Short-term plasticity shapes activity pattern-dependent striato-pallidal synaptic transmission

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Kim J, Kita H. Short-term plasticity shapes activity pattern-dependent striato-pallidal synaptic transmission. J Neurophysiol 109: 932–939, 2013. First published November 28, 2012; doi:10.1152/jn.00459.2012.—The cortico-striato (Str)-globus pallidus external segment (GPe) projection plays major roles in the control of neuronal activity in the basal ganglia under both normal and pathological conditions. The present study used rat brain-slice preparations to address our hypothesis that the gain of this disynaptic projection is dynamically controlled by activations of short-term plasticity mechanisms of Str-GPe synapses. The Str-GPe projection neurons fire with very different frequency and firing patterns in vivo depending on the condition of the animal. The results show that the Str-GPe synapses have very strong short-term enhancement mechanisms and that repetitive burst activation of the Str-GPe synapses, which mimic oscillatory burst firing of Str neurons, can sustain enhanced states of synaptic transmission for tens of seconds. The results reveal that the short-term enhancement of Str-GPe synapses contributes to the generation of pauses in the firing of GPe neurons and that signal transfer function in the Str-GPe projection is highly dependent on the firing pattern of Str neurons. Some studies reported that postsynaptic GABAergic responses recorded from GPe neurons to repetitive stimulation of Str exhibited a progressive facilitation during stimulation that developed in hundreds of milliseconds (Sims et al. 2008; Zucker and Regehr 2002). A number of studies also observed a moderate paired-pulse facilitation of the Str-GPe inputs (Cooper and Stanford 2001; Hashimoto and Kita 2008; Ogura and Kita 2000; Rueda-Orozco et al. 2009; Sims et al. 2008). Others reported progressive depression during stimulation (Rav-Acha et al. 2005, 2008) or slowly developing strong, long-term depression after the termination of repetitive stimulation (Rueda-Orozco et al. 2009). One of the aims of this study was to examine systematically the short-term plasticity of Str-GPe synapses.

Another aim was to gain insight about the induction of pauses in the most abundant type of high-frequency firing neurons in GPe (DeLong 1971). We have suspected that Str inputs generate the pauses and that the increased pause and burst activity of GPe neurons observed after DA depletion is due, in part, to the increased gain of the cortico-Str-GPe projection (Elías et al. 2007; Kita and Kita 2011a, b). Str-GPe synapses are known to generate weak (<10 pA), unitary inhibitory postsynaptic currents/inhibitory postsynaptic potentials (IPSCs/IPSPs) in GPe (Kita 2007; Tecuapetla et al. 2009), implying that a synchronous activation of a large number of Str projection neurons is required to induce pauses in GPe. However, since the population of spontaneously active Str projection neurons in resting animals appeared to be small, even after DA depletion (Kita and Kita 2011b), it was puzzling how such a small number of Str neurons could generate pauses in GPe. The present study addressed these questions using rat brain-slice preparations.

METHODS

Slice preparations. Animal handling and all procedures were in compliance with the National Institutes of Health Guide for Care and Use of Laboratory Animals and approved by the University of Tennessee Health Science Center Institutional Animal Care and Use Committee. Sprague-Dawley juvenile rats (16–21 days old) were used. Previous studies suggested that the physiological features of Str-GPe and Str-substantia nigra pars reticulata (SNr) synapses in rodents become adult-like by approximately postnatal day 16 (Connelly et al. 2010; Ogura and Kita 2000). Rats were anesthetized with intraperitoneal injection of a mixture of ketamine (85 mg/kg) and xylazine (15 mg/kg) and perfused through the heart with cold, oxygenated (95% O₂–5% CO₂ gas mixture) solution containing (in mM): 252 sucrose, 3 KCl, 1.24 NaH₂PO₄, 26 NaHCO₃, 0.5 CaCl₂, 6.3 MgSO₄, 0.2 thiourea, 0.2 ascorbic acid, and 20 glucose. After decapitation, the brains were removed rapidly, and blocks containing Str and GPe were obtained. Oblique sagittal slices (350 μm thick) were
cut from the blocks on a vibrating blade microtome (Leica VT1000S; Leica Microsystems, Nussloch, Germany). The slices were incubated in oxygenated artificial cerebrospinal fluid (ACSF) containing (in mM): 126 NaCl, 3 KCl, 1.24 NaH₂PO₄, 26 NaHCO₃, 2.4 CaCl₂, 1.3 MgSO₄, 0.2 thiourea, 0.2 ascorbic acid, and 10 glucose at 34°C for 30 min and then at room temperature until the recordings were started.

Electrophysiological recordings. The slices were transferred to a recording chamber with continuous perfusion of oxygenated ACSF at a flow rate of 1 ml/min. After placing the slice in the chamber, the temperature was increased gradually from room temperature to 32°C. Whole cell patch-clamp recording pipettes with a tip diameter of ~1.5 μm were pulled from 1.5 mm, thin-wall, borosilicate glass capillaries on a horizontal electrode puller (P-97; Sutter Instrument, Novato, CA). The whole cell recording pipettes contained (in mM): 135 K-gluconate, 5 KCl, 10 HEPES, 1 EGTA, 2 Mg-ATP, 0.2 Na-GTP, 10 phosphocreatine, and 0.2% Neurobiotin, with pH adjusted to 7.3 with KOH. The pipette resistance was 3–6 MΩ. Whole cell liquid junction potentials were calculated to be ~11.6 mV for the internal solution, and membrane potentials were not corrected. Neurons and recording pipettes were visualized using an infrared differential interference contrast microscope (BX50WI; Olympus, Tokyo, Japan) with a ×40 water-immersion objective and charge-coupled device camera (4990 series; Cohu Electronics, San Diego, CA). The neurons were voltage clamped at ~50 mV to eliminate the generation of action potentials. Our goal was to demonstrate the short-term enhancement of Str-GPe inputs in a setting with minimal deviations from normal physiological conditions. Thus the treatments to decrease membrane conductance, such as intracellular K⁺ and Na⁺ channel blockers, were not used. We believe that the conditions are adequate for acquiring the necessary data, even though the voltage clamp of distal dendrites is imperfect. In the current clamp recording of GPe neurons, the firing rates were maintained at ~20 Hz by current injection through recording pipettes. Data were corrected and digitized with a sampling rate of 20 kHz using a MultiClamp 700B amplifier and an analog-to-digital converter board, Digidata 1322A (Molecular Devices, Sunnyvale, CA). Signals were filtered at 3 kHz and recorded on a hard disk using data acquisition and analysis software, pCLAMP 10 (Molecular Devices).

To activate Str-GPe fibers, electrical stimuli (each pulse 200 μs in duration) were applied through a bipolar-stimulating electrode (tip distance of 0.2–0.5 mm), placed in the Str. To block glutamatergic currents and isolate IPSCs and IPSPs, ACSF contained AMPA/kainate receptor antagonist 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f] quinoxaline-7-sulfonamide (10 μM; Tocris Cookson, Ellisville, MO) and N-methyl-D-aspartate antagonist 3-(2-carboxypropyrazin-4-yl)-propyl-1-phosphonic acid to block AMPA/kainate and N-methyl-D-aspartate responses. Application of 10 μM gabazine completely abolished the fast IPSCs.

### RESULTS

**Type of neurons recorded.** The recordings were obtained from GPe neurons having spontaneous firing of 0–20 Hz and spike amplitudes >60 mV. The neurons generated repetitive firing without prominent spike accommodation upon depolarizing current injection, and hyperpolarizing currents induced either prominent or moderate sags due to an inwardly rectifying hyperpolarization-activated current (Chan et al. 2004; Cooper and Stanford 2000; Günay et al. 2008). Intracellular staining with Neurobiotin revealed that these were also the most prominent rodent GPe neurons having medium-sized fusiform- or multipolar-shaped somata and long, slowly tapering, smooth dendrites (data not shown) (Kaneda et al. 2007; Kita and Kitai 1991).

Frequency-dependent, short-term plasticity. To reveal frequency-dependent plasticity of Str-GPe synapses, postsynaptic responses of GPe neurons to test and conditioning repetitive Str stimuli were recorded. For this experiment, the test stimuli were given every 15 s, and ~10 mV pulses were applied 5 s following each test stimulation to monitor the input impedance of the neuron. We used 2 repetitive stimulation schedules: single burst of 20 repetitive pulses with frequencies of 2–100 Hz (a) or 10 bursts of 10 repetitive pulses with 20 or 50 Hz and various interburst intervals (IBIs; b). **B:** stimulus intensity was adjusted to evoke 30–50 pA inhibitory postsynaptic currents (IPSCs) in test stimulation unless noted otherwise. For all recordings, artificial cerebrospinal fluid contained 10 μM 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfonamide and 30 μM 3-(2-carboxypiperazine-4-yl)-propyl-1-phosphonic acid to block AMPA/kainate and N-methyl-D-aspartate responses. Application of 10 μM gabazine completely abolished the fast IPSCs.

![Fig. 1. A: diagrams show stimulus (stim.) and the membrane-clamp schedules used in this study. Globus pallidus external segment (GPe) neurons were voltage clamped at ~50 mV to block autonomous firing. Single test stimuli were given every 15 s, and ~10 mV pulses were applied 5 s following each test stimulation to monitor the input impedance of the neuron. We used 2 repetitive stimulation schedules: single burst of 20 repetitive pulses with frequencies of 2–100 Hz (a) or 10 bursts of 10 repetitive pulses with 20 or 50 Hz and various interburst intervals (IBIs; b). B: stimulus intensity was adjusted to evoke 30–50 pA inhibitory postsynaptic currents (IPSCs) in test stimulation unless noted otherwise. For all recordings, artificial cerebrospinal fluid contained 10 μM 1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfonamide and 30 μM 3-(2-carboxypiperazine-4-yl)-propyl-1-phosphonic acid to block AMPA/kainate and N-methyl-D-aspartate responses. Application of 10 μM gabazine completely abolished the fast IPSCs.**

### SHORT-TERM ENHANCEMENT OF STRIATO-PALLIDAL SYNAPSES

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in the present study due to the use of a wide range of conditioning frequencies.

Figure 3 shows changes of IPSC amplitudes after termination of the conditioning stimulation. The first test stimulation was applied 5 s after the termination of a conditioning stimulation and every 15 s thereafter. In all cases, the amplitude of IPSCs to the first test stimulation was significantly larger than the preconditioning baseline amplitude (Fig. 3A). The slowly
decaying enhancement of synaptic transmission observed after the termination of conditioning stimulation will be hereafter called postconditioning enhancement, although the enhancement is most likely a combination of an augmentation and a post-tetanic potentiation. These two forms have different kinetics and underlying mechanisms but often coexist. Both develop with similar time constants, but the latter decays more slowly than the former and can last for 30 s to several minutes [see Zucker and Regehr (2002) for review]. The degree of the enhancement was dependent on the frequency of the conditioning stimulation with a saturation occurring at ~50 Hz. It should be noted that 50 and 100 Hz stimulation induced strong enhancement of IPSCs, which supported the hypothesis that a shunting could decrease the IPSC amplitude during high-frequency conditioning. The decay time constant of the post-conditioning enhancement was estimated using an exponential regression to the responses to test stimuli applied every 15 s. The decay constant was also conditioning frequency dependent and was ~25 s for the 5-Hz and 45 s for the 100-Hz conditioning stimulation. The slower decay with higher stimulus frequency may be due to an increased contribution of the post-tetanic potentiation component over the augmentation component in the higher-frequency conditioning stimulation.

Responses to repetitive burst stimuli. It is known that some Str-GPe neurons maintain repeated burst firing after DA depletion (Kita and Kita 2011a; Mallet et al. 2006; Tseng et al. 2001; West and Grace 2002). We have characterized the bursts in DA-depleted Str of lightly anesthetized rats using the “surprise” method of Legendy and Salcman (1985) and defining the burst as having the surprise value as greater than or equal to three and the number of spikes as greater than or equal to three. The average burst duration of spontaneously active Str-GPe neurons was ~260 ms, with nine spikes/burst (i.e., ~30 Hz) and an average interburst interval (IBI) of 2.4 s (Kita and Kita 2011b). It is conceivable that the decay time of the postconditioning synaptic enhancement is slow enough to maintain the enhanced condition for the duration of pauses between bursts. To test this possibility, responses of GPe neurons to 10 sets of burst Str stimuli, each burst consisting of 10 pulses at 20 or 50 Hz and IBI of 2–40 s, were recorded (Fig. 4). The stimulus intensity was pre-adjusted to evoke ~30 pA IPSCs in a 15-s interval, single-pulse trial stimuli. In both 20 and 50 Hz burst stimuli, the IPSCs were enhanced three to four times during the first burst stimulation, as described above. It was apparent that with the 20 and 50 Hz with 2-s IBI stimuli, the responses to the second and succeeding burst stimulation began at a higher level of four to seven times the baseline IPSC amplitude and then decayed during each burst (Fig. 4, A and B). The carryover of the enhancement to the next burst was still observed with 10-s IBIs (Fig. 4, C and E) but was not apparent with 40-s IBIs (Fig. 4D). We performed current clamp recordings to show that the carryover of enhanced IPSPs contributes to the generation of pauses in repetitively firing GPe neurons. The neurons recorded were maintained to fire at ~20 Hz by current injection.

Fig. 4. Repetitive burst activation enhanced Str-GPe synapses. A–D: group data show changes in IPSC amplitude recorded from GPe neurons during Str burst stimuli, 10 sets of 10 pulses with different frequencies and IBIs. For each neuron, the amplitudes of the IPSCs were normalized by the average of 4 IPSCs evoked by 4 single stimuli given prior to burst stimuli in 15-s intervals. A and B: IPSCs of GPe neurons to 20 and 50 Hz burst stimulation with 2-s IBIs. The IPSCs to 1st burst stimuli were greatly enhanced (brown lines). The IPSCs to succeeding burst stimuli were started from an enhanced amplitude and declined during each burst (Fig. 4, A and B). The carryover of enhanced IPSPs contributes to the generation of pauses in repetitively firing GPe neurons. The neurons recorded were maintained to fire at ~20 Hz by current injection.
Effects of D2 agonist and low extracellular Ca\textsuperscript{2+}. Application of DA D2 receptor (D2R) agonists decreases the probability of GABA release from Str-GPe terminals (Cooper and Stanford 2001; Shin et al. 2003; Watanabe et al. 2009). Lowering Ca\textsuperscript{2+} concentration in the extracellular fluid also decreases the probability by reducing Ca\textsuperscript{2+} influx into the presynaptic terminals. We have investigated whether reducing the GABA release probability affects the development of the short-term enhancement. Bath application of the D2R agonist quinpirole, 10 \mu M, reduced the amplitude of Str stimulation-induced IPSCs in GPe neurons, as reported previously (Cooper and Stanford 2001; Shin et al. 2003; Watanabe et al. 2009). Although the amplitude was decreased, the enhancement of IPSCs to burst Str stimulation was still observed in the presence of quinpirole. However, the speed of the enhancement development was slower in quinpirole than in the control (Fig. 5, A–C). Reduction of extracellular Ca\textsuperscript{2+} from 2.4 to 1.2 mM had similar results (Fig. 5, D–F). These results show that even in conditions that reduce the influx of Ca\textsuperscript{2+} to presynaptic terminals, the short-term enhancement of Str-GPe synapses to repetitive activation does occur but with slower development speed.

**DISCUSSION**

**Activation pattern-dependent, short-term enhancement of Str-GPe synapses.** The primary aim of this study was to reveal how the different patterns of activation of Str-GPe synapses affect the efficacy of synaptic transmission. Str projection neurons require synaptic inputs to evoke firing and fire in a very different manner depending on the activation of afferent inputs. If the stimulus intensity is very low, IPSCs in a single stimulus mode. Four neurons were tested with both 20 and 50 Hz burst stimuli, with 2-s IBI. In both stimulus conditions, the inhibitory effect of the burst stimuli grew and reached a complete pause of firing (Fig. 4, F and G). The number of bursts needed to reach a complete pause was dependent on the strength of the stimulus. With strong, high-frequency bursts, the pause duration outlasted that of the burst stimuli due to activation of other receptors, such as GABA\textsubscript{B} (Fig. 4G) (Kaneda et al. 2007). These results demonstrate that when multiple burst activity of Str neurons occurs with intervals shorter than the decay time of the repetitive activation-induced enhancement, the enhancement developed during prior burst activation of Str-GPe inputs can be carried over to the next burst activity.

Similar to the 20-pulse conditioning stimulation experiments described earlier, the rate of the IPSC decay was stronger for the 50-Hz than the 20-Hz burst stimuli (Fig. 4, A and B). The most likely factor for this decrease was the shunting—i.e., the postsynaptic input-impedance increase generated by prior IPSCs—at the dendritic synaptic sites of Str axons. To test this possibility, responses to a low-intensity, near-threshold (to evoke IPSCs) stimulus in the control and in quinpirole. A–C: examples of responses of a GPe neuron show enhancement of IPSCs to 20 Hz, 20 pulse burst stimuli in the control and in quinpirole. C: group data compare the development of enhancement before and after quinpirole. The exponential regression curves were computed to compare the progress of the enhancement. The dimension of the time constants (\(\tau\)) is the stimulus interval. D–F: lowering extracellular Ca\textsuperscript{2+} from 2.4 to 1.2 mM resulted in similar effects to quinpirole.

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**Fig. 5.** The dopamine D2 receptor agonist quinpirole (10 \mu M) and lowering extracellular Ca\textsuperscript{2+} from 2.4 to 1.2 mM reduced IPSC amplitude and slowed development of repetitive stimuli-induced enhancement. A and B: examples of responses of a GPe neuron show enhancement of IPSCs to 20 Hz, 20 pulse burst stimuli in the control and in quinpirole. C: group data compare the development of enhancement before and after quinpirole. The exponential regression curves were computed to compare the progress of the enhancement. The dimension of the time constants (\(\tau\)) is the stimulus interval. D–F: lowering extracellular Ca\textsuperscript{2+} from 2.4 to 1.2 mM resulted in similar effects to quinpirole.
inputs that are dependent on the animal’s condition. Unit recordings in wakeful rodents and monkeys showed that spontaneously active, presumed Str projection neurons, which had a low-frequency phasic activity (and were thus named phasically active neurons), were only occasionally encountered and that most of the neurons, which could be driven by cortical stimulation, were quiescent or only occasionally fired when animals were at rest. An intracellular recording from wakeful animals showed that some spontaneously active neurons show a depolarized membrane with slow, irregular fluctuations intermixed with high-frequency depolarizing events and trigger more random, yet still phasic, low-frequency firing (Mahon et al. 2006). This occasional Str firing in wakeful animals should evoke very weak inhibitions in GPe neurons, because Str stimulation-induced unitary IPSCs/IPSPs are very small (Kita 2007; Ogura and Kita 2000; Tecuapetla et al. 2009).

In drowsy or anesthetized animals, the membrane potential of Str projection neurons shifts between hyperpolarized and depolarized states in synchrony with cortical slow waves, suggesting that cortical activity drives the membrane oscillations. In most of the Str neurons, the depolarized stages are mostly subthreshold, and only occasional spikes are triggered from depolarized states. In a small population of Str neurons, the depolarized states are suprathreshold, and the neurons fire an oscillatory burst with several spikes (Mahon et al. 2006; Stern et al. 1998; Tseng et al. 2001; Wilson and Groves 1981). The neurons with an oscillatory burst were encountered only occasionally in unit recordings in normal, lightly anesthetized rats (Kita and Kita 2011a). However, after DA depletion, Str-GPe neurons firing with a slow oscillatory burst were encountered more frequently in both anesthetized and wakeful animals (Chen et al. 2001; Kita and Kita 2011a; Mallet et al. 2006; Pang et al. 2001; Tseng et al. 2001; West and Grace 2002). This study revealed that repetitive activation of Str-GPe synapses shows a strong short-term enhancement, similar to those reported by Sims et al. (2008). This study further revealed that the repetitive activation-induced enhancement of Str-GPe synapses decays slowly, with a decay constant of 20–40 s. Based on these results, it is likely that these oscillatory burst-firing neurons in vivo may maintain enhanced synaptic inhibition during IBL, and synchronous burst activity of a relatively small number of Str neurons may effectively generate pauses in the firing of GPe neurons. In DA-depleted animals, the pre- and postsynaptic DA suppression of Str-GPe synapses is removed (Cooper and Stanford 2001; Floran et al. 1997; Shin et al. 2003; Watanabe et al. 2009), which results in further increases in the Str-GPe inhibition, generating stronger pauses and rebound burst firing.

The short-term enhancement of Str-GPe synapses may also play significant roles in the control of movement in normal animals. Unit recordings from presumed Str projection neurons in monkeys and rodents showed that most behavioral, event-related unit activities occur as a train of firing, lasting from 100 ms to over 1 s, with a maximum frequency of up to 100 Hz (Chen et al. 2001; Kimura et al. 1990; Kubota et al. 2009). The results of this study suggest that the train of activation of Str-GPe synapses will generate very strong postsynaptic inhibitions in GPe neurons. When repetitive trains of activation occur with <40-s intervals, within which many behavioral tasks to be learned can be retried, the enhancement developed during the previous train of activation will be carried over to the subsequent trains of activation. Thus the enhancement provides a form of learning or reinforcement mechanism.

This study confirmed the result of Sims et al. (2008) that the reduction of extracellular Ca\(^{2+}\) concentration reduces the amplitude of Str-GPe IPSCs, probably by reducing the probability of GABA release. However, it does not eliminate the short-term enhancement of Str-GPe synapses. The effects of bath application of quinpirole on synaptic enhancement were similar to the reduction of extracellular Ca\(^{2+}\), suggesting that quinpirole may reduce the Ca\(^{2+}\) influx to presynaptic terminals in a similar manner to that of the somato-dendritic membrane [see Momiyama and Koga (2001) and Surmeier et al. (2010) for a review]. Studies in other brain sites showed that the short-term synaptic enhancement mechanisms involve Ca\(^{2+}\) influx to presynaptic terminals (Catterall and Few 2008; Xu et al. 2007; Zucker and Regehr 2002). The present results demonstrated that the short-term enhancement of the Str-GPe synapse could take place under normal conditions, in which the extracellular Ca\(^{2+}\) concentration is ~1.2 mM, and some level of D2R activation is present, as well as in parkinsonian conditions, in which the D2R-mediated presynaptic suppression is removed.

Other possible modes of plasticity. Str-SNr synapses also show short-term enhancement (Connelly et al. 2010). Thus both Str-GPe and Str-SNr synapses have short-term enhancement mechanisms. These studies, which demonstrated short-term enhancement, all used moderate intensities and a moderate number of repetitive stimuli. However, it is possible that different modes of stimulation or different experimental conditions might induce different modes of synaptic plasticity. Rav-Acha and associates (2005) reported that 5–33 Hz repetitive Str stimuli induced rapid, frequency-dependent suppression of IPSCs recorded from GPe neurons. It is not certain what experimental differences drive short-term suppression or enhancement, as discussed by Sims and associates (2008). Differences could include submaximal vs. moderate stimulus intensity, and the former may activate GPe-Str axons in addition to Str-GPe neurons (Ogura and Kita 2000). The synapses formed by GPe axons show short-term depression (Baufreton and Bevan 2008; Connelly et al. 2010). It is also possible that submaximal stimulation activated a larger number of axons to release more transmitters and activated other receptors, such as pre- and postsynaptic GABA\(_{A}\) receptors. Another difference among the prior studies was the ages of animals used in the experiments. Rav-Acha et al. (2005) used 9- to 16-day-old, Sims et al. (2008) used 20- to 21-day-old, and we used 16- to 21-day-old rats, which raises the possibility of short-term plasticity changes during development, as shown in Str-SNr synapses (Connelly et al. 2010). Rueda-Orozco and associates (2009) reported another mode of plasticity. They showed that a conditioning stimulus with a large number of repetitive pulses, two trains of 100 Hz, and 1 s-long stimuli, delivered to Str with an intertrain interval of 10 s (i.e., a total of 200 stimulus pulses), induced a slowly developing, strong, long-term depression of Str-GPe IPSCs. Although responses during the conditioning stimulation were not described, the IPSC amplitude recorded soon after the conditioning stimulation was similar to the baseline, suggesting that short-term plasticity was not induced. The authors suspected that the depression may be postsynaptically mediated, because there were no changes to the paired pulse ratio (Rueda-Orozco et al. 2009).
Although the stimulus conditions differed, the remaining experimental conditions between the Rueda-Orozco study (2009) and our study were similar. It is possible that the use of long trains of high-frequency conditioning stimulation may deplete the readily releasable pool of presynaptic neurotransmitter vesicles or that the development of strong, long-term depression mechanisms may have masked the short-term enhancement.

Functional implications. Most Str-GPe synapses have been known to generate small, unitary IPSCs/IPSPs in GPe (Kita 2007; Ogura and Kita 2000; Tecuapetla et al. 2009). Thus a general consensus is that a synchronous activation of a large number of Str neurons is required to generate effective inhibition in GPe neurons. The results of the present study suggest that the strong, short-term enhancement mechanisms of Str-GPe synapses allow synchronous activation of a relatively small number of Str neurons to generate powerful behavioral, event-related inhibitions in GPe. Furthermore, the slow decay of the enhancement provides a learning or reinforcement mechanism during repeated practices, which is often attributed to Str functionality. This study also suggests that under DA-depleted conditions, overactive Str-GPe neurons will generate more powerful behavioral, event-related inhibitions and more frequent pauses and rebound burst firing in GPe, which then invokes a cascade of alterations in the activity of the basal ganglia (Kita and Kita 2011a).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: J.K. and H.K. conception and design of research; J.K. performed experiments; J.K. and H.K. prepared figures; J.K. and H.K. drafted manuscript; J.K. and H.K. edited and revised manuscript; J.K. and H.K. approved final version of manuscript.

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