SEQUENTIAL MOTOR BEHAVIOR AND THE BASAL GANGLIA

Evidence from a serial reaction time task in monkeys

Robert S. Turner, Kevin McCairn, Donn Simmons and Izhar Bar-Gad[1]

1. INTRODUCTION

An important aspect of motor skill lies in the ability to acquire and utilize representations of ordered sequences of motor acts, thereby allowing one to select and execute a sequence of movements as a whole. The importance of this ability becomes evident when one considers alternatives; for instance, having to tie one's shoes every morning based on the conscious selection of each constituent movement of the tying sequence. Understanding the neural control of motor sequences is also important because of the prevalence of human neuropathologies in which movement sequences are impaired differentially [e.g., Parkinson's disease (Benecke et al., 1987)] and because of the widening use of surgical therapies for those disorders (e.g., deep brain stimulation).

The importance of basal ganglia (BG) networks for sequential motor control remains a topic of debate (Marsden, 1984; Mink, 1996). Several lines of research suggest that the motor circuit of the BG plays an important role in sequential behaviors (reviewed recently by Keele et al., 2003; Graybiel, 2004). One of the most prevalent hypotheses is that the BG contributes to the "proceduralization" of action sequences (Eichenbaum and Cohen, 2001). Procedural learning provides the capacity for series of events or actions to be recalled as a whole [i.e., as "chunks" (Graybiel, 1998)] with minimal attentional load. It is possible that the BG contributes both to the laying down of new procedural memories (e.g., as a "teacher") and to the recall or expression of already-learned procedures (Cromwell and Berridge, 1996; Aldridge and Berridge, 1998; Hikosaka et al., 2002). Several investigators have made a strong case for a role for the BG in switching between components of a familiar sequence (i.e., between the constituent movements of "natural units of action" or "chunks")(Brotchie et al., 1991; Graybiel, 1998; Keele et al., 2003; Aldridge et al., 2004). Other investigators have challenged the importance of the BG in this function (Wenger et al., 1999; Smith et al., 2001; Exner et al., 2002; Penhune and Doyon, 2002; Rhodes et al., 2004), especially for the production of short familiar sequences (Verwey et al., 2002).

[1] Robert S. Turner, Kevin McCain and Izhar Bar-Gad, Department of Neurological Surgery, UCSF, San Francisco CA 94122.

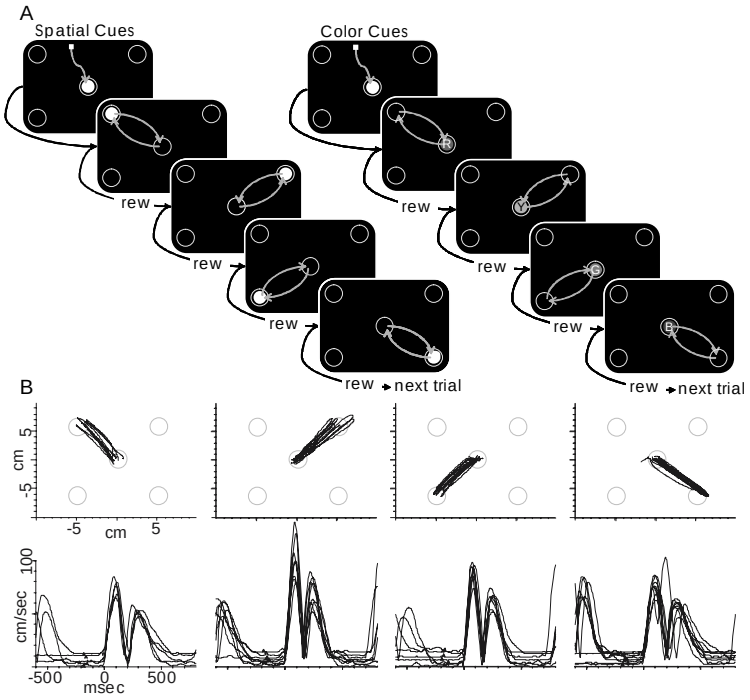

Figure 1. *A.* Schematic of the SRTT paradigm is shown. Animals moved an on-screen cursor through four out-and-back movements between a central fixation target and four peripheral targets (*gray open circles*). Each successful out-and-back movement was rewarded (*rew*). Instructions for which target to capture were delivered through a cue's spatial location (*left*) or its color (*right*). *R,* red; *Y,* yellow; *G,* green; *B,* blue. *B.* Animals performed each out-and-back movement as a whole, with no pause between peripheral-capture and return-to-center components. Spatial trajectories (*top*) and tangential velocities (*bottom*) are shown for several repetitions of each component of the sequence illustrated in *A.* Single-trial velocities, aligned on movement onsets, show a characteristic two-peaked profile, the first for the outward movement and the second for return-to-center. Early velocity deflections in some trials reflect the terminal portion of preceding out-and-back movements.

We have explored BG involvement in the production of familiar sequences using a non-human primate version of the serial reaction time task (SRTT, Nissen and Bullemer, 1987). The SRTT paradigm has been extremely useful for exploring the psychophysics and functional neuroanatomy of human sequential motor behavior (reviewed by Keele et al., 2003). In the prototypical SRTT, a subject is prompted to move her/his hand to a seemingly-random series of target locations. The subject can show learning specific to a surreptitiously-ordered portion of the target series in the absence of awareness of its ordered nature. The primary measure of learning is a reduction in reaction times (RTs; the interval from a "go" signal to the onset of movement), in particular as compared with RTs when the subject is presented later with a random target series. Here we describe an SRTT paradigm for monkeys that shows many similarities to what has been described for humans. We also present preliminary results using this task to explore BG encoding of sequence-related information and the effects on SRTT performance of reversible inactivation of BG output. Our results cast doubt on a major role for the BG motor circuit in selecting constituent movements of sequences that are short and familiar.

2. A PRIMATE MODEL OF THE SERIAL REACTION TIME TASK

Despite its dominance in human studies of sequence learning, SRTT paradigms have seldom been described for non-human primates (Procyk et al., 2000; Lee and Quessy, 2003). The SRTT can be distinguished from other sequence learning paradigms [e.g., trial-and-error learning (Miyachi et al., 1997; Rand et al., 1998)] by the absence of external cues indicating whether the series of stimuli is ordered or not, and by no requirement that a subject actually learn anything. SRTT learning can occur incidentally, independent of reward contingency or intention to learn.

We developed an SRTT-like task for macaques that replicates many of the characteristics of the human version. Three rhesus monkeys learned to move a joystick-controlled cursor into a series of target zones displayed continuously on an LCD monitor (Fig. 1*A*). Visual cues, indicating which target to capture by their spatial location or color, led an animal through a sequence of four out-and-back movements. The actual targets to be captured changed from block-to-block. Typically, 10-trial blocks of "random" sequences were interleaved with 50-trial blocks of "fixed" sequences. For random trials, the four targets changed at random from trial-to-trial, with each target appearing between 0 and 4 times. Two types of "fixed" sequences were presented: 1) Novel fixed sequences were used to study the acquisition and transfer of new sequence knowledge. In these sequences, targets were presented in a fixed order as determined by random selection from all orderings of 4 items with replacement. 2) Over-learned fixed sequences (e.g., Fig. 1*A*) were used to measure the full extent of learning possible and to assess BG involvement in the production of familiar sequences. Over-learned sequences were practiced extensively for weeks prior to collection of the data reported here. Different over-learned sequences were used at different times in each animal.

2.1. SRTT Learning in the Macaque

For all three animals, RTs shortened gradually following the introduction of a novel fixed sequence (Fig. 2*A*). RTs for random sequence blocks did not deviate significantly from the mean for random trials presented prior to learning. The learning-related reduction in RTs was modeled as a piece-wise linear function of trial number (Fig. 2*A*). The pre-asymptotic slope of the line reflected the rate of learning (msec reduction in RT per sequence trial performed). Across 33 learning sessions in three animals, RTs declined slowly during the initial 200-500 trials of a novel sequence (Fig. 2*B*, *Novel*), after which RTs asymptoted at a significantly lower level (~70 msec below the RTs of random trials). Knowledge acquired on the first day of training aided performance of the same sequence on the following day, as reflected by substantially faster learning rates (Fig. 2*B*, *Recall*).

2.2. Sequence Knowledge Independent of Motor Effectors and Sensory Cues

How sequence knowledge is represented in the CNS has been studied in humans by "transferring" subjects to a different task following an initial session of SRTT learning. By dissociating a task's sensory cues from motor output, these experiments have shown that sequence knowledge is represented centrally as a series of abstract motor responses, independent of any one end-effector. Multiple studies have shown that subjects can utilize previously-acquired sequence knowledge to improve RTs on a transfer task that requires different movements than those executed during initial training (Cohen et al.,

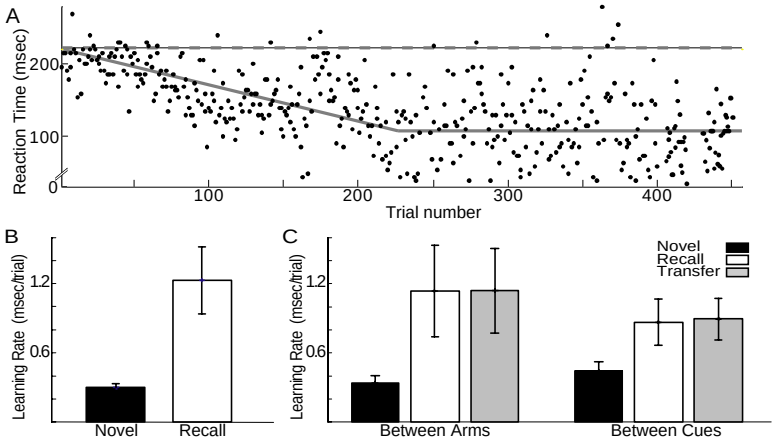

Figure 2. *A.* An example of the slow reduction in RTs following introduction of a novel fixed sequence. •, RTs from single trials. *Horizontal dashed line*, mean RT during random sequences. *Solid gray line*, piece-wise linear fit to the novel sequence RTs. *B.* The mean rate of reduction in RTs (i.e., *Learning Rate*, ±SEM) is plotted. Novel fixed sequences were learned slowly on the day they were first introduced (*Novel*), but recall of the learned sequence led to a rapid fall in RTs on the following day (*Recall*). *C.* Sequence knowledge transferred readily between arms (*left*, *Transfer*) and between color and spatial cues (*right*, *Transfer*).

1990; Keele et al., 1995). The fact that SRTT learning typically occurs in motor rather than perceptual systems was demonstrated by showing efficient transfer of sequence knowledge to tasks that present different sensory stimuli but require the same motor responses (Willingham et al., 2000). Thus, the consensus view from human studies is that sequences are represented as a series of abstract motor responses, independent of the specific end effectors and sensory cues used in a task. We found similar results for SRTT learning in non-human primates.

Transfer experiments were performed on the day following initial learning of a novel sequence. For these experiments, subjects first performed a block of random trials followed by a block of the novel fixed sequence used the previous day. Animals were then transferred to trials in which either the opposite hand was used to move the joystick or the alternate type of visual cues was presented. The rate of learning following either form of transfer was significantly faster than that during initial learning of the novel sequence and it was statistically indistinguishable from that for simple next-day recall of the sequence (Fig. 2*C*). Full transfer between arms indicates that sequence knowledge was equally available to the motor control apparatus of both forelimbs. Combined with similar transfer between cue types, these results closely parallel what has been described commonly for human SRTT learning. Sequence knowledge is typically represented as a series of motor responses, abstracted from specific movements or effectors.

In summary, our model of SRTT learning in non-human primates provides distinct advantages that supplement other sequence learning paradigms. The SRTT provides a way to study sequence learning independent from confounding factors such as attentional load, sense of effort, strategy, cognitive set, and subject awareness. During SRTT learning, the task stimuli and motor responses remain unchanged and knowledge of results, as far as whether the sequence is being learned correctly, is unavailable. Unlike trial and error learning, only one target is presented at a time and no “wrong” movements

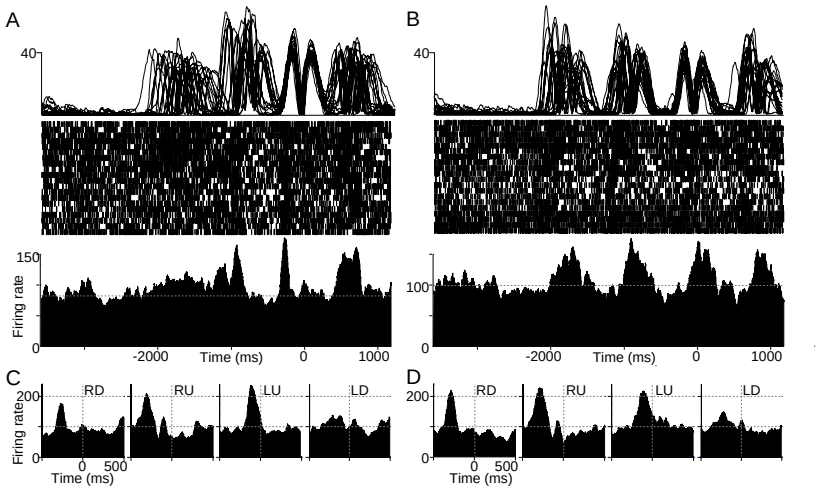

Figure 3. Task-related activity of a GPi neuron is shown during performance of learned and random sequences (*left* and *right*, respectively). Perimovement changes in firing were very similar under the two conditions. All of the data shown in *A* and *B* are aligned on the peripheral target touch of the 3rd movement. Single-trial tangential velocities (*top*) show that transitions from one movement to the next were often very rapid under the learned condition (*A*) in contrast to the clearly-defined pauses between movements under the random condition (*B*). Differences between learned and random conditions are evident in rasters (*middle*) and spike density functions (SDFs, *bottom*), but data from the random condition were not sorted according to peripheral target. *C* and *D*, Perimovement discharge was very similar under learned and random conditions in SDFs sorted according to target. Histograms are aligned on the time of movement reversal at the peripheral target. Data from the random trials (*D*) are averaged by target independent of the target's ordinal position in the sequence. *RD*, right down; *RU*, right up; *LU*, left up; *LD*, left down.

are made. Thus, learning-related changes in task performance cannot be attributed to altered performance strategies or movement kinematics. Also, it is unlikely that cognitive set plays a role in SRTT learning because subjects are given no instructions concerning learning and learning can accrue without awareness of the presence of a sequence. Finally, implementation of an animal model of SRTT learning, in which invasive studies can be performed, can work synergistically with ongoing studies of SRTT learning (e.g., Bischoff-Grethe et al., 2004). Below, we provide preliminary results from our studies of BG involvement in the performance gains associated with long-term SRTT training.

3. NEURONAL CORRELATES IN THE PALLIDUM OF SRTT PERFORMANCE

We investigated the prevalence of pallidal task-related activity that differed between random and learned SRTT sequences. Given the many reports of sequence-related activity in the BG (e.g., Kermadi et al., 1993; Kermadi and Joseph, 1995; Mushiake and Strick, 1995; Ueda and Kimura, 1997; Aldridge and Berridge, 1998; Jog et al., 1999; Miyachi et al., 2002; Kimura et al., 2003) and the extensive literature pointing to BG involvement in motor sequencing (see Introduction), it was reasonable to predict that activity in the pallidal motor territory would show a preference for movements performed

as a part of a learned sequence. To our surprise, we found little evidence for qualitative differences in pallidal activity related to sequence familiarity..

Standard single unit recording methods were used to sample the extracellular activity of neurons in external and internal segments of the globus pallidus (GPe and GPi, respectively). Recordings were obtained from two animals performing the SRTT paradigm described above. Random and over-learned sequences were presented in separate blocks. The results shown in Fig. 3 serve as an exemplar for a large majority of the >400 cells sampled across the motor territory of both pallidal segments. Despite the presence of clear differences in RTs between learned and random conditions, we found very few sequence-related effects on perimovement discharge. Clearly, this preliminary conclusion must be confirmed through quantitative analysis. The far-reaching implications of the result, if confirmed, are discussed in the general conclusion.

4. SEQUENCE RECALL DURING GPI INACTIVATION

To examine the importance of the BG motor circuit for the recall of familiar sequences, we reversibly inactivated sites in the posterior GPi in two animals as they performed the SRTT. Muscimol, a GABAergic agonist, was microinjected at a range of sites throughout the posterior GPi (1µg/µl, 0.5µl-2.0µl). Because this part of GPi constitutes the principal output nucleus of the BG sensorimotor circuit, inactivation here should disrupt motor functions that depend on BG signaling. Injection sites were chosen based on prior microelectrode mapping to identify nuclear boundaries and regions responsive to proprioceptive stimulation.

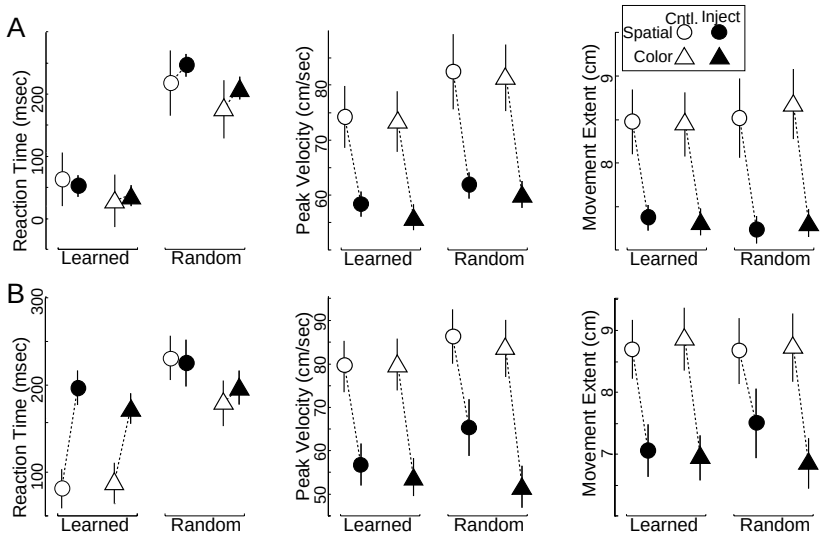

Figure 4. Example data illustrate the two most common effects of muscimol microinjection into the sensorimotor GPi. *A.* In most cases, GPi inactivation had a minimal effect on RTs [*left*, compare pre-injection (*open symbols*) versus post-injection means (*filled symbols*)]. This was true irrespective of whether animals performed over-learned fixed sequences (*Learned*) or random sequences (*Random*), or whether cues provided information by their spatial location (*circles*) or color (*triangles*). In contrast, muscimol injections consistently reduced movement velocity (*middle*) and extent (*right*). *B.* In a minority of cases, GPi inactivation lead to a selective slowing of RTs during performance of over-learned fixed sequences. Error bars ±SEM.

If the BG motor circuit contributes to the selection of component movements within a learned sequence, then GPi inactivation should interfere with that selection process and thereby block the expression of RT savings. However, among 25 injections performed in two animals, the majority had minimal effects on RTs, independent of whether sequences were over-learned or random (Fig. 4*A*, *left*). In keeping with previous reports (Horak and Anderson, 1984b; Mink and Thach, 1991; Inase et al., 1996), GPi inactivation consistently reduced both peak velocity and movement extent (Fig. 4, *right*). Interestingly, a minor fraction of the injections did block RT savings for a learned sequence (Fig. 4*B*). These results indicate that any BG role in selecting sequence components likely involves a subcircuit within the general BG sensorimotor region (Hoover and Strick, 1993). Large parts of the BG motor circuit can be functionally disconnected from downstream motor control areas with no effect on the efficient selection and initiation of component movements within an over-learned sequence.

5. CONCLUSION

A variety of experimental approaches will be required to develop a detailed, biologically-grounded model of sequential motor control. Among the approaches used to date, the SRTT has been perhaps the most productive for studying sequence learning in humans. This paradigm has led to the demonstration of a form a procedural learning that can occur incidentally, independent of reward contingency or intention to learn (Nissen and Bullemer, 1987), and the demonstration that this form of learning very likely involves motor control regions of the CNS, including the BG (e.g., Grafton et al., 1995; Hazeltine et al., 1997; Bischoff-Grethe et al., 2004). A central remaining question is whether distinct roles can be assigned to the different components of this network. To address this question there are obvious benefits to replicating the SRTT in a non-human primate. Although SRTT-like learning has been described in non-primate species (e.g., Baunez and Robbins, 1999), there are clear advantages to using a species with close structural and functional similarities to the human CNS. We have developed an SRTT paradigm for monkeys that shows many similarities to what has been described for humans. Of particular significance is that our model consistently shows a gradual reduction in RTs within one learning session. Gradual reductions in RT like this are a hallmark of SRTT learning in humans when subjects are unaware of the ordered sequence (i.e., during "implicit" learning; Keele et al., 2003). It is notable that other features of the implicit form of SRTT learning in humans were also found in our animal model (i.e., recall of sequence knowledge independent of changes in sensory cues or end effectors). Thus, we conclude that our model of SRTT learning allows investigation of the neural substrates of implicit-like sequence learning in a non-human primate. Here, we have presented preliminary results on involvement of the BG motor circuit in the expression of familiar sequences learned under SRTT conditions.

5.1. BG Contributions to Motor Sequences

With our monkey model of the SRTT, we have address a narrowly-defined hypothesis: that the BG motor circuit contributes a switching type of function that aids automatic chaining from one component to the next in a well-learned sequence of movements (Brotchie et al., 1991; Cromwell and Berridge, 1996; Graybiel, 1998; Keele et al., 2003; Aldridge et al., 2004). We investigated the prevalence in the pallidum of

activity related preferentially to the production to familiar sequences based on the rationale that prominent encoding of sequence-related information would suggest an important role in sequence performance. We also investigated the effects of GPi inactivation based on the view that acute blockade of normal BG output should disrupt or alter aspects of behavior that the BG contributes to. Results from both experiments were not strongly supportive of the hypothesis stated above.

Very few pallidal cells in our recording study had perimovement activity related selectively to the performance of familiar sequences. These results should be interpreted with caution given the number of recording studies that describe sequence-related discharge in BG structures (Kermadi et al., 1993; Kermadi and Joseph, 1995; Mushiake and Strick, 1995; Ueda and Kimura, 1997; Aldridge and Berridge, 1998; Jog et al., 1999; Miyachi et al., 2002; Kimura et al., 2003). Most relevant for the present discussion is the study of Mushiake and Strick (1995), who found that some pallidal neurons had activity selective for memory-guided sequential movements. The sequence-specific activity was concentrated in the pallidal region that other studies have shown to project via thalamus to the supplementary motor area (Hoover and Strick, 1993). That study, along with many others, clearly confirms that neuronal activity in the BG can distinguish between a variety of movement contexts including sensory-guided versus memory-guided or sensory-triggered versus self-initiated (Hikosaka and Wurtz, 1983; Kimura et al., 1992; Turner and Anderson, 2005). Previous recording studies, however, do not specifically address the question whether the BG motor circuit is activated preferentially for familiar sequences under SRTT-like conditions. This is not a minor distinction because few tasks aside from the SRTT control for differences in context (e.g., task stimuli, movement kinematics, reward contingencies, knowledge of results) that are unrelated to the expression of procedurally-acquired sequence knowledge. Our recording results suggest that activity in the pallidal motor circuit has little involvement in the expression of sequence knowledge under SRTT conditions.

Our GPi inactivation results also bring into question the importance of the BG motor circuit for the expression of procedural sequence knowledge. In contrast to strong and consistent effects on movement kinematics, GPi inactivation had infrequent and variable effects on the RT savings associated with familiar sequences. These results are not without precedent. It has been shown repeatedly that acute or permanent inactivation of the GPi motor territory in normal primates has a minimal effect on movement initiation (Horak and Anderson, 1984b; Mink and Thach, 1991; Inase et al., 1996). More recent work suggested indirectly that motor sequencing might also be preserved following acute pallidal inactivation (Wenger et al., 1999). Additionally, ablation of the avian equivalent of the BG does not interfere with the execution of already-learned song (clearly, a sequential behavior; Nottebohm et al., 1976; Bottjer et al., 1984) although it does interfere with new song acquisition. Finally, many studies in humans have produced results that are consistent. Leaving aside for the moment studies of Parkinson's disease (PD) itself, ablation of the posteroventral GPi (i.e., pallidotomy) is an effective and well-accepted neurosurgical treatment for PD (Marsden and Obeso, 1994; Laitinen, 1995; Baron et al., 1996; Smeding et al., 2005). Despite that fact that pallidotomy ablates a large, sometimes bilateral (Green et al., 2004), portion of the GPi motor territory, few if any motor deficits result (Limousin et al., 1999). Significantly, there is no evidence that pallidotomy disrupts the performance of already-learned sequential behaviors (e.g., hand writing, shoe tying), although some reports suggest that pallidotomy interferes with new procedural learning (Brown et al., 2003; Sage et al., 2003).

How do we harmonize the view laid out above with the well-recognized motor sequencing deficits observed in PD (Benecke et al., 1986, 1987) and with reports that inactivation of the motor striatum interferes with production of already-learned sequences (Cromwell and Berridge, 1996; Miyachi et al., 1997)? One reasonable explanation is that striatal dysfunction is likely to have effects on BG-recipient circuits that are very different from the effects of GPi inactivation. The striatal dysfunctions associated with dopamine depletion lead to abnormally-pattern activity in the GPi (Miller and DeLong, 1988; Filion and Tremblay, 1991). The resultant parkinsonian symptoms can be blocked by temporary or permanent inactivation of the GPi (Laitinen, 1995; Baron et al., 2002). Striatal lesions also induce abnormal pallidal firing patterns (Sachdev et al., 1991), and it is reasonable to predict that GPi inactivation would also block the behavioral abnormalities associated with those lesions. Thus, as has been inferred from the success of ablative therapies for PD, abnormally-patterned BG outflow appears to have far more deleterious effects on the functions of BG-recipient structures than the simple interruption of BG outflow.

In conclusion, our preliminary studies using a monkey model of the SRTT cast doubt on a major role for the BG in the performance enhancements associated with simple familiar sequences. Recently the concept has arisen that motor sequences are represented differently in the CNS depending on the complexity of the sequence (Rhodes et al., 2004). It may be possible to represent short familiar sequences, like the ones we used, at the cortical level, independent of BG involvement (Verwey et al., 2002). Indeed, transient inactivation of the primary motor cortex has been shown recently to selectively disrupt the performance of over-learned motor sequence (Lu and Ashe, 2005). It remains quite possible that a subcircuit within the BG motor territory does contribute to the expression of SRTT RT savings, as suggested by the handful of GPi inactivations that did block RT savings. Additionally, the BG may reserve important roles in learning new sequences or in the production of more complex sequences in which it is necessary to switch between or concatenate sequence chunks that are represented elsewhere.

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