Facilitation of Visuomotor Associative Learning by the Basal Ganglia

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The notion that the basal ganglia were involved in motor control developed in the late 19th and early 20th centuries. Samuel Kinnier Wilson is given credit for coining the term ''extrapyramidal'' to describe a motor system distinct from the pyramidal system in his 1912 treatise describing hepatolenticular degeneration.[1] The recognition that other neurological disorders with obvious motor disturbances such as Parkinson disease, Huntington disease, and hemiballismus involve the basal ganglia further evidenced their role in motor control.

In the second half of the 20th century, however, studies using targeted lesions and pharmacological manipulations in animals began demonstrating that the basal ganglia were also involved in learning and memory.[2] In particular, recent electrophysiological studies in behaving animals have demonstrated that the basal ganglia are involved in visuomotor associative learning, a type of instrumental conditioning in which, given a particular environmental situation or visual stimulus, the animal must choose a response.[3] Because the ''correct'' response is typically indicated by some type of reward, the animal must learn to make arbitrary associations between a stimulus and its corresponding ''correct'' response.

The pioneering work of Wolfram Schultz[4] and colleagues provided a mechanism for reward sensitivity by demonstrating that the firing rate of dopaminergic neurons in the substantia nigra pars compacta encodes a reward signal (proportional to the difference between expected and received reward). Because the dorsal striatum (composed of the caudate nucleus and putamen) is the principal target of substantia nigra pars compacta neurons and the main input stage of the basal ganglia, considerable effort has focused on studying learning-related changes in this region. The dorsal striatum also receives projections from virtually all areas of cortex, providing it with rich contextual cues about the environment. This unique convergence of information puts the dorsal striatum in an opportune position to integrate information about environmental stimuli and reward, as is necessary for associative learning. In support of this framework, recent studies have illustrated dynamic modulation of striatal activity during reinforcement-driven associative learning.[5-7]

Although prior work has concentrated on the role of the striatum in learning, relatively little is known regarding the role of the output nuclei. Output structures of the basal ganglia, the globus pallidus internus (GPi) and substantia nigra pars reticulata, tonically inhibit the thalamic motor nuclei and superior colliculus, respectively. The GPi is involved in skeletomotor control and is the focus of this study. Because the GPi and substantia nigra pars reticulata are the only structures that significantly project out of the basal ganglia,[8] their activity should encode this associative processing and relay it to thalamocortical circuits to influence motor behavior. We therefore recorded the activity of GPi neurons in monkeys trained to perform a visuomotor associative learning task.

METHODS

Preparation and Behavioral Task

Two adult male rhesus monkeys (*macaca mulatta*) were studied in accordance with Massachusetts General Hospital guidelines on animal research. A titanium head post and stereotactically placed plastic recording chamber (Crist Instruments, Hagerstown, Maryland) were affixed to the skull. A craniectomy was performed at the base of the recording chamber, exposing the dura. The chamber was periodically cleaned using sterile technique and otherwise kept sealed with a plastic cap.

During recording sessions, animals were comfortably seated with head fixation in a primate chair facing a video monitor. A solenoid-controlled liquid reward delivery system was positioned at the mouth. A joystick was attached to the front of the chair. Eye position was continuously recorded and required to remain within 1° of the fixation point.

The animals were required to learn the association between visually presented objects and a joystick movement in 1 of 4 possible directions (Figure 1A). Each trial began with a fixation period of 500 milliseconds, followed by presentation of the object for 500 to 1000 milliseconds. A change in color of the central fixation point served as a go cue, at which time

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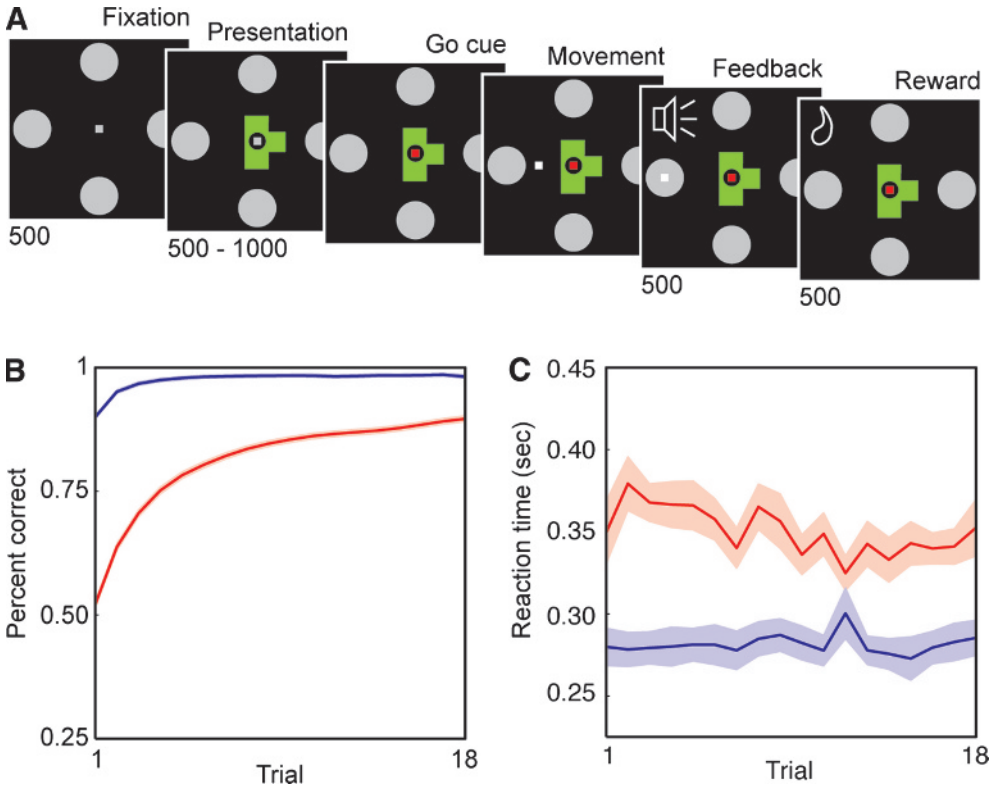

FIGURE 1. Task and behavior. A.) the behavioral task (see Methods). The duration of each epoch (in milliseconds) is noted below the representative screen. B.) behavioral learning curves for familiar (blue) and novel (red) objects averaged over both animals' performance. The dark line represents the mean; the lighter shaded region represents the standard error. C, reaction times for correct familiar (blue) and novel (red) object trials.

joystick movement toward 1 of the 4 targets was allowed. Once the target was reached, a high (correct choice) or low (incorrect choice) feedback tone sounded for 500 milliseconds, followed by water reward in the case of a correct choice.

In each block of trials, 4 objects were presented, 1 per trial, in pseudorandom fashion. Two objects were familiar to the animals from previous training with known constant joystick direction associations. The other 2 objects were randomly generated novel shapes with unknown joystick direction associations. The animals had to learn, by trial and error with water reinforcement, the correct joystick direction associated with the novel objects. Incorrect trials were repeated until the correct choice was made. Block switches occurred without overt warning after each of the 4 objects was answered correctly 17 times. The new block would contain 2 different familiar objects and 2 newly generated novel objects.

Electrophysiology

Before each recording session, a sterile electrode grid was affixed within the recording chamber. Acute recordings were performed with 0.5- to 1.0-MΩ tungsten microelectodes (FHC, Bowdoin, Maine). Signals were band-pass filtered between 200 Hz and 5 kHz and sampled at 20 kHz (Spike2, CED, Cambridge, United Kingdom). Spikes were sorted with a template-matching algorithm (Spike 2). Eye position and joystick deflection were sampled and recorded at 1 kHz.

Data Analysis

We used a state-space smoothing algorithm for point processes to estimate the learning curve as the animals learned the correct associations.[9] This algorithm uses a Bernoulli probability model to estimate the animal's continuous learning from his binary performance on each trial. The learning criterion point was defined as the first trial when the lower 99% confidence bound of the learning curve surpassed chance (25% for 4 possible targets). The criterion trial therefore represents the estimated point at which the animal first learned the correct association. Only learning blocks reaching criterion were included in subsequent analyses.

Firing rates were calculated within a 500-millisecond window centered on the task epochs (fixation, image presentation, go cue, movement, reward). To identify the subset of neurons that had activity related to the task, we calculated the Pearson correlation coefficient (r) between the learning curve and firing rates. Only correct trials were included in this analysis.

RESULTS

Behavioral Data

Within a learning block, animals were presented with 2 familiar and 2 novel objects. From previous training, the animals knew the correct joystick direction associated with the familiar objects. Performance on familiar object trials was

therefore close to 100% from the beginning of the block. Performance on novel object trials improved over the course of the block as the correct association was learned. These results are shown in Figure 1B, which depicts learning curves (see Methods) averaged over both animals' performance. On average, the animals completed 6.3 ± 0.2 (mean ± SEM) learning blocks within a single day, for a total of 460 blocks. Criterion performance (see Methods) was achieved in 72% of blocks, on trial number 9.3 ± 0.8 (counting the preceding incorrect and correct trials). Reaction times for the familiar objects were shorter than those for novel objects, consistent with better performance on familiar object trials (Figure 1C).

Neuronal Data

We recorded the activity of 73 individual GPi neurons across both animals. These neurons had a high baseline firing rate of 35.4 Hz, averaged across all recordings, consistent with their known capacity for tonic inhibition of thalamic neurons. Peri-event time histograms and firing rates were calculated centered on the 6 salient features of the behavioral paradigm: fixation, object presentation, go cue, initiation of movement, feedback period, and reward administration.

Predominant changes in neuronal firing tended to occur either at the go cue or at the initiation of movement. Thus, example raster plots of GPi neurons aligned to the go cue are shown in Figure 2. Figure 2A depicts a neuron representative of a group that increased its firing rate at the go cue. As mentioned earlier, the GPi sends GABAergic inhibitory projections to the ventral anterior and ventral lateral nuclei of the thalamus, which in turn project to primary and supplementary motor cortex.[10] Thus, increased GPi activity would tend to suppress downstream thalamocortical circuits and the motor programs they encode.[11] Figure 2B, on the other hand, depicts a neuron that decreased its firing rate at the go cue. This decrease in firing would result in the release of inhibition, or facilitation, of the thalamocortical circuit to which it projected.

We therefore categorized all recorded neurons based on their change in firing at the go cue compared with the firing rate during fixation (Figure 3). Of the 73 total neurons, 52 neurons (71%) increased firing to any degree, and 21 (29%) decreased firing to any degree. Limiting the changes to only those that were statistically significant (1-way analysis of variance by epoch with Tukey highest-significant-difference posthoc test, $P < .05$), 36 neurons (49%) increased firing at the go cue with regard to fixation, and 11 (15%) decreased. Thus, approximately 3 times more neurons increased firing than decreased.

Relationship to Learning

We then sought to determine whether neuronal firing patterns were related to the process of learning new stimulus-response associations. We limited this analysis to those blocks

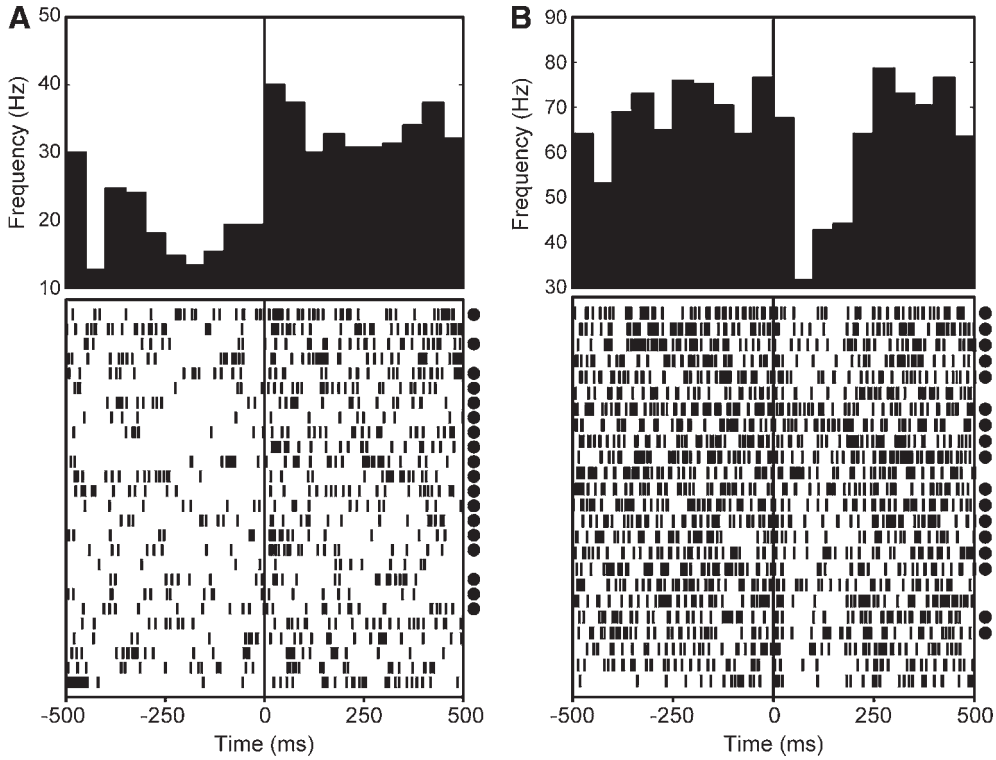

FIGURE 2. Example neuron rasters. A, an example of the raster (bottom) and peristimulus time histogram (PSTH; top) are shown for a neuron that increased its firing at the go cue (time 0). The raster depicts sequential trials, starting from the bottom row. Solid circles to the right represent correct trials. B, example raster and PSTH for a neuron that decreased its firing at the go cue.

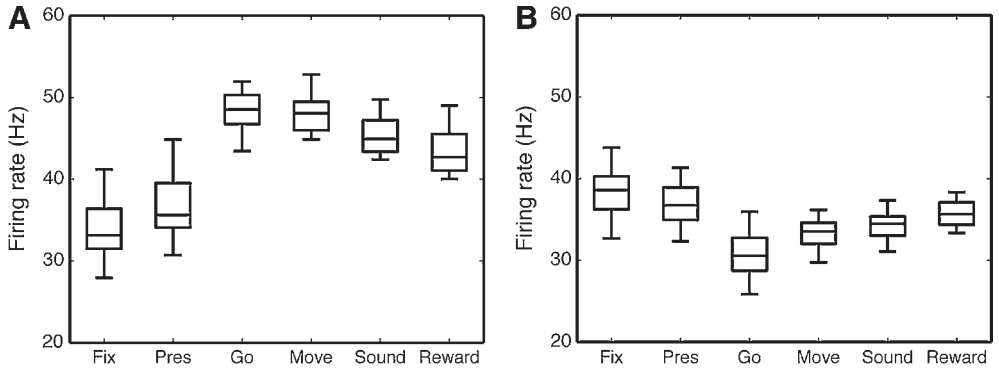

FIGURE 3. Population neuronal data. Population-averaged data for all neurons that significantly increased (A, n = 36) or decreased (B, n = 11) their firing rate at the go cue. The box-and-whisker plot depicts the median (middle line), quartiles (box), and 1 SD (whisker). Fix, fixation; Pres, presentation.

in which the association for at least 1 of the 2 novel objects was learned to criterion performance. Because we did not necessarily expect all recorded neurons to be involved in the learning process, we first correlated firing rates with behavioral performance (learning curves) on a trial-by-trial basis for all novel object trials achieving criterion and designated those neurons with firing that correlated with learning as ''learning-related neurons.''[7]

Of the 73 neurons recorded, 21 (29%) showed learning-related changes. The composition of this subpopulation of neurons differed from that of the overall population in terms of their change in firing rate. Eleven (52%) of the 21 learning-related neurons increased firing at the go cue, and 10 (48%) decreased. In other words, the learning-related neurons composed only 21% (11 of 52) of the total number of increased firing neurons and 48% (10 of 21) of the decreased firing neurons. Considering only those neurons with a change that was significant compared with fixation (1-way analysis of variance by epoch with Tukey highest-significant-difference posthoc test, $P < .05$), 8 (38%) increased and 6 (29%) decreased firing.

Thus, the learning-related neurons were disproportionately composed of decreased firing neurons. Given the inhibitory role of GPi projections, this finding implies that the learning-related neurons played a prominent role in releasing the inhibition of particular downstream thalamocortical motor programs to facilitate a particular action.

To determine whether there was any behavioral correlate supporting the hypothesis that GPi neurons facilitate particular motor programs during learning, we examined behavioral parameters as a function of the stage of learning. To do so, we again restricted the analysis to blocks in which criterion performance was achieved on novel objects. Data were then aligned to the criterion trial (designated trial 0) rather than the first correct trial. This realignment corrected for differences in the rate of learning across blocks and allowed for interblock comparison between similar stages of learning. This analysis was performed for the learning curves and reaction time data.

Criterion-aligned learning curves showed a sigmoidal shape for novel object trials (Figure 4A). Reaction time data also showed a different profile when aligned to the criterion trial (Figure 4B). Instead of a smooth monotonic profile, there was a dip in reaction time after the initial 2 or 3 trials such that for several trials before achieving criterion, reaction times were significantly lower than that of the criterion trial (2-tailed

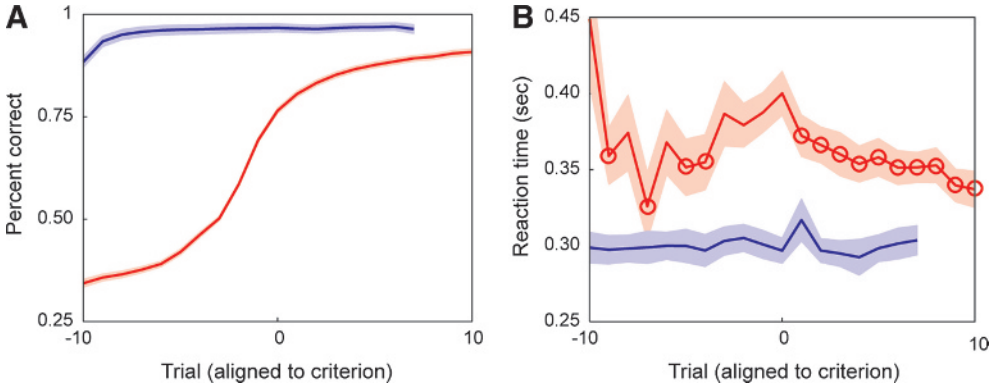

FIGURE 4. Criterion-aligned performance and reaction time. A, to compare learning curves across blocks, performance on novel object trials (red) was aligned to the criterion trial (see Methods). Because there was no learning on familiar object trials (blue), alignment was not applicable. B, criterion-aligned reaction times for all novel object blocks (red). Open circles represent significant differences from familiar object trials.

t test, $P < .05$). The nadir of this dip was approximately 7 trials before criterion. By the time criterion performance was achieved, novel object reaction times had increased compared with the precriterion nadir and then decreased monotonically in postcriterion trials as the association was learned with increasing confidence and performance approached that for familiar objects.

DISCUSSION

Here, we report several findings from single-unit GPi recordings in a pair of monkeys trained to perform a visuomotor associative learning task. First, a majority of GPi neurons were responsive to the go cue. The modulation of their firing rates at the go cue was heterogeneous, and the ratio of those that tended to increase their outflow to those that decreased it was approximately 3:1. Owing to their effects on downstream thalamocortical targets, GPi projection neurons increasing and decreasing their firing at the go cue will hereafter be referred to as ''inhibiting'' and ''facilitating,'' respectively. Second, a subset of neurons was found to manifest learning-related activity; ie, modulation of their firing rates was correlated with the animals' behavioral learning curves. This learning-related population was relatively enriched in facilitating neurons; the ratio of facilitating to inhibiting neurons was approximately 1:1. Finally, when making novel visuomotor associations, the animals manifested a transient dip in their reaction times that preceded establishment of the learning criterion by approximately 7 trials. Taken together, these findings suggest that the dynamic modulation of GPi output may provide a mechanism for facilitating the selection of profitable actions during associative learning.

Most studies interrogating GPi motor outflow have invoked basic repetitive movement tasks such as cued reaching or flexion and extension protocols across single joints. Several groups have reported independent populations of facilitating and inhibiting neurons that modulate their firing in peri-movement epochs, and the relative sizes of these 2 populations tend to be in rough agreement with those observed here, with approximately 70% inhibiting and 30% facilitating.[12-14] It has also been reported that the ratio of activating to inhibiting neurons can vary. A dramatic (and permanent) shift in preference for inhibiting neurons during passive limb movement has been noted in monkeys rendered parkinsonian with MPTP.[15] It also appears that GPi neurons prefer different task contexts; inhibiting neurons were shown to be more prevalent in a memory-contingent motor task, whereas facilitating neurons preferred a sensory-contingent motor task.[16] Our findings are unique in that our behavioral task contained a learning component, allowing us to demonstrate that the GPi can dynamically shift its output within a task.

The functional architecture of the basal ganglia is often framed in terms of 2 opposing parallel loops: the ''direct'' cortex-striatum-GPi pathway that tends to excite downstream thalamocortical motor programs and the ''indirect'' cortex-striatum-GPe-subthalamic nucleus-GPi pathway that tends to suppress them.[17,18] As the principal skeletomotor output nucleus of the basal ganglia, the GPi represents the point of convergence of these 2 circuits. The balance of inputs from these 2 competing pathways is thought to govern the outflow of the GPi.[11] Viewed in the framework of the direct/indirect model, our findings suggest that input to the GPi may shift as a function of the learning state. The enrichment in facilitating neurons may reflect a learning-related toggle from a baseline of indirect-pathway dominance (and thus relative suppression of downstream targets) towards a more facilitatory direct-pathway–mediated state. Such a change could also account for the transient dip in reaction times during novel object blocks occurring well before the attainment of learning criterion (Figure 4B).

Although the standard direct/indirect model is instructive, its parsimony can be limiting. In particular, it lacks the specificity to resolve the mechanisms underlying a variety of movement disorders.[19] Recently, a center-surround paradigm[11] has been advanced to complement the connectivity described in the direct/indirect model. This hypothesis maintains that one role of the basal ganglia is to encourage focused selection of motor programs via the inhibition of competing circuits. In other words, the basal ganglia suppress motor programs that would otherwise interfere with the efficient execution of contextually selected programs deemed to be more profitable. Our results are consistent with such a framework. For example, the relative prevalence of learning-related neurons that decreased their activity at the go cue could represent a ''facilitatory center'' that disinhibits a relatively focused set of motor programs, and the preponderance of inhibiting neurons in the general population could represent an ''inhibitory surround'' that suppresses a broader repertoire of competing programs.

The synthesis of the center-surround and direct/indirect models[20] provides a valuable framework for our understanding of the basal ganglia. A weakness, however, is that the neurophysiological data contributing to these models have been derived primarily from simple, repetitive stimulus-response paradigms. The basal ganglia, in contrast, interact with stimuli from a rich and constantly evolving external environment. It is not surprising, then, that our current models offer limited insight into the schemes that permit these structures to effect rapid and meaningful behavioral accommodation to a torrent of highly variable external cues. Our associative learning paradigm injects a dynamic element into the interrogation process, and it has yielded data suggesting that there are patterns of activity in both the caudate[7] and now the GPi that correlate with different components of

learning. Future work will continue to explore the individual contributions of these structures and how their interplay mediates information flow through the basal ganglia.

Disclosure

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