequential pattern. Neurons were activated vigorously during syntactic chain grooming (Figure 2) and remarkably, syntactic grooming was more potent than similar nonchain grooming movements (41% vs. 14%; p<0.001), and even though syntactic chain grooming is infrequent compared to nonchain grooming. Although the striatum is actively engaged in motor control, few neurons could be categorized as strictly movement related. Most neurons responsive to syntactic chain sequences failed to respond in the same way to similar movements made during nonchain grooming (84% dorsolateral; 100% ventromedial; Figure 3). That is revealing because neurons related to movement should respond in a similar way in both behavioral contexts. Conversely, neurons that code sequential pattern should respond differently when similar movements are emitted in different sequential patterns.

The preferential relationship of neuronal firing to chain grooming was universal throughout the neostriatum (Figure 3A). On the other hand, one crucial feature of syntax implementation was coded uniquely only by neurons in the dorsolateral 'syntax site'. Dorsolateral neurons were three times (18% vs. 5%) more likely to have multiple responses during two or more phases of the chain sequence (Figure 3B). Most ventromedial neurons, in contrast, were likely to be activated during only one phase of the chain, especially an early phase (usually Phase I). These differences suggest that dorsolateral neurons may code holistic sequence-specific properties of grooming syntax, which is consistent with a role in encoding the sequential pattern as a whole. Implementation of the entire sequence from start to completion might require such neurons, especially those neurons with multi-phase responses that code late phases as well as early phases of the sequence.

Beyond simple correlation of neuronal activity to sequence, the *intensity* of neuronal firing also reflected regional differences and syntactic coding. Normalized changes in firing rates were calculated relative to a baseline before the chain. The special role for the dorsolateral 'syntax zone' of the neostriatum was further indicated by the fact that its increase of 116% was almost 4 times greater (ANOVA, $p < 0.05$) than the average increase in the ventromedial region (30%).[22]

2.3. Breaking the Neuronal Syntax Code

The principal type of syntax code we observed was dynamic temporal spike patterns,[50] which are probably meditated by both patterned input and the intrinsic properties of medium spiny neurons.[51] Both the cerebral cortex and thalamus provide excitatory input to the striatum. Since cerebral cortical lesions fail to disrupt behavioral grooming syntax, subcortical inputs may be of greatest importance for syntactic coding of grooming sequences (although future studies would be needed to confirm that hypothesis). Tonic changes of spike rate are another potential coding mechanism for sequences. However, we found that that tonic rates distinguish poorly between different grooming contexts.[22] This does not rule out other coding functions of tonic firing.

The onset time of neuronal activation usually coincided with or followed the onset of individual chain phases (Figure 2). This timing relationship suggested that dorsolateral neostriatal activity probably does not initiate the sequence nor generate the syntactic pattern of serial order. Instead, the neostriatum is more likely to be involved in monitoring a syntactic signal generated elsewhere and implementing that signal into

behavior. A role in the implementation (rather than generation) of syntactic grooming sequences is consistent with the results of neostriatal lesion studies of the neural basis of behavioral grooming syntax described above.
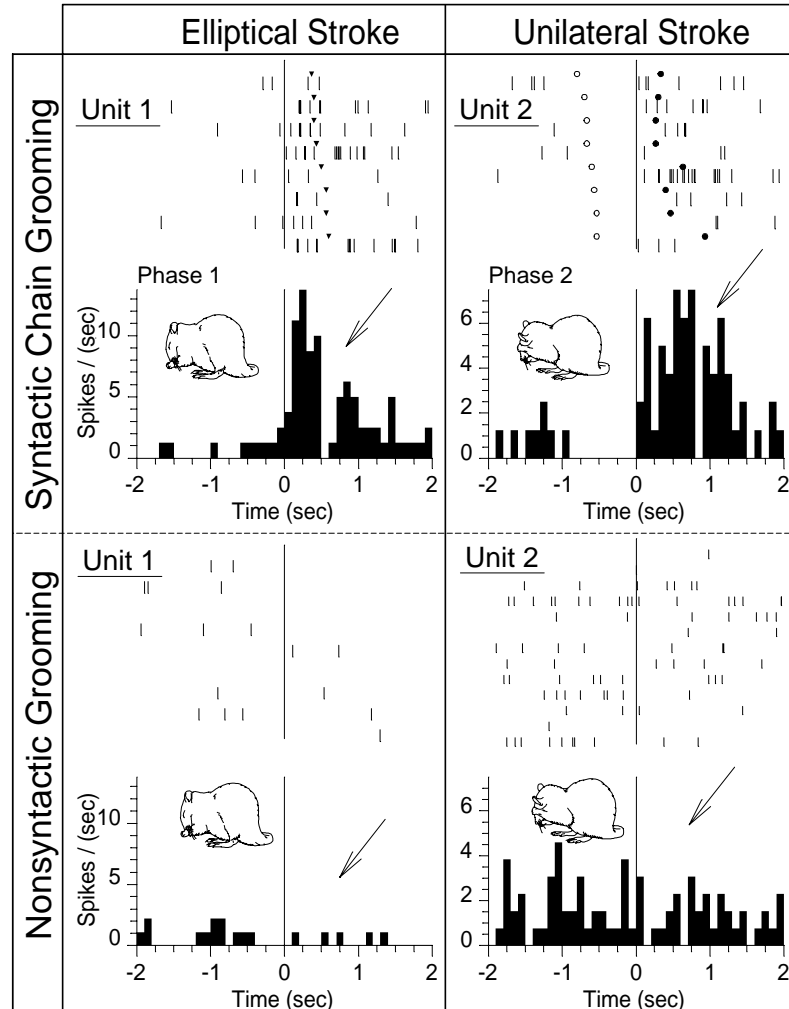

Figure 2. Neuronal activation correlated to chain grooming (top row) and on the same neuronal units, the absence of responses to similar nonchain grooming movements (bottom row). Raster markers indicate the onset of previous and/or subsequent phases. Arrows point to response or same time points with the absence of a response.
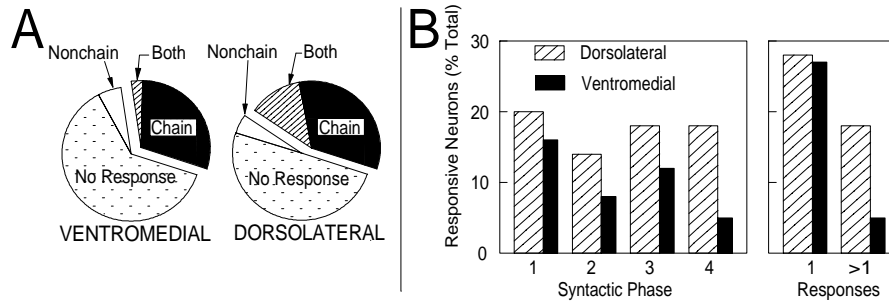
Figure 3: A) Percentage of total neurons responsive during each chain phase Percentage with 1 or >1 response per neurons. B) Proportions of neurons with chain, nonchain, both and no response are indicated by area. Excised portions of the circles indicate proportion of neurons responsive to chain.

The distinctive affiliation of neuronal activation to syntactic patterns of grooming suggests that grooming-related information processing in the striatum is preferentially concerned with controlling syntactic sequences.[22] Activation with nonsyntactic grooming is not only weaker and less common than during syntactic grooming, the patterns of neuronal responses during similar movements differ across these sequential contexts. Thus, striatal neurons appear to code the serial order of natural actions, and not the simple motor properties of constituent grooming movements.

Although both dorsolateral and ventromedial regions had neurons that were sensitive to syntactic grooming sequences, dorsolateral neurons had larger increases in activity than ventromedial neurons during syntactic chains. Dorsolateral neurons were also more likely to respond during multiple phases of a syntactic grooming chain. This suggests that dorsolateral neurons may uniquely code syntactic patterns of movement serial order as a higher-order property, distributed over the duration of the chain. By contrast, activity of neurons in the ventromedial region actually declined during some phases of syntactic grooming chains, and ventromedial neurons were less likely to code either multiple phases or terminal phases.[22] These findings suggest that the dorsolateral region may be concerned with syntactic phase-to-phase transitions, or overall sequential structure, while ventromedial activity is concerned more simply with the onset of the chain.

2.4. Sequence Related Coding in Striatal Afferent Targets

An understanding of how striatal input is transformed at the output of the basal ganglia will provide useful insight about information processing related to motor sequence production. Do neurons in striatal target structures such as substantia nigra pars reticulata (SNpr) utilize syntactic information from neostriatum, and show similar preferential relationships to sequence behavior?[52] Preliminary work in our laboratory by Meyer-Luehmann and colleagues suggest that SNpr neurons do indeed code sequential patterns of grooming in a preferential manner.[53] Further, analyses by Hadden and coworkers suggest that the functional connectivity among nigral neurons itself may be also modulated dynamically by syntactic grooming behavior.[54]

For example, recordings from 47 SNpr neurons in 11 rats showed that 54% of the neurons changed activity during syntactic grooming sequences. Like in the striatum, SNpr neural activation was usually stronger during syntactic chains (52% of responsive neurons) or even unique to syntactic chains (16%). No neuron was active during nonsyntactic grooming alone. Nevertheless, the SNpr also has features of sequential coding that distinguish it from neostriatum. For example, unlike striatum, most SNpr neurons (76%) were active only during the first two phases of the sequence and all but one neuron (96%) was active during Phase I, the onset of the grooming sequence (containing 5-6 rapid small strokes of both paws around the nose). SNpr activity associated with later phases of the sequence grooming (25%) was usually weaker and sometimes even inhibitory. The bias toward active coding of the early part of the sequence was also evident in higher median firing rates observed usually in the first phase of the sequence.

2.5. Dynamic Functional Re-Wiring in SNpr

Perhaps most fascinating, recent computational analyses indicate that the actual functional interactions of effective connectivity between pairs of neurons in SNpr may vary according to the sequential context of grooming behavior. Hadden and colleagues[54] used a cross-correlation analysis[55,56] to infer functional connections between 90 pairs of neurons during three behavioral states: syntactic grooming chains (the rule-driven sequential pattern described above), non-chain grooming (sequentially flexible patterns of grooming movements), and quiet resting.

Strikingly, the type of interaction varied with behavioral state. Identifiable specific interactions within neuron pairs were least likely during quiet resting behavior (17%). During grooming behavior, interactions became more likely, but then still varied with sequential context, being found in 34% of syntactic chains, and being most likely during sequentially flexible (49%). The most frequent type of interaction was serial activation. In serial activation, spikes of one neuron in the pair reliably preceded spikes in the other neuron (47% of pairs), which suggested activation of one caused the other to follow. A second type of interaction was simultaneous excitation, which suggested that both neurons in the pair were being activated together by a third source. In simultaneous excitation, both of the two neurons within a pair (25%) exhibited correlated spikes that were nearly identical in onset. Finally, inhibitory coupling was a third type of interaction that was overall least common (10%). In this interaction, spikes by one neuron were associated with the absence of spikes by the other member.

The most remarkable observation was that a change in the sequential pattern during grooming behavior was often associated with an actual switch in functional coupling from one interaction type to another observed within a single pair of neurons. For example, a behavioral switch from flexible grooming to a syntactic grooming chain caused (or was caused by) a switch in interaction type among neurons for 76% of pairs observed in SNpr. Although constituent movements are similar in the two forms of grooming behavior, the change in sequential organization was accompanied by a functional re-wiring of paired neuronal interactions.

According to current models of basal ganglia circuitry[57,58] neostriatal output nuclei such as SNpr receive an excitatory input from subthalamic nucleus and an inhibitory input

from the striatum. Excitatory subthalamic input may be the source of the strong SNpr activation during the first phase of the chain, whereas neostriatal inputs might contribute more during later phases of the chain. Excitatory signals from subthalamic neurons plausibly might also trigger the most common forms of functional interaction observed between pairs of SNpr neurons, serial activation and simultaneous activation. The potential role of these factors in causing switches among functional connections between SNpr neurons remains to be explored. In summary, these results show that functional connectivity between SNpr neurons is modulated by behavioral states associated with the sequential organization of natural grooming movements. Functional coupling among SNpr neurons appears to become dynamically re-wired as it tracks action syntax.

3. CONCLUSIONS

These experiments show that neuronal activity in the neostriatum and substantia nigra pars reticulata of rats codes grooming syntax, a basic sequential feature of natural rodent behavior. The serial order of movements is the critical factor in determining neuronal activation, and not the elemental movements themselves. Sequential coordination of grooming movements is coded in different ways by neurons in different regions of the basal ganglia. A 'syntax zone' in the dorsolateral neostriatum may play a more important role in coding the full sequence as a whole, and in implementing it into behavior. By contrast, ventromedial zones of the neostriatum may be concerned more simply with component movements and with just the onset of the chain pattern. This conclusion from our functional electrophysiological studies is consistent with those of earlier behavioral lesion studies.

How does this proposed role for the basal ganglia in stereotyped grooming sequences in rats relate to basal ganglia function in human movement, thought, and language? Our results support the possibility is that an ancestral brain role to focus serial element selection and inhibit competing programs[57] to coordinate innate sequences of movements may have had preadaptative utility for the evolution of modified basal ganglia circuits that could be applied toward controlling learned behavioral sequences.[39] Such evolutionary modifications of basal ganglia 'action syntax' preadaptations for sequential motor learning of might also set the evolutionary stage for the further special adaptations in human brains needed for "real syntax", to sequence the serial pattern of language and thought.[5,59,60-62]

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