Differential cortical activation of the striatal direct and indirect pathway cells: reconciling the anatomical and optogenetic results by using a computational method

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Morita K. Differential cortical activation of the striatal direct and indirect pathway cells: reconciling the anatomical and optogenetic results by using a computational method. J Neurophysiol 112: 120–146, 2014. First published March 5, 2014; doi:10.1152/jn.00625.2013.—The corticostriatal system is thought to play crucial roles in learning and action selection. Anatomical studies have shown that two types of corticostriatal neurons, intratelencephalic (IT) and pyramidal tract (PT) cells, preferentially project to dopamine D1 or D2 receptor-expressing striatal projection neurons, respectively. In contrast, an optogenetic study has shown that stimulation of IT axons evokes comparable responses in D1 and D2 cells and that stimulation of PT axons evokes larger responses in D1 cells. Since the optogenetic study applied brief stimulation only, however, the overall impacts of repetitive inputs remain unclear. Moreover, the apparent contradiction between the anatomical and optogenetic results remains to be resolved. I addressed these issues by using a computational approach. Specifically, I constructed a model of striatal response to cortical inputs, with parameters regarding short-term synaptic plasticity and anatomical connection strength for each connection type. Under the constraint of the optogenetic results, I then explored the parameters that best explain the previously reported paired-pulse ratio of response in D1 and D2 cells to cortical and intrastriatal stimulations, which presumably recruit different compositions of IT and PT fibers. The results indicate that 1) IT→D1 and PT→D2 connections are anatomically stronger than IT→D2 and PT→D1 connections, respectively, consistent with the previous findings, and that 2) IT→D1 and PT→D2 synapses entail short-term facilitation, whereas IT→D2 and PT→D1 synapses would basically show depression, and thereby 3) repetitive IT or PT inputs have larger overall impacts on D1 or D2 cells, respectively, supporting a recently proposed hypothesis on the roles of corticostriatal circuits in reinforcement learning.

corticostriatal circuit; paired-pulse ratio; short-term synaptic plasticity; computational modeling; reinforcement learning

THE CORTICOSTRIATAL SYSTEM is thought to play crucial roles in learning and action selection (Gerfen and Surmeier 2011), and its dysfunction has been suggested to cause various neuropsychiatric disorders (Shepherd 2013). There are two types of corticostriatal neurons, intratelencephalic (IT) cells and pyramidal tract (PT) cells (Cowan and Wilson 1994; Levesque et al. 1996; Parent and Parent 2006; Reiner et al. 2010), and two types of striatal projection neurons, striatonigral (direct pathway) and striatopallidal (indirect pathway) medium spiny neurons (dMSNs and iMSNs) that express dopamine D1 and D2 receptors, respectively (Gerfen and Surmeier 2011). Regarding the connections between these distinct cell populations, anatomical studies have shown that IT and PT cells preferentially target dMSNs and iMSNs, respectively (Lei et al. 2004; Reiner et al. 2010). However, it has remained elusive whether IT and PT cells differentially activate dMSNs and iMSNs as suggested from the anatomical findings (see Ballion et al. 2008; Reiner et al. 2010).

A recent study (Kress et al. 2013) addressed this issue by using optogenetics and revealed that stimulation of IT axons evoked comparable responses in dMSNs and iMSNs and that stimulation of PT axons caused about twice larger responses in dMSNs than in iMSNs, apparently opposite to the anatomical suggestion. This study, however, applied only brief stimulation. Synaptic response to repetitive inputs can generally evolve through short-term synaptic plasticity (Buonomano and Maass 2009; Sussillo et al. 2007), and as a result, synapses that show negligible response to a single spike can nevertheless show quite strong responses to multiple spikes (Kapfer et al. 2007; Silberberg and Markram 2007). Moreover, the nature of short-term plasticity can dramatically differ depending on presynaptic (Beierlein and Connors 2002) and postsynaptic neuron types (Blackman et al. 2013; Markram et al. 1998). Therefore, to understand how information flows between cortex and striatum, it is crucial to know the overall time-dependent impacts of multiple IT or PT inputs on dMSNs and iMSNs. Moreover, the apparent contradiction between the anatomical and optogenetic results should be resolved so that we can have a clear picture.

Empirical examination of (potentially) synapse type-dependent short-term plasticity may not be so straightforward, since optogenetic stimulation used for specifying synapse type may simultaneously activate a large number of synapses on a single striatal neuron and thus may potentially cause nonlinear phenomena in the dendrite such as saturation. Moreover, it is not even obvious how to empirically resolve the apparent contradiction between the anatomical and optogenetic findings. Therefore, I instead employed a computational approach. Specifically, I constructed a model of striatal response to cortical inputs, with parameters regarding short-term synaptic plasticity and anatomical connection strength for each connection type. I then examined whether the anatomical and optogenetic results can be consistent with each other, and what are the overall impacts of repetitive IT or PT inputs on dMSNs and iMSNs, through exploration of the model’s parameters that best explain a third set of existing empirical results, in particular the reported (Ding et al. 2008) paired-pulse ratio (PPR) of the response in dMSNs and iMSNs to cortical and intrastriatal
stishments, which presumably recruit different components of IT and PT fibers.

MATERIALS AND METHODS

Model of short-term synaptic plasticity. I modeled short-term plasticity of corticostriatal synapses by using a mathematical model (Markram et al. 1998; Mongillo et al. 2008; Tsodyks and Markram 1997) that describes the dynamics of two variables, \( x \) (0 < \( x \) < 1) and \( u \) (0 < \( u \) < 1), that represent the normalized amount of available resources and the fraction of resources used by each spike, respectively:

\[
\frac{dx}{dt} = \frac{(1 - x)}{D} - u x \delta(t - t_{sp})
\]

\[
\frac{du}{dt} = \left( U - u \right) / F + U(1 - u) \delta(t - t_{sp}),
\]

where \( U \) is a parameter representing the baseline level of \( u \); \( D \) and \( F \) are the time constants for recovery from depression and facilitation, respectively; \( \delta \) is the Dirac delta function; and \( t_{sp} \) is the time of presynaptic neuronal spike. The amplitude of postsynaptic conductance at each spike is given by \( u(t = t_{sp} - 0) \times x(t = t_{sp} - 0) \), where \( t_{sp} \) = 0 means “immediately before \( t_{sp} \)”.

Given a set of spike timings \( \left\{ t_{sp}^{(i)} \right\}, \left\{ t_{sp}^{(2)} \right\}, ..., \left\{ t_{sp}^{(k)} \right\} \), the values of \( x \) and \( u \) at (immediately before) each spike \( t = t_{sp} \) = 0, which I denote \( x_k \) and \( u_k \), respectively, can be calculated as follows (c.f., Markram et al. 1998; Tsodyks and Markram 1997):

\[
x_{k+1} = x_k \times (1 - u_k) \times \exp(-\Delta t/D) + 1 \times \exp(-\Delta t/D)
\]

\[
u_{k+1} = u_k \times \exp(-\Delta t/F) + u \times \left\{1 - u_k \times \exp(-\Delta t/F)\right\},
\]

where \( \Delta t = t_{sp}^{(i)} - t_{sp}^{(i-1)} \). The peak amplitude of excitatory postsynaptic current (EPSC) in response to the \( k \)-th spike [\( t = t_{sp}^{(i)} \)], denoted here as \( A^{(k)} \), is proportional to the peak amplitude of postsynaptic conductance when the membrane potential is clamped at a low value (so that NMDA conductance is inactivated) and thus can be written as:

\[
A^{(k)} = C \times u_k \times x_k,
\]

where \( C \) is a parameter representing the theoretical maximum amplitude of a (single) synaptic response (i.e., response amplitude in the condition where \( x = u = 1 \); “theoretical” means that in reality \( x \) and \( u \) develop according to the above differential equations so that they may not be able to simultaneously take the maximal value of 1).

Modeling the PPR of striatal response to cortical/intrastriatal stimulation. By using the above-mentioned model, I simulated postsynaptic response in dMSNs or iMSNs to cortical or intrastriatal stimulation in the experimental study (Ding et al. 2008), which applied two consecutive stimulations with various intervals and examined the ratio of the second EPSC amplitude to the first, called the paired-pulse ratio (PPR); in that study (Ding et al. 2008), to determine EPSC amplitudes in response to paired stimulations with short intervals, the first EPSC was fitted with a biexponential EPSC-like function, and the amplitude of the second EPSC was determined after subtraction of the first EPSC. I assumed that four types of corticostriatal synapses (IT→dMSNs, IT→iMSNs, PT→dMSNs, and PT→iMSNs) have (potentially) different short-term plasticity dynamics characterized by different sets of parameters of the above-mentioned model: \( D_{IT}, F_{IT}, U_{IT}, C_{IT} \), \( D_{PT}, F_{PT}, U_{PT}, C_{PT} \), and \( D_{PT}, F_{PT}, U_{PT}, C_{PT} \), respectively. For each of these four types of connections, the peak amplitude of EPSC in response to the first and second spikes \( \left\{ A^{(k)}_{IT}, A^{(k)}_{IT}, A^{(k)}_{PT}, A^{(k)}_{PT} \right\} \), where \( k = 1 \) or 2), with varying interspike interval \( t_{sp}^{(i)} = \{0 \text{ ms and } 20, 50, 100, 200, 500, \text{ or } 1000 \text{ ms} \} \), was calculated according to the equations described in the previous section.

It is known that IT cells project to the striatum bilaterally, whereas PT cells target only the ipsilateral striatum (Cowan and Wilson 1994; Levesque et al. 1996; Parent and Parent 2006; Reiner et al. 2010), and so striatal neurons are considered to receive cortical inputs from three sources: 1) ipsilateral IT cells, 2) contralateral IT cells, and 3) ipsilateral PT cells (see Fig. 1B). In the experimental study (Ding et al. 2008), cortical or intrastriatal stimulation was applied in parasagittal slices (275–300 \( \mu \)m) (in experiments shown in Fig. 1A; coronal and horizontal slices were also used in other experiments). Such cortical stimulation in parasagittal slices is considered to activate axons from two of the three cortical input sources mentioned above, i.e., axons of ipsilateral IT and PT cells but not those of contralateral IT cells, except for possible occurrence of an axon reflex (i.e., transmission of activation of the axon branches of contralateral IT cells into ipsilateral cortex; see below). In contrast, intrastriatal stimulation presumably activates fibers from all of the three cortical input sources. Therefore, I calculated the PPR of the response in dMSNs and iMSNs to cortical stimulation, respectively, as follows:

\[
\frac{N_{id}A^{(k)}_{IT} + N_{ip}A^{(k)}_{PT}}{N_{id}A^{(k)}_{IT} + N_{ip}A^{(k)}_{PT}}
\]

\[
N_{id}A^{(k)}_{IT} + N_{ip}A^{(k)}_{PT}
\]

and approximated the PPR of the response in dMSNs and iMSNs to intrastriatal stimulation, respectively, as follows:

\[
\frac{N_{id}A^{(k)}_{IT} + N_{id}A^{(k)}_{IT} + N_{ip}A^{(k)}_{PT}}{N_{id}A^{(k)}_{IT} + N_{ip}A^{(k)}_{PT}}
\]

\[
N_{id}A^{(k)}_{IT} + N_{id}A^{(k)}_{IT} + N_{ip}A^{(k)}_{PT}
\]

where \( N_{id}, N_{ip}, \) and \( N_{pt} \) are parameters representing the number of synapses from ipsilateral IT cells, contralateral IT cells, and ipsilateral PT cells to dMSNs, respectively, and \( N_{id}, N_{id}, \) and \( N_{pt} \) represent the number of synapses from these three types of cortical cells to iMSNs, respectively. Notably, in the above it is assumed that synaptic terminals of ipsilateral IT cells and those of contralateral IT cells on the same type of MSNs have the same property of short-term plasticity. I conducted a large part of model fitting analyses in the present study with this assumption, but I also conducted analyses without this assumption, i.e., assuming instead that ipsilateral and contralateral IT terminals on the same type of MSNs can entail different short-term plasticity (see below).

In fact, cortical stimulation could partially recruit axons from contralateral IT cells via the axon reflex, although it is not very likely in the experiment using parasagittal slices that I modeled (see RESULTS, Further confirmation of robustness of approach and exploration of better fit, and Fig. 5B for more details). Therefore, I also considered the case in which the PPR of the response in dMSNs and iMSNs to cortical stimulation are instead calculated as follows:

\[
\frac{N_{id}A^{(k)}_{IT} + N_{id}A^{(k)}_{IT} + N_{ip}A^{(k)}_{PT}}{N_{id}A^{(k)}_{IT} + N_{ip}A^{(k)}_{PT}}
\]

\[
N_{id}A^{(k)}_{IT} + N_{id}A^{(k)}_{IT} + N_{ip}A^{(k)}_{PT}
\]

where \( r \) represents the ratio of the axon reflex and was set to 0.25 for the case shown in Fig. 5B (\( r \) was set to 0 in the other cases). Another possible deviation from the above formulas is that electrical stimulation applied in the study by Ding et al. (2008) activated different types of fibers to different degrees (see RESULTS, Further confirmation of robustness of approach and exploration of better fit, for more details). As a particular example of such a possibility, I also considered the case in which intrastriatal stimulation activates IT axons to a potentially larger degree than PT axons, and so the PPRs of the response in dMSNs and iMSNs to intrastriatal stimulation are calculated as follows:
\[
\left\{1 + b\right\} \left[ N_{Id} A_{Id}(t^+) + N_{Cl} A_{Cl}(t^+) \right] + N_{Pp} A_{Pp}(t^+) \bigg/ \left\{1 + b\right\} \left[ N_{Id} A_{Id}(t^-) + N_{Cl} A_{Cl}(t^-) \right] + N_{Pp} A_{Pp}(t^-) \\
\left\{1 + b\right\} \left[ N_{Id} A_{Id}(t^+) + N_{Cl} A_{Cl}(t^+) \right] + N_{Pp} A_{Pp}(t^+) \bigg/ \left\{1 + b\right\} \left[ N_{Id} A_{Id}(t^-) + N_{Cl} A_{Cl}(t^-) \right] + N_{Pp} A_{Pp}(t^-),
\]

where \( b \geq 0 \) represents the degree of the biased activation of IT axons compared with PT axons. The value of \( b \) was set to 0 to 0.5 for modeling of the experiments of Ding et al. (2008) and another study also examined PPR in dMSNs and iMSNs to intrastriatal stimulation (Kreitzer and Malenka 2007), respectively. Notably, possible effects of neuromodulators and GABA released in the striatum by intrastriatal stimulation will be considered later (but not in the above), and those of thalamic inputs, as well as other possible factors, were not considered (see Discussion).

Exploration of the model’s parameters that best explain the observed PPRs. I explored parameters of the model that best explain the experimental data for the PPR (Ding et al. 2008) in the following ways. For the parameter optimization, I used the results of the recent optogenetic study by Kress et al. (2013), introduced in the Introduction as a constraint. Specifically, the optogenetic study has shown that stimulation of IT axons evoked comparable responses in dMSNs and iMSNs (according to Fig. 1g of Kress et al., the ratio of the response amplitude appears to be about dMSNs/iMSNs = 1:0.78 on average, although the difference was not statistically significant), whereas stimulation of PT axons caused about a twice larger response in dMSNs than in iMSNs (according to Fig. 2g of Kress et al., the ratio of the response amplitude appears to be about dMSNs/iMSNs = 1:0.49 on average, and the difference was statistically significant). Since the amplitude of a synaptic response to a single input (or an initial input) is calculated to be \( U \times C \), as can be seen from the equations described above, the amplitude of the overall response to a stimulation of all the synapses of a given type is calculated to be \( U \times C \times \) times the number of synapses [i.e., \( N_{Id} = N_{Id} + N_{Cl} \), \( N_{Ii} = N_{Ii} + N_{CtStr} \), \( N_{Pp} \), and \( N_{Pd} \) for IT→dMSNs, IT→iMSNs, PT→dMSNs, and PT→iMSNs connections, respectively]. Therefore, assuming that all (ipsilateral and contralateral) IT axon terminals, or all PT axon terminals, on individual recorded MSNs were stimulated in the experiments by Kress et al., I assumed

\[
(U_{Id} \times C_{Id} \times N_{Id}) \times (U_{Ii} \times C_{Ii} \times N_{Ii}) = 1:0.78
\]

\[
(U_{Pp} \times C_{Pp} \times N_{Pp}) \times (U_{Pd} \times C_{Pd} \times N_{Pd}) = 1:0.49
\]

as a constraint derived from the results of the optogenetic study. I further assumed

\[
U_{Id} \times C_{Id} \times N_{Id} = U_{Pp} \times C_{Pp} \times N_{Pp} = 1,
\]

where the first equality represents that the amplitude of the response in dMSNs to stimulation of IT axons is comparable to the amplitude of the response to PT stimulation, to be consistent with the reported results of the optogenetic study that the peak amplitudes of evoked EPSCs in dMSNs of the response to IT and PT stimulations appear to be comparable [although direct comparison was not made by Kress et al. (2013)], whereas the second equality just represents a scaling (assuming different values should merely cause proportional changes in the amplitude of the response in all the conditions without affecting PPR values).

With these constraints, I conducted parameter optimization in two different ways, either with or without a priori assumptions (constraints) about anatomical connection strength. First, I describe the first way, in which I made a priori assumptions on anatomical connection strength. Specifically, for the theoretical maximum amplitude of a synaptic response, I assumed either assumption 1-1: \( C_{Id} = C_{Ii} = C_{Pp} = C_{Pd} = C_{CtStr}, \) meaning that the theoretical maximum amplitude is assumed to be equal for every type of synapse, or assumption 1-2: \( C_{Id} = C_{Ii} = C_{CtStr} \) and \( C_{Pp} = C_{Pd} = 2^2 \times C_{CtStr}, \) meaning that PT synapses have \( 2^2 = 4 \) times larger theoretical maximum amplitudes than IT synapses, as potentially expected from the anatomical finding that PT axon terminals have about twice larger mean diameter (thus presumably about \( 2^2 = 4 \) times larger surface area) than IT axon terminals (Lei et al. 2004; Reiner et al. 2003). Regarding the number of synapses, I assumed either assumption 2-1: \( N_{Id} = N_{Ii} = N_{Pp} = N_{Pd}, \) meaning that IT cells and PT cells equally project to dMSNs and iMSNs, or assumption 2-2: IT cells and PT cells preferentially (but not exclusively) project to dMSNs and iMSNs, respectively, as shown by double labeling for corticostratial terminals and the spines of MSNs in rats (Lei et al. 2004) and also as suggested by the observation of the size of synaptic terminals in rat (Lei et al. 2004) and monkey (Reiner et al. 2010). Notably, in RESULTS, the combination of assumptions 1-1 and 1-2, 1-1 and 2-2, 1-2 and 2-2 are referred to as the control condition (see Figs. 2Aa and 3A), the “partial anatomy” condition (see Figs. 2Ab and 3B), and the “full anatomy” condition (see Figs. 2Ac and 3C), respectively (the combination of assumptions 1-2 and 2-1 was not examined). As for assumption 2-2, the double labeling study (Lei et al. 2004) has shown that among the spines of dMSNs, 50.9% and 21.3% receive inputs from IT cells and PT cells, respectively, whereas among the spines of iMSNs, 12.6% and 50.5% receive inputs from IT cells and PT cells, respectively. On the basis of these values, I assumed

\[
N_{Id} = 50.9\alpha, N_{Pd} = 21.3\alpha
\]

and

\[
N_{Ii} = 12.6\beta, N_{Pp} = 50.5\beta,
\]

where \( \alpha \) and \( \beta \) are new parameters, assuming that certain proportions of (ipsilateral and contralateral) IT axon terminals/PT axon terminals were randomly/stochastically labeled in the experiments of Lei et al. (2004). The same study (Lei et al. 2004) also reported that 23.7% and 10.2% of the IT terminals project to spines of dMSNs and iMSNs, respectively, whereas 12.4% and 40.1% of the PT terminals project to spines of dMSNs and iMSNs, respectively. These indicate

\[
50.9\alpha:12.6\beta = 23.7:10.2.
\]

It is calculated from the top equation that \( \beta/\alpha = 1.7386 \), whereas the same \( \beta/\alpha \) is calculated to be 1.3640 from the bottom equation. Therefore, taking the average of these values, I assumed that \( \beta/\alpha = (1.3686 + 1.3640)/2 = 1.5513 \). With these assumptions, for the case with assumption 1-1: \( C_{Ii} = C_{Pp} = C_{Pd} = C_{CtStr} \), the above-mentioned constraint equations can be expressed as follows:

\[
U_{Id} = 1/(C_{CtStr} \times 50.9\alpha) = (1/50.9) \times (1/(\alpha C_{CtStr}))
\]

\[
U_{Ii} = 0.78/(C_{CtStr} \times 12.6\beta) = 0.78/(C_{CtStr} \times 12.6 \times 1.5513) = 0.78/(19.54638 \times 1/(\alpha C_{CtStr}))
\]

\[
U_{Pp} = 1/(C_{CtStr} \times 21.3\beta) = (1/21.3) \times (1/(\alpha C_{CtStr}))
\]

\[
U_{Pd} = 0.49/(C_{CtStr} \times 50.5\beta) = 0.49/(C_{CtStr} \times 50.5 \times 1.5513) = 0.49/(78.34065 \times 1/(\alpha C_{CtStr})),
\]

where I considered a new (combined) parameter \( \omega = (1/(\alpha C_{CtStr})) \), which scales the parameters \( (U_{Id} \times U_{Ii} \times U_{Pp} \times U_{Pd}) \) (approximately representing the baseline release probability) at once as shown in the above equations. There are in total 8 (time constants for short-term plasticity) + 1 (\( \omega \)) = 9 free parameters, and I systematically varied their values at initial conditions, from which the optimization procedure was started (see below). A similar procedure has been taken for the case with assumption 1-2: \( C_{Ii} = C_{Pp} = C_{CtStr} \) and \( C_{Pd} = C_{Pd} = 2^2 \times C_{CtStr} \), as well. In the case of assuming equal numbers of synapses for
any of the IT→dMSN, IT→iMSN, PT→dMSN, and PT→iMSN connections (the above assumption 2-1), I practically assumed
\[ N_d = N_i = N_p = (50.9a + 21.3a + 12.6b + 50.5b)/4 \]
and derived equations that describe \((U_{id}, U_{ip}, U_{dp}, U_{pd})\) with the single scaling parameter \(\alpha\) in the same manner as described above (not shown). To calculate PPR, it is necessary to additionally assume the ipsilateral-to-contra-lateral ratio (ipsi/contra ratio) of the numbers of IT synapses (i.e., \(N_{Id}\), \(N_{Ip}\), and \(N_{Pd}\)) and I assumed \(N_{Id}/N_{Ip} = 1:1\) (i.e., \(N_{Id} = N_{Ip} = 0.5 \times N_{Id}\) \(N_{Pd} = N_{Id} = 0.5 \times N_{Id}\) in all the cases, with assumptions 1-1 or 1-2 and 2-1 or 2-2, in the first way of parameter optimization with a priori assumptions on anatomical connection strength.

In the second way of parameter optimization, I did not make a priori assumptions on anatomical connection strength, except for the ipsi/contra ratio of the IT connection strength. Specifically, I treated eight parameters representing time constants for short-term plasticity \([D_{Id}, F_{Id}, D_{Ip}, F_{Ip}, D_{Pd}, F_{Pd}, D_{pd}, F_{pd}]\), four parameters representing the baseline level of the fraction of resources used by each spike \((U_{id}, U_{ip}, U_{pd}, U_{pd})\), and four new (combined) parameters, \(W_{Id} = C_{Id} \times N_{Id}\), \(W_{Ip} = C_{Ip} \times N_{Ip}\), \(W_{Pd} = C_{Pd} \times N_{Pd}\), and \(W_{pd} = C_{pd} \times N_{pd}\), which represent the overall anatomical strength of the connections (taking both the theoretical maximum amplitude of a synaptic response and the number of synapses into account), as parameters that are to be optimized under the above constraint equations. There are in total 8 + 4 + 4 = 16 parameters while there exist 4 constraint equations, and thus the remaining degrees of freedom are 16 - 4 = 12. I systematically varied the values of 12 parameters regarding short-term plasticity \([D_{Id}, F_{Id}, U_{id}, D_{Ip}, F_{Ip}, U_{ip}, D_{Pd}, F_{Pd}, U_{pd}, D_{pd}, F_{pd}, U_{pd}]\) at initial conditions, from which the optimization procedure was started (see below; note that the parameters for anatomical connection strength \((W_{Id}, W_{Ip}, W_{Pd}, W_{pd})\) at initial conditions, from which the optimization procedure was started). To calculate PPR to cortical and intrastriatal stimulations, it is again necessary to assume the ipsi/contra ratio of the IT connection strength [i.e., \(W_{Id} = C_{Id} \times N_{Id}\)\(; W_{Id} = C_{Id} \times N_{Id}\) and \(W_{Ip} = C_{Ip} \times N_{Ip}\); \(W_{Pd} = C_{Pd} \times N_{Pd}\); and \(W_{pd} = C_{pd} \times N_{pd}\)], whose value (and not the values of \(U_{id}, U_{ip}, U_{pd}, U_{pd}\) individually) at the initial condition was varied, but I still imposed the above beta distribution for \((U_{id}, U_{ip}, U_{pd}, U_{pd})\) as a prior. I explored a set of parameters \(\alpha\) that maximizes log(P(PPRExp)\(P(\alpha)\)) by using the optimization function “imsearch” in MATLAB (MathWorks) with the values of “MaxFunEvals” and “MaxIter” options increased (both of these values were set to 30,000 for the analyses shown in Fig. 5B, 40,000 for those shown in Figs. 7 and 8, and 20,000 for the other cases; I set the larger values for the cases of Figs. 5B, 7, and 8 so that the function properly terminates for all the initial conditions that were tested; see below). Because this function might only give a local solution, the optimization procedure was repeated by setting various initial conditions [in the first way of parameter optimization: 50 or 100 ms for each of \(D_{F}, D_{Pd}, F_{Pd}\), and \(\alpha\) in the case shown in Fig. 3A; see RESULTS, Further confirmation of robustness of approach and exploration of better fit].

To summarize the above, first I derived four constraint equations, and then I described two different ways of parameter optimization: the first way, with a priori assumptions about the theoretical maximum amplitude of a synaptic response and the number of synapses (with either assumption 1-1, equal amplitude for any types of synapses, or assumption 1-2, larger amplitude for PT synapses than IT synapses, and either assumption 2-1, equal numbers of synapses for any types of synapses, or assumption 2-2, larger numbers of IT→dMSN and PT→iMSN synapses than IT→iMSN and PT→dMSN synapses, respectively); and the second way, without a priori assumptions about them. In the first or second way of parameter optimization, there are 9 or 12 degrees of freedom, respectively. I explored best values for the parameters to explain the PPR data shown in Fig. 3, D and F, of Ding et al. (2008), which are replicated in Fig. 1A in the present article. Specifically, from their figure, I (manually) extracted the mean values, as well as the SEs, of the PPR in the case with interstimulus intervals (ISIs) of 20, 50, 100, 200, 500, or 1,000 ms for each of the \(2 \times 2 = 4\) conditions (i.e., responses in dMSNs and iMSNs to cortical and intrastriatal stimulation). Using these extracted values, I explored the maximum a posteriori parameter estimates, i.e., a set of parameters \(\alpha\) that maximizes, in an approximate sense as described below, the posterior score (the right-hand side of the following):

\[ P(\alpha|PPRExp) \propto P(PPRExp|\alpha)P(\alpha) \]

where PPRExp is the experimentally observed PPR (mean values). The likelihood P(PPRExp|\alpha) is the probability that PPRExp is generated from the above-mentioned model with the set of parameters \(\alpha\) in the presence of certain noises. The nature of the noises is unknown, and so I assumed, for practical purposes, that the probability distribution of observed PPR values is a normal distribution, whose mean is the value calculated from the model with the set of parameters \(\alpha\) and whose standard deviation is the SE of the mean of observed data, P(PPRExp|\alpha) is a product of the probabilities that the observed PPR mean values for each ISI and condition are generated from such normal distributions. P(\alpha) is the prior probability of the parameters. By definition, the time constants for recovery from depression and facilitation (\(D\) and \(F\)) should be nonnegative, and the baseline level of the fraction of resources used by each spike (\(U\)) should be between 0 and 1. Moreover, extremely large values of \(U\) or \(\alpha\), as well as values of \(\alpha\) that are extremely close to the boundaries 0 or 1, would be physiologically implausible. Therefore, I assumed the following gamma and beta distributions (see Fig. 2C):

\[ D \text{ and } F \text{ (in s)} \sim \text{gamma}(1, 1) \]

\[ U \sim \text{beta}(1, 1, 1) \]

Gamma and beta distributions (with different parameters) have been used as a prior in maximum a posteriori parameter estimation (Christakou et al. 2013). Notably, in the first way of parameter optimization, with a priori assumptions about anatomical connection strength, parameters \((U_{id}, U_{ip}, U_{pd}, U_{pd})\) representing the baseline level of the fraction of resources used by each spike (approximately representing the baseline release probability) were described by the single scaling parameter \(\alpha\), whose value [and not the values of \((U_{id}, U_{ip}, U_{pd}, U_{pd})\) individually] at the initial condition was varied, but I still imposed the above beta distribution for \((U_{id}, U_{ip}, U_{pd}, U_{pd})\) as a prior. I explored a set of parameters \(\alpha\) that maximizes log(P(PPRExp|\alpha)) by using the optimization function “imsearch” in MATLAB (MathWorks) with the values of “MaxFunEvals” and “MaxIter” options increased (both of these values were set to 30,000 for the analyses shown in Fig. 5B, 40,000 for those shown in Figs. 7 and 8, and 20,000 for the other cases; I set the larger values for the cases of Figs. 5B, 7, and 8 so that the function properly terminates for all the initial conditions that were tested; see below). Because this function might only give a local solution, the optimization procedure was repeated by setting various initial conditions [in the first way of parameter optimization: 50 or 100 ms for each of \(D\) and \(F\), and for \(\alpha\) in the case with assumption 2-1 or 5, 10, 15, . . . , 40 (in the case with assumption 2-1) or 5, 10, 15, or 20 (in the case with assumption 2-2); large initial values for \(\alpha\) would make the value of \(U\) outside of the presumed prior distribution and were not considered); in total, 2,048 or 1,024 conditions, respectively; in the second way of parameter optimization: 50 or 100 ms for each of \(D\) and \(F\), and 0.3 or 0.6 for each of \(U\); in total, 2\(^{12}\) = 4,096 conditions. There was no instance where exactly the same sets of parameter values were obtained through optimization procedures started from different initial conditions.

Possibility that ipsilateral and contralateral IT synapses entail different short-term plasticity. In the modeling and parameter optimization described above, it was assumed that the property of short-term synaptic plasticity can differ depending on whether the presynaptic cell type is IT or PT and whether the postsynaptic cell type is dMSN or iMSN, but not on whether the presynaptic IT cell type is in the ipsilateral or contralateral cortex. I also conducted modeling and parameter optimization without this last assumption, namely, with an alternative assumption that ipsilateral and contralateral IT terminals on the same type of MSNs can entail different short-term plasticity. For that assumption, parameters for short-term plasticity (\(D, F, U\)) and anatomical connection strength \([W (= C \times N)]\) were separately set for ipsilateral and contralateral IT cells. The ipsi/contra ratio of IT connection strength was assumed to be 1:1 by assuming \(W_{Id} = W_{Ip} = 1:1\), and the equations

\[ U_{id} \times C_{Id} \times N_{Id} = 1 \text{ and } U_{ip} \times C_{Ip} \times N_{Ip} = 0.78 \text{ constituting the constraint for replacement replaced} \]
with $U_{\text{it}} \times W_{\text{it}} + U_{\text{ct}} \times W_{\text{ct}} = 1$ and $U_{\text{it}} \times W_{\text{it}} + U_{\text{ct}} \times W_{\text{ct}} = 0.78$. I considered two different assumptions: 1) intrastriatal stimulation in the study by Ding et al. (2008) activated IT axons to an extent 1.5 times larger than in PT axons, just the same as the assumption made in the case of the model fitting shown in Fig. 6, to compare the resulting quality of fit to the case of Fig. 6 in the same condition in this regard, and 2) intrastriatal stimulation in the study by Ding et al. (2008) activated IT axons and PT axons to a similar extent (the same as the assumption made in the cases of Figs. 3–5). With each of these two assumptions, I conducted parameter optimization similarly to the second way of parameter optimization, without a priori assumptions about anatomical connection strength as described above, with 4,096 initial conditions examined (50 or 100 ms for each of $D$ and $F$; the initial value of $U$ was set to 0.5).

**Simulation of the postsynaptic response to repetitive cortical inputs.** For each of the four types of connections (IT→dMSNs, IT→iMSNs, PT→dMSNs, and PT→iMSNs) (or 6 types in the case assuming potentially differential short-term plasticity for ipsilateral and contralateral IT terminals), excitatory postsynaptic potential (EPSP) was calculated according to the following equations:

$$\frac{dV}{dt} = \left(1/C_m\right) \times \left[g_{\text{leak}}(E_{\text{leak}} - V) + g_{\text{AMPA}}(E_{\text{Glu}} - V)\right]$$

$$g_{\text{AMPA}}(t) = 5 \times C \times N \times \sum_{\text{presynaptic spikes}} \left\{u(t_{\text{sp}} - 0) \times \left(1 - t/(t_{\text{AMPAdelay}})\right)\right\}$$

$$= 5 \times C \times N \times \sum_{\text{presynaptic spikes}} \left\{u(t_{\text{sp}} - 0) \times \sum_{\text{r}} \left[1 - \exp\left(-\left(t - t_{\text{r}}\right)/\tau_{\text{AMPAdelay}}\right)\right]\right\}$$

where $t_{\text{sp}}$ is the spike time of the presynaptic neuron, $u$ is the unit step function, and $\tau_{\text{AMPAdelay}}$ is the delay constant of the AMPA conductance (2 ms). The value 5 in the head of the second equation is a constant value that is arbitrarily set here just for scaling; in the parameter optimization procedure described above, there was another arbitrary constant value for scaling in the constraint equations (as mentioned above); changing these values will not change relative amplitudes of response between different types of connections. The temporal evolution of $V$ (i.e., EPSPs) in response to 11 presynaptic (population) spikes with the interval 80 ms (i.e., 12.5 Hz) was numerically calculated by using the ode23s function in MATLAB with the values of “RelTol” and “AbsTol” options increased, and the resulting values of $V$ were plotted in Figs. 3, 4, 5, and 6.

Notably, in reality, IT cells and PT cells are known to have different firing properties. Specifically, IT cells exhibit prominent spike-frequency adaptation when they are stimulated by constant current, whereas PT cells show little adaptation (Morishima and Kawaguchi 2006). If these features are taken into account, the impact of IT cells would begin to decay after a few or several hundreds of milliseconds (even if the synapses entail short-term facilitation), whereas that of PT cells could stably sustain (depending on short-term plasticity). Also notably, it has been shown by Ding et al. (2008) that the corticostriatal synapses have rich NMDA components. In the optogenetic study that I referred to by Kress et al. (2013), MSNs were held at a hyperpolarized potential (~80 mV, not corrected for liquid junction potential of approximately ~11 mV) when EPSCs were recorded. Therefore, contribution of voltage-dependent NMDA current might not be large, and I considered only AMPA current in the above simulations. However, in reality the observed EPSCs (Kress et al. 2013) could include at least some components stemming from NMDA receptor activation on the dendrites.

Possible effects of neuromodulators/GABA released in the striatum by intrastriatal stimulation. The observed difference in the PPR between experiments with cortical and intrastriatal stimulations (Ding et al. 2008) could be, at least in part, due to neuromodulators (dopamine or acetylcholine) or GABA that could be released in the striatum due to intrastriatal stimulation. Specifically, in the case of intrastriatal stimulation, the first stimulation can activate not only glutamatergic fibers but also dopaminergic, cholinergic, or GABAergic fibers innervating MSNs or cholinergic/GABAergic interneurons, and released neuromodulators/GABA can affect the amplitude of the response to the second stimulation so as to modulate PPR. In contrast, in the case of cortical stimulation, such direct stimulation (from electrode) of those fibers/cells within the striatum does not occur (although it is still possible that the cells/axons within the striatum are activated by corticostriatal fibers that are activated by electrode in the cortex; potential effects of it were not considered in the present study). To examine the possibility that the observed difference in PPR between cortical and intrastriatal stimulations stems from the effects of neuromodulators (dopamine or acetylcholine) or GABA released in the striatum due to intrastriatal stimulation, I modeled the possible effects of released neuromodulators or GABA on the EPSC response to the second intrastriatal stimulation by a function depending on the time from the first stimulation, separately for the possible effect in dMSNs and that in iMSNs. Specifically, I considered a function consisting of the difference of exponentials with rise and decay time constants ($\tau_r$ and $\tau_d$, respectively):

$$f(t) = -\exp(-t/\tau_r) + \exp(-t/\tau_d),$$

where $t$ represents time, and modeled the possible effect of released neuromodulators/GABA on the EPSC response to the second intrastriatal stimulation by the following function depending on the time from the first stimulation:

$$g(t) = M \times \left[1 + \frac{1}{f(t_{\text{peak}})} \right] \times f(t),$$

where $t_{\text{peak}} = \tau_r \times \tau_d \times \log(\tau_r/\tau_d)(\tau_r - \tau_d)$ is the time at which $f(t)$ takes the maximum value $f(t_{\text{peak}})$ and $M$ represents a signed amplitude of the effect, separately for the effect in dMSNs and that in iMSNs. I then explored a set of parameters (i.e., rise and decay time constants and signed amplitude for dMSNs and that in iMSNs) that best explains the difference between PPR values for cortical stimulation and those for intrastriatal stimulation (Ding et al. 2008) without assuming the effects of synapse type-dependent differential short-term plasticity. Specifically, for both dMSNs and iMSNs, I simulated PPR for intrastriatal stimulation at given ISIs ($T_{\text{ISI}} = 20, 50, 100, 200, 500, 1,000$ ms), denoted as PPR$^{\text{Exp}}_{\text{TISI}}$, from the experimentally observed mean value of PPR for cortical stimulation, denoted as PPR$^{\text{Exp}}_{\text{TISI}}$, as follows:

$$\text{PPR}^{\text{Sim}}_{\text{TISI}}(T_{\text{ISI}}) = \left[1 + g(T_{\text{ISI}})\right] \times \text{PPR}^{\text{Exp}}_{\text{TISI}}(T_{\text{ISI}}).$$

I then explored a set of parameters ($\tau_r$, $\tau_d$, and $M$) that approximately maximizes the likelihood $P(\text{PPR}^{\text{Sim}}_{\text{TISI}} = \text{PPR}^{\text{Exp}}_{\text{TISI}} | \tau_r, \tau_d, M)$ for dMSNs or for iMSNs, where PPR$^{\text{Exp}}_{\text{TISI}}$ represents the hypothetical (unobservable) true value of PPR for intrastriatal stimulation, under the assumption that the distribution of PPR$^{\text{Exp}}_T$ values is a normal distribution whose mean and standard deviation are the experimentally observed mean and SE, respectively, and also 0 < $\tau_r$ ≤ $\tau_d$ for both dMSNs and iMSNs. The optimization procedure was repeated by setting various initial conditions (20, 40, or 80 ms for $\tau_r$, 50, 100, or 200 ms for $\tau_d$, and 0.2 or 0.2 for $M$ separately for dMSNs and iMSNs). Notably, the model incorporating short-term synaptic plasticity described in the previous sections was not used in the analyses described in this section.

Examination of possible effects of spatial configuration of synapses in the dendrite. To examine possible effects of spatial configuration of synapses in the dendrite, I obtained a 189-compartment spiking neuron model of MSNs in the nucleus accumbens (Wolf et al. 2005).
in the NEURON simulation environment (Hines and Carnevale 1997) from ModelDB (http://senselab.med.yale.edu/ModelDB; model accession no. 112834). The model has four primary dendritic branches, and each primary branch bifurcates twice so that there are 8 secondary branches and 16 tertiary branches, as schematically shown in Fig. 1A. I applied repetitive synaptic inputs with increasing conductance (1×, 1.5×, 2×, 2.5×, and 3× values of the model’s original AMPA and NMDA conductance at 100, 180, 260, 340, and 420 ms), roughly mimicking short-term facilitation of synaptic conductance, to four synapses with three different spatial configurations: 1) four synapses on different primary dendritic branches (schematically shown as black circles in Fig. 11A), 2) four synapses on different tertiary dendritic branches (red circles), and 3) four synapses on the same single tertiary dendritic branch (blue circles). EPSC in soma was then measured by using the “SEClamp” function of NEURON with the voltage clamped at the baseline value.

RESULTS

Computational modeling of striatal response to cortical and intrastriatal stimulations. According to the results of the experiments on the PPR of striatal synaptic response (Fig. 1A) (Ding et al. 2008), in dMSNs (D1 MSNs), synaptic response to cortical stimulation and response to intrastriatal stimulation entail a similar level of short-term facilitation. In contrast, in iMSNs (D2 MSNs), synaptic response to cortical stimulation is much more facilitating than response to intrastriatal stimulation. These results are largely in line with a preceding study (Kreitzer and Malenka 2007) in that PPR for intrastriatal stimulation is more facilitatory in dMSNs than in iMSNs. The reason of the differential PPR for cortical and intrastriatal stimulations in iMSNs remains unresolved, but it has been pointed out (Kreitzer and Malenka 2008) that heterogeneity of cortical inputs could be involved. Indeed, cortical and intrastriatal stimulations may significantly differ in the composition of activated corticostriatal fibers. It has been shown that IT cells project to the striatum bilaterally, whereas PT cells target only the ipsilateral striatum (Cowan and Wilson 1994; Levesque et al. 1996; Parent and Parent 2006; Reiner et al. 2010). Intrastriatal stimulation could presumably activate all the input fibers, i.e., fibers from contralateral IT cells as well as those from ipsilateral IT and PT cells (Fig. 1B). In contrast, cortical stimulation in the experiment using parasagittal slices presumably could not activate the fibers from the contralateral IT cells, except for the possible occurrence of an axon reflex (i.e., transmission of activation of the axon branches of contralateral IT cells into ipsilateral cortex; see Further confirmation of robustness of approach and exploration of better fit). Then, the fact that cortical stimulation, but not intrastriatal stimulation, caused facilitation in iMSNs (Fig. 1A, red lines) could result from contralateral IT inputs to iMSNs exhibiting depression. Moreover, if ipsilateral IT inputs to iMSNs are similarly depressive, the observed overall facilitating nature of cortical inputs to iMSNs seems difficult to explain unless PT inputs to iMSNs are facilitatory. On the contrary, as for synaptic response in dMSNs, cortical and intrastriatal stimulations caused similar facilitation (Fig. 1A, black lines), indicating that contralateral IT inputs to dMSNs are facilitatory (or at least not prominently depressive). Then, if ipsilateral IT inputs to dMSNs are similarly facilitating, the fact that overall cortical inputs to dMSNs are not more facilitatory than those to iMSNs (even slightly less facilitatory, although not statistically significantly: Fig. 1A, top) seems difficult to explain unless PT inputs to dMSNs are more depressive than PT inputs to iMSNs. Although such conjectures about pre- and postsynaptic neuron type-dependent short-term plasticity seem to hold intuitively, whether they are formally supported needs to be examined through rigorous computational modeling and parameter optimization. Moreover, relationships between these findings on PPR (Ding et al. 2008) and the findings regarding connec-

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Fig. 1. Physiology and anatomy of the corticostriatal connections. A: experimentally observed paired-pulse ratio (PPR) of the response to (ipsilateral) cortical (top) or intra-

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stratal stimulation (bottom) in the direct pathway medium spiny neurons (dMSNs; black) or indirect pathway medium spiny neurons (iMSNs; red). [Reprinted from Ding et al. (2008) with permission.] B: heterogeneous composition of corticostriatal projec-

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tions. Striatal neurons receive cortical inputs from 3 sources: ipsilateral intratelencephalic (IT) cells, contralateral IT cells, and ipsilat-

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eral pyramidal tract (PT) cells. Intrastriatal stimulation presumably activates fibers from all 3 sources, whereas ipsilateral cortical stimulation would not activate fibers from the contralateral IT cells, except for possible occurrence of an axon reflex [i.e., transmission of activation of the axon branches of contralateral IT cells into ipsilateral cortex (orange dashed line); see Ma-

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tails]. Vertical black dashed lines indicate that recordings were made in parasagittal slices in the experiments shown in A that have been modeled.
constructed a model of striatal response (and PPR) to cortical and intrastriatal stimulations. The model is a combination of a computational model of short-term synaptic plasticity (Markram et al. 1998; Tsodyks and Markram 1997) for each of the four types of connections (IT→dMSN, IT→iMSN, PT→dMSN, and PT→iMSN), which describes temporal dynamics of the amount of available synaptic resources and the fraction of resources used by each spike with four parameters: 

\[D\) and \(F\) (time constants for recovery from depression and facilitation, respectively), \(U\) [baseline level of the fraction of resources used by each spike (approximately representing the baseline release probability)], and \(C\) (theoretical maximum amplitude of a synaptic response). Such short-term plasticity models for the four types of synapses were combined with weighting parameters \((N)\) that represent the numbers of each type of synapse. The product of \(C\) and \(N\) \((W = C \times N)\) represents the overall anatomical connection strength for each connection type (c.f., Fig. 2Aa). If the values of the parameters \(D, F, U,\) and \(W\) for each connection type, and also the ipsi/contra ratio of the IT connection strength, are determined, the model gives the values of PPR of the response to cortical or intrastriatal stimulations, as well as the amplitude of response to single stimulation of IT or PT axons, in dMSNs and iMSNs. In turn, it is possible to explore a set of parameters that best explains the observed pattern of PPR (Ding et al. 2008) (Fig. 1A) under the constraint of the results of the optogenetic study on the response amplitudes to single stimulation of IT or PT axons (Kress et al. 2013). I conducted such parameter optimization in two different ways, with a priori assumptions (constraints) about cell type-dependent anatomical connection strength or without a priori assumptions about them (except for the ipsi/contra ratio of the IT connection strength). More specifically, I explored a set of parameters that approximately maximizes a posteriori probability (with presumed priors for parameters; Fig. 2C) that the observed data set was generated from the model (see MATERIALS AND METHODS for details).

Parameter optimization with a priori assumptions about anatomical connection strength. First, I describe parameter optimization with a priori assumptions about cell type-dependent anatomical connection strength. If the apparently contradictory anatomical and optogenetic results are in fact consistent with each other, it is expected that the model, constrained by the optogenetic results, gives a better fit when assumptions derived from the results of actual anatomical experiments are made than when fake (incorrect) anatomy is assumed. In fact, the anatomical studies have reported two lines of findings. The first one regards the number of synapses. Specifically, it has been shown that IT cells and PT cells preferentially (but not exclusively) project to dMSNs and iMSNs, respectively, by double labeling for corticostriatal terminals and the spines of MSNs in rats (Lei et al. 2004). Such connection preferences have also been suggested by the observation of the size of synaptic terminals in rat (Lei et al. 2004) and monkey (Reiner et al. 2010). The second finding is about the size of synapses. In particular, it has been found by electron microscopy that individual PT axon terminals have about twice larger mean diameter (thus presumably about \(2^2 = 4\) times larger surface area) than IT axon terminals (Lei et al. 2004; Reiner et al. 2003). Given that the maximum amplitude of a synaptic response can be roughly in proportion to the number of neurotransmitter receptor channels on the surface of the synapse, which can be proportional to the surface area, it can be expected, from the observed size difference, that PT synapses have about four times larger maximum response amplitude than IT synapses.

On the basis of these findings and considerations, I conducted parameter optimization of the model with three different assumptions about anatomical connection strength: 1) both the number of synapses \((N)\) and the theoretical maximum amplitude of a synaptic response \((C)\) are equal for all the types of synapses (as a control condition; Fig. 2Aa), 2) the number of synapses varies with synapse type as shown in the double-labeling experiment (Lei et al. 2004); i.e., IT→dMSN and PT→iMSN synapses outnumber IT→iMSN and PT→dMSN synapses, respectively, but the theoretical maximum amplitude of a synaptic response is equal for all the synapse types (referred to as the partial anatomy condition; Fig. 2Ab); and 3) both the number of synapses and the theoretical maximum amplitude of a synaptic response vary with synapse type as expected from the anatomical findings (Lei et al. 2004; Reiner et al. 2003, 2010); for the latter, PT synapses are assumed to have \(2^2 = 4\) times larger theoretical maximum amplitudes than IT synapses (referred to as the full anatomy condition; Fig. 2Ac) (see MATERIALS AND METHODS for details). In all the cases, the ipsi/contra ratio of the IT connection strength was assumed to be 1:1.

There are in total \((3 + 1) \times 4 = 16\) parameters \((D, F, U,\) and \(W = C \times N)\) for IT→dMSN, IT→iMSN, PT→dMSN, and...
PT→iMSN; c.f., Fig. 2Aa]. Meanwhile, there are four constraint equations derived from the results of the optogenetic study (Kress et al. 2013) corresponding to the amplitude of response in dMSNs and iMSNs to IT or PT stimulation. Also, four parameters ($W_{Id}$, $W_{Ii}$, $W_{Pd}$, $W_{Pi}$) were additionally determined according to the above-mentioned a priori assumptions about anatomical connection strength (any 1 of the 3 different assumptions), except for a single degree of freedom representing an arbitrary scaling (i.e., only the ratio between different connection types were assumed). Therefore, there remain $16 - 4 - (4 - 1) = 9$ degrees of freedom, and I systematically varied the values of $2 \times 4 = 8$ parameters regarding the time constants for short-term plasticity ($\{D_{Id}, F_{Id}\}$, $\{D_{Ii}, F_{Ii}\}$, $\{D_{Pd}, F_{Pd}\}$, $\{D_{Pi}, F_{Pi}\}$) and 1 parameter for the scaling as values at initial conditions for the optimization procedure. Since the degrees of freedom (9) are relatively large, there are likely to exist many local optimums in the parameter space, and it is difficult to reach the true optimum by an execution of the
optimization procedure, which typically converges to the best of local optimums that could ever been reached in a search started from a particular initial condition. Therefore, to explore as many local optimums as practically possible, I repeated the optimization procedure by setting various initial conditions (in total, 2,048 or 1,024 conditions; see MATERIALS AND METHODS for details).

Figure 3 shows the results for the control condition (A), the partial anatomy condition (B), and the full anatomy condition (C). Panels Ac, Bc, and Cc in Fig. 3 showed the simulated PPR values by the model with the very best parameters in each condition. As shown in Fig. 3Ac, in the control condition, the model could reproduce the features of the empirical PPR data (Fig. 1A) to some extent; specifically, the model correctly reproduces the observation that in iMSNs PPR for cortical stimulation is more facilitatory than PPR for intrastral stimulation. However, the model’s fit is rather poor; PPR to cortical stimulation was more facilitatory in iMSNs than in dMSNs for most ISIs in the experiments, whereas the model predicts the opposite. In comparison with this poor fit, the simulated PPR values in the full anatomy condition (Fig. 3Cc) look much closer to the empirical PPR data, and the results in the partial anatomy condition (Fig. 3Bc) appear to be intermediate. More quantitative comparison of the quality of fit across the different conditions can be made by examining the approximated a posteriori scores for optimization. Panels Ab, Bb, and Cb in Fig. 3 show the histogram of the log of the approximated a posteriori scores obtained as a (local) optimum starting from the various initial conditions that were tested, and the rightmost part (dark gray bars) indicates the best 5% local optimums in each condition. As shown, fit is poorest in the control condition, better in the partial anatomy condition, and even nicer in the full anatomy condition. The same tendency that incorporation of the actually observed anatomical features into the model gives a better fit also appeared in the log likelihood, which is a measure of the quality of fit without contributions of the presumed prior probabilities of the parameters (see Fig. 9A). Given that the model was constrained by the optogenetic results, these results of model fitting indicate that the apparently contradictory anatomical and optogenetic results are in fact consistent with each other.

Figure 3Cd shows the mean and standard deviation of the estimated parameters for short-term plasticity among the best 5% local optimums, as well as the estimates in the very best local optimum (crosses), in the full anatomy condition. As shown in the graphs, although precise values of the estimated parameters vary depending on local optimums (initial values for optimization), basic tendencies are kept largely consistent. The estimated best parameters correspond to the case where the time constant for recovery from depression (D) is larger than the time constant for recovery from facilitation (F) for IT→iMSN and PT→dMSN synapses (although the standard deviation of D is quite large for PT→dMSN), whereas the opposite is the case for PT→iMSN synapses, and U (approximately representing the baseline release probability) is large for IT→iMSN synapses and small for PT→iMSN synapses. Since depressive synapses generally have large D, small F, and/or large U values, whereas facilitatory synapses have the opposite, small D, large F, and/or small U values (Markram et al. 1998; Tsodyks and Markram 1997), these results indicate that IT→iMSN synapses are basically depressive, whereas PT→iMSN synapses are basically facilitatory. Figure 3Ce shows responses to repetitive IT or PT inputs in dMSNs or iMSNs predicted from the model with the very best parameters. As expected from the estimated parameter values above, response in iMSNs indeed shows depression for IT stimulation and facilitation for PT stimulation. As for the other two types of synapses, for which it appears to be difficult to tell whether facilitation or depression is dominant from the estimated parameters only, the simulation results indicate that IT→dMSN inputs entail facilitation, whereas PT→dMSN inputs initially show slight facilitation but then show more prominent depression, at least for the examined input trains with the interval 80 ms (i.e., 12.5 Hz). By virtue of these differential short-term plasticities, together with the differential anatomical connection strengths that were assumed in the model in this full anatomy condition, whereas the simulated initial response to IT stimulation is comparable between dMSNs and iMSNs and that to PT stimulation is larger in dMSNs, in agreement with the optogenetic results (Kress et al. 2013; this match is reasonable because the optogenetic results were used as a constraint in the optimization), repetitive IT and PT inputs are expected to have larger overall impacts on dMSNs and iMSNs, respectively, according to the simulation results. Notably, in the control condition (Fig. 3A) and the partial anatomy condition (Fig. 3B), although the quality of fit was worse than that in the full anatomy condition, as mentioned above, the estimated features of short-term plasticity as well as the overall impacts of
Assumed anatomical connection strength ($W = C$)
repetitive IT/PT inputs (Fig. 3, Ad, Ae, Bd, and Be), appear to be largely similar to the case of the full anatomy condition, although there are several differences, especially in the response to PT stimulation in dMSNs. This might indicate robustness of our approach.

Parameter optimization without a priori assumptions about anatomical connection strength. As shown above, in the fitting of the PPR data by the model constrained by the optogenetic results, better fit was obtained when the assumptions derived from the actual anatomical findings were made than when fake anatomy was assumed. This would certainly indicate that the results of the anatomical experiments are in fact consistent with the apparently contradictory optogenetic results. However, since only three conditions (control, partial anatomy, and full anatomy) were compared in the above while there are numerous other possibilities, the emerging question is whether even better fit could be obtained if different anatomical assumptions are made. I addressed this issue by a different method of parameter optimization, namely, optimization without a priori assumptions about anatomical connection strength. Instead of assuming the ratios between the number (N) and the theoretical maximum response amplitude (C) of synapses for different connection types as was done above, the parameter W (= C × N), representing the overall anatomical connection strength, was left as a free parameter for all of the four types of connections, while the ipsi/contra ratio of the IT connection strength was still assumed to be 1:1 (but the case with ipsi/ contra = 2:1 was also examined later; see below). There are, again, in total (3 + 1) × 4 = 16 parameters [D, F, U, and W (= C × N) for IT→dMSN, IT→iMSN, PT→dMSN, and PT→iMSN; Fig. 2B] and 4 constraint equations derived from the optogenetic results (amplitude of response in dMSNs and iMSNs to IT or PT stimulation), and this time there is no further constraint. Therefore, there remain 16 − 4 = 12 degrees of freedom, and I systematically varied the values of 3 × 4 = 12 parameters regarding short-term plasticity (D, F, U) as values at initial conditions for the optimization procedure.

Figure 4A shows the histogram of the log of the approximated a posteriori scores obtained as a (local) optimum starting from the various initial conditions that were tested, with the rightmost part (dark gray bars) indicating the best 40 (~1%) local optima, and Fig. 9B shows the distributions of the log likelihood, a measure of the quality of fit without taking into account the presumed prior probabilities of the parameters. Comparing this Fig. 9B with Fig. 9A, bottom, which shows the case of optimization with anatomical assumptions derived from the empirical data (the full anatomy condition; Fig. 3C), the quality of fit (log likelihood) in the case without anatomical assumptions (see Fig. 9B) looks just comparable to, and not much better than, that in the case with the empirical data-derived anatomical assumptions, even though the degree of freedom in model fitting is larger in the case without anatomical assumptions. Figure 4E shows the mean and standard deviation of the estimated parameters for anatomical connection strength [W (= C × N), calculated by substituting the estimated values of U into the constraint equations] in the best 40 local optima, as well as the estimates in the very best condition (crosses). As shown in the graph, the best parameters correspond to the case where IT→dMSN and PT→iMSN connections are anatomically stronger than IT→iMSN and PT→dMSN connections, respectively. Strikingly, this pattern of connection predominance, obtained purely from the physiological and optogenetic results through parameter optimization, matches the actual anatomical results.

Moreover, Fig. 4E further shows that the estimated PT→iMSN connection is particularly strong, and the PT→dMSN connection is weaker than the PT→iMSN connection but stronger than the IT→iMSN connection. Since the estimated parameter W is the product of the number of synapses (N) and the theoretical maximum amplitude of a synaptic response (C), such a tendency, where PT→MSN connections are generally strong compared with IT→MSN connections, appears to match the different line of anatomical findings that PT synapses are larger than IT synapses, if the model’s parameter C indeed has correspondence with the size of the actual synapses. More specifically, the overall pattern of Fig. 4E appears to be in good agreement with the pattern expected from the combination of the two different lines of actual anatomical findings (Fig. 3Ca, right): one is that IT→dMSN and PT→iMSN synapses outnumber IT→iMSN and PT→dMSN synapses, respectively (Lei et al. 2004), and the other is that PT terminals are larger than IT terminals (Lei et al. 2004; Reiner et al. 2003, 2010).

To summarize, the model fitting without anatomical assumptions resulted in a quality of fit that is comparable to that obtained in the fitting with anatomical assumptions derived from the empirical results, and the estimated anatomical connection strengths match the two lines of empirical findings, the IT→dMSN and PT→iMSN connection preferences and the larger size of PT synapses than IT synapses. These results further support the indication obtained from the fittings with anatomical assumptions that the apparently contradictory anatomical and optogenetic findings are in fact consistent with each other. Figure 4C shows the mean and standard deviation of the estimated parameters for short-term plasticity among the best 40 local optima, as well as the estimates in the very best local optimum (crosses), and Fig. 4D shows the responses to repetitive IT or PT inputs in dMSNs and iMSNs simulated by the model with the very best parameters. Crucially, the estimated features of short-term plasticity, as well as the overall impacts of repetitive inputs, appear to be largely similar to those obtained in the fitting with anatomical assumptions derived from the empirical results (the full anatomy condition; Fig. 3, Cd and Ce), indicating the robustness of my approach and the obtained results. Given all these results, it is tempting to try to intuitively explain, at least partially, how the appar-
**A**

Number of initial conditions

Log of a posteriori score

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**B**

Cortical stimulation

- dMSN (D1 MSN)
- iMSN (D2 MSN)

Intrastriatal stimulation

- dMSN (D1 MSN)
- iMSN (D2 MSN)

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**C**

IT -> dMSN

IT -> iMSN

Recovery time constants (ms)

Baseline fraction of resources used by each spike

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**D**

EPSP (mV)

Time (ms)

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**E**

Estimated anatomical connection strength

$W = N \times C$
ently contradictory anatomical and optogenetic results can be consistent with each other. As I described early in RESULTS, it is possible to guess from the results of the PPR experiments (Ding et al. 2008) that IT→dMSN and PT→iMSN synapses are more facilitatory than IT→iMSN and PT→dMSN synapses, respectively. Facilitatory synapses typically have lower baseline release probability than depressive synapses, and the difference in the baseline release probability can be severalfold or more (Markram et al. 1998; Tsodyks and Markram 1997). Indeed, looking at the estimated values of the parameter $U$ (which approximately represents the baseline release probability) in the model fitting (Fig. 4C), $U$ for IT→dMSN synapses is less than half of $U$ for IT→iMSN synapses, and even more dramatically, $U$ for PT→iMSN synapses is more than several times smaller than $U$ for PT→dMSN synapses. Then, if the theoretical maximum amplitude of a synaptic response and the number of synapses activated by a single optical stimulation of PT axons (as used in the optogenetic study, Kress et al. 2013) are comparable between PT→dMSN and PT→iMSN connections, the response in iMSNs should be more than several times smaller than the response in dMSNs. In reality, however, the response in iMSNs was indeed smaller than the response in dMSNs, but the difference was only about twice (Kress et al. 2013). This indicates that PT→iMSN connections in fact have a larger number of synapses and/or larger theoretical maximum amplitude of a synaptic response, consistent with the actual anatomical findings (Lei et al. 2004; Reiner et al. 2003, 2010).

Further confirmation of robustness of approach and explanation of better fit. In the above-described fitting analyses, it was presumed that connection strength from ipsilateral IT cells to MSNs and that from contralateral IT cells to MSNs are equal (both being half of the total strength), but interhemispheric connections (i.e., connections from contralateral IT cells) could be weaker than intrahemispheric connections. Therefore, I also examined the case in which connection strengths from contralateral IT cells to MSNs were assumed to be half of the strength from ipsilateral IT cells to MSNs (Fig. 5Aa); model fitting was conducted without anatomical assumptions other than this ipsi/contra ratio, in a similar way to the fitting described in the previous section. Figure 5, Ab–Af, shows the results. Comparing these results with Fig. 4, although the calculated a posteriori scores are somewhat smaller than the values in the original case, assuming equal strengths for ipsilateral and contralateral IT inputs, and the fit of the PPR data is somewhat worse [the log likelihood (see Fig. 9C, top) is also smaller than in the original case (see Fig. 9B)], the overall features of estimated short-term plasticity and anatomical connection strength are largely preserved.

Next, there is also another potential concern in the model. Specifically, although it was presumed in the above fitting analyses that cortical stimulation applied in the PPR experiments (Ding et al. 2008) did not activate axons from contralateral IT cells, those axons could possibly be activated through an “axon reflex,” that is, activation of branches of these axons into ipsilateral cortex, given that IT cells send branched axons to both striatum and cortex in the opposite hemisphere. The effect of such an axon reflex can be prominent, as shown in experiments in anesthetized rats (Wilson 1986). However, the experiments that I modeled [Fig. 3 of Ding et al. (2008)] used parasagittal slices, and it would not be certain whether or to what degree such an axon reflex occurs [it occurs only if the branch point of contralateral IT axon toward ipsilateral cortex (orange dashed lines in Fig. 1B) and axon toward ipsilateral striatum is within the slice]. Nevertheless, I also conducted parameter optimization in the case where cortical stimulation recruits a quarter of axons from contralateral IT cells via an axon reflex (Fig. 5Ba); the ratio of the ipsilateral and contralateral IT connection strength was set to 1:1 as in the original case, and model fitting was conducted without anatomical assumptions other than the effects of axon reflex and the ipsi/contra ratio of IT connection strength. Figure 5, Bb–Bf, shows the results. As shown, although the fit of the PPR data is again somewhat worse than the fit in the original case, the overall features of estimated short-term plasticity and anatomical connection strength are largely preserved. These results (Fig. 5, A and B) would further support the robustness of my approach and the obtained results.

There is a problem, however, in that the model’s fit of the PPR data is not excellent. Specifically, although the model largely reproduces the overall features of the data, there are some deviations, especially in PPRs in iMSNs in response to cortical stimulation with small ISIs ($\leq 50$ ms), both in the original models (Figs. 3C and 4) and more prominently in the models with alternative assumptions (Fig. 5, A and B). It seems that the dramatic difference in PPR in iMSNs between cortical stimulation and intrastratal stimulation observed in the experiments by Ding et al. (2008) (see Fig. 1A) makes fitting difficult. In fact, a preceding study that also examined PPR in dMSNs and iMSNs to intrastratal stimulation (Kreitzer and Malenka 2007) consistently found that PPRs in dMSNs were more facilitatory than those in iMSNs, but the difference was much milder. More specifically, in that study, PPRs in iMSNs were facilitatory (up to ~1.2) rather than depressive as in Ding et al. (2008) (although they were less facilitatory than PPRs in dMSNs), as shown in Fig. 6C. The reason for the difference between these two studies is unclear, but it might be because intrastral stimulations used in the two studies somehow differed, for instance, in the spatial arrangement of electrode, and thereby particular type(s) of fibers were activated more (or less) in one of these studies. On the basis of such a conjecture, I conducted model fitting and simulation with an assumption that intrastratal stimulation in the study by Ding et al. (2008) activated IT axons to a larger extent than PT axons, whereas intrastratal stimulation in the study by Kreitzer and Malenka (2007) activated IT axons and PT axons to a similar extent (see MATERIALS AND METHODS for details); model fitting was conducted without anatomical assumptions other than these and the ipsi/contra ratio of IT connection strength, which was assumed to be 1:1. Figure 6 shows the results. As shown in Fig. 6, A and B, fit of the PPR data of Ding et al. (2008) was much
improved (as also appeared in the log likelihood shown in Fig.
9D), and the PPR data of Kreitzer and Malenka (2007) also
appear to be successfully reproduced (open circles and dashed
lines in Fig. 6B, bottom). Importantly, estimated short-term
plasticity properties (Fig. 6D), simulated responses to repeti-
tive inputs in the case of the very best parameter set (Fig. 6E),
and estimated anatomical connection strength (Fig. 6F)
are largely unchanged from the original case (Fig. 4, C–E).
Or perhaps even more, the estimated anatomical connection
strength (Fig. 6F) appears to match the pattern expected from
the actual anatomical findings (Fig. 3Ca, right) to a better
extent than the original case (Fig. 4E).

In all the model fitting analyses described so far, it has been
assumed that synaptic terminals of ipsilateral IT cells and those
of contralateral IT cells on the same type of MSNs entail the
same short-term plasticity. Generally, it has been demonstrated
that the property of short-term plasticity can depend on pre-
synaptic (Beierlein and Connors 2002) and postsynaptic neu-
ron types (Blackman et al. 2013; Markram et al. 1998). If such
dependence stems from physiological and/or gene expression
features of the neurons, it seems possible that ipsilateral and
contralateral IT terminals on the same type of MSNs share the
property of short-term plasticity, given that ipsilateral and
contralateral IT cells would share many physiological and/or
gene expression features (presumably more features than those
shared by IT cells and PT cells, although not certain). How-
ever, it is also possible that the terminals originating from
ipsilateral and contralateral IT cells entail different short-term
plasticity. I examined how well the empirical PPR data (Ding
et al. 2008) can be explained if this latter possibility is taken
into account by conducting a new set of model fitting, without
anatomical assumptions other than assuming that the ipsi/
contra ratio of the IT connection strength is 1:1 and also that
intrastratal stimulation in the study by Ding et al. (2008)
activated IT axons to a larger extent than PT axons (as assumed
above for the case shown in Fig. 6 to compare the resulting
quality of fit to that case (the best case so far examined) in
the same condition in this regard; but I also conducted model
fitting without this last assumption (shown later)).

Figure 7 shows the results. As shown in Fig. 7A, the PPR
data were fitted fairly well. The quality of the fit appears to be
comparable to that in the previous model fitting analysis
described above (Fig. 6B). Indeed, when comparing Fig. 9D
and Fig. 9E, top, which show the log likelihood in these two
analyses, although the distribution in Fig. 9D is wider and the
center of gravity looks to be significantly smaller than that in
Fig. 9E, top, the rightmost portion of the distributions appears
to be at similar log likelihood values.

Figure 7, B–D, show the estimated parameters for short-term
plasticity, simulated responses to repetitive inputs in the case of
the very best parameter set, and estimated anatomical
connection strength in the new fitting analysis. As shown in
Fig. 7, B and C, with this new model, it was estimated that
ipsilateral and contralateral IT terminals have quite different
properties of short-term plasticity. The match between the
estimated pattern of anatomical connection strength (Fig. 7D)
and the pattern expected from the actual anatomical findings
(Fig. 3Ca, right) is worse than the case of the previous model
fitting analysis (Fig. 6F); the pattern in the case of the very best
parameter set (crosses in Fig. 7D) is quite different from the
expected pattern, and the pattern averaged across the best 40
parameter sets (bars in Fig. 7D) looks closer to the expected
pattern but still not very close.

Figure 8 shows the results of a separate model fitting
analysis with the alternative assumption that intrastratal
stimulation in the study by Ding et al. (2008) activated IT
axons and PT axons to a similar extent, and Fig. 9E, bottom,
shows the distribution of log likelihood for this alternative.
As shown in these figures, the quality of fit in this case looks
comparable to the case of Fig. 7 described just above, and
the estimated pattern of anatomical connection strength
(Fig. 8D) appears to deviate from the pattern expected from
the actual anatomical findings (Fig. 3Ca, right) even further.
Therefore, when the results are taken together, given that
the new sets of fitting analyses give relatively poor consistency
with the actual anatomical results and also do not give a dramatically
better fit to the PPR data than the previous fitting analysis despite
having the larger degree of freedom, it could be said that the
possibility of differential short-term plasticity for ipsilateral and
contralateral IT terminals seems not to be strongly supported, although
such a possibility still cannot be denied.

Possible effects of dopamine released in the striatum by
intrastratal stimulation. So far it was assumed that the observed
difference in the PPR (especially in iMSNs) between
cortical and intrastratal stimulations (Ding et al. 2008) (Fig.
1A) was due to the presumable difference in the composition
of activated corticostriatal fibers. However, the differential PPR
could be, at least in part, due to effects of neuromodulators
(dopamine or acetylcholine) or GABA that could be released in
the striatum by intrastratal stimulation. Specifically, in the
case of intrastratal stimulation, the first stimulation can acti-
vate not only glutamatergic fibers but also dopaminergic,
cholinergic, or GABAergic fibers innervating MSNs or chlo-
linerigic/GABAergic interneurons (Tepper and Bolam 2004),
and released neuromodulators/GABA can affect the amplitude
of glutamatergic synaptic response to the second stimulation so
as to modulate PPR, whereas in the case of cortical stimulation,
direct stimulation (from electrode) of those fibers/cells within
the striatum does not occur. To explore such possibilities, I
modeled the possible effects of neuromodulators (dopamine
or acetylcholine) or GABA released in the striatum by intrastratal
stimulation on the EPSC response to the second intrastratal
stimulation by a function depending on the time from the
first stimulation with three free parameters, rise and decay time
constants ($\tau_r$ and $\tau_d$, respectively) and a signed amplitude ($M$),
separately for the possible effect in dMSNs and that in iMSNs.

Fig. 6. Exploration of better fit through examination of a case with a different assumption. It was assumed that intrastratal stimulation in the study by
Ding et al. (2008) activated IT axons to an extent 1.5 times larger than PT axons, whereas intrastratal stimulation in another study that also examined
PPR (Kreitzer and Malenka 2007) [shown in C; reprinted by permission from Macmillan Publishers Ltd: Nature (Kreitzer and Malenka 2007), copyright
2007] activated IT axons and PT axons to a similar extent. The ratio of ipsilateral to contralateral IT connection strength was assumed to be 1:1.
Configurations of A, B, and D–F are the same as those of Fig. 4, A–E, except that the filled circles connected by the solid line and the open circles
connected by the dashed line in B, bottom, show PPR values simulated by the model (with the very best set of parameters) as the values of Ding et al.
(2008) and Kreitzer and Malenka (2007), respectively.

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**A**

Number of initial conditions

![Graph showing the number of initial conditions](image)

Log of a posteriori score

Number of initial conditions vs. Log of a posteriori score.

**B**

**Cortical stimulation**

- dMSN (D1 MSN)
- iMSN (D2 MSN)

![Graph showing paired pulse ratio](image)

**Interstimulus interval (ms)**

Paired pulse ratio vs. Interstimulus interval (ms).

**Intrastriatal stimulation**

- dMSN (D1 MSN)
- iMSN (D2 MSN)

![Graph showing paired pulse ratio](image)

**Interstimulus interval (ms)**

Paired pulse ratio vs. Interstimulus interval (ms).

**D**

**IT -> dMSN**

![Graph showing recovery time constants](image)

**IT -> iMSN**

![Graph showing recovery time constants](image)

Recovery time constants (ms)

Baseline fraction of resources used by each spike

**E**

**dMSN (D1 MSN)**

![Graph showing EPSP (mV) vs. Time (ms)](image)

**iMSN (D2 MSN)**

![Graph showing EPSP (mV) vs. Time (ms)](image)

**Interstimulus interval (ms)**

EPSP (mV) vs. Time (ms).

**F**

**Estimated anatomical connection strength**

![Graph showing estimated anatomical connection strength](image)

IT, PT

dMSN, iMSN

Estimated anatomical connection strength ($w = y \times C$).
Fig. 7. Results of model fitting under the assumption that synapses made by ipsilateral and contralateral IT cells onto the same type of MSNs can entail different short-term plasticity. It was assumed that the ratio of ipsilateral to contralateral IT connection strength is 1:1, and intrastratal stimulation in the study by Ding et al. (2008) activated IT axons to an extent 1.5 times larger than PT axons (as assumed in the case of Fig. 6). Configurations of A–D are the same as those of Fig. 4, B–E, except that B and C show the results for ipsilateral and contralateral IT cells separately.
effects of neuromodulators/GABA released by intrastriatal stimulation. As shown in Fig. 10A, the slight difference in the PPR for cortical and intrastriatal stimulations in dMSNs (Fig. 1A, black lines) could be explained if there exists an excitatory effect of neuromodulators/GABA with the rise and decay time constants around 70 ms (Fig. 10A, black lines; the estimated best parameters for $\tau_r$, $\tau_d$, and $M$ are 70.0 ms, 70.0 ms, and 0.0888, respectively). This could be achieved by dopamine, since dMSNs express dopamine D1 receptors, which have excitatory effects on the neuronal responsiveness (Gerfen and Surmeier 2011). On the other hand, for iMSNs, the estimated effect that could possibly explain the drastic difference in the PPR for cortical and intrastriatal stimulations (Fig. 1A, red lines) is an inhibitory one (Fig. 10A, red lines). This polarity again matches the effect of dopamine: iMSNs express dopamine D2 receptors that have inhibitory effects on the neuronal responsiveness (Gerfen and Surmeier 2011). However, contrary to the case of dMSNs, it seems unlikely that dopamine acting through D2 receptors can achieve such a modulation as estimated here for the following reason. The estimated $\tau_r$, $\tau_d$, and $M$ values for Fig. 10A (red lines) are 0.543 ms, 371 ms, and $-0.3267$, respectively. Although the extreme smallness of the estimated value of $\tau_r$ would be due to the particular form of the presumed function for the effect of neuromodulators/GABA, it seems to be obvious that the PPR data cannot be explained unless an inhibitory effect in iMSNs develops on a time scale at least faster than 20 ms, because the difference in the PPR for cortical and intrastriatal stimulations in iMSNs is most prominent with the shortest interspike interval (20 ms) that was tested (Fig. 1A, red lines). However, D2 receptors, as well as D1 receptors, are G protein-coupled metabotropic receptors that would need much more time to exert inhibitory effects. Possible effects of neuromodulators other than dopamine, particularly acetylcholine, and GABA are discussed below.

**DISCUSSION**

Regarding the corticostriatal connections, there have been three independent sets of empirical findings: 1) the anatomical findings on the connection preference and the synapse size, 2) the optogenetic findings on the amplitude of responses to single stimulations of IT or PT axons, and 3) the physiological findings on the striatal PPR for cortical and intrastriatal stimulations. Given these findings, two questions have been raised: question 1) can the apparently contradictory findings 1 and 2 above still be consistent with each other? and question 2) what are the overall impacts of repetitive IT or PT inputs on the MSNs? I have tried to answer these questions through computational modeling and parameter optimization. As for question 1, the answer turns out to be “yes,” because the optimization assuming the actually observed anatomy gives a better fit than the optimization assuming the fake, incorrect anatomy, and moreover, the optimization without anatomical assumptions gives results that match the actual anatomical findings. As for question 2, the results of the two ways of optimization consistently suggest that repetitive IT or PT inputs are likely to have larger overall impacts on dMSNs or iMSNs, respectively, by virtue of both the anatomical connection preferences and the
Fig. 8. Results of model fitting conducted in the same way as in Fig. 7, except that intrastriatal stimulation in the study by Ding et al. (2008) activated IT axons and PT axons to a similar extent (as assumed in cases other than those of Figs. 6 and 7). Configurations are the same as those of Fig. 7.
short-term plasticity
ipsi- and contra-IT

Confirmation of assumptions

Differential IT/PT activation by intrastriatal stimulation

Exploration of better fit

Differential IT/PT activation by intrastriatal stimulation

Equal IT/PT activation by intrastriatal stimulation

synapse type-dependent short-term plasticity. It should be noted, however, that these conclusions were obtained under the assumption that ipsilateral and contralateral IT terminals entail the same short-term plasticity; possible violation of this assumption was examined in a separate analysis, and the results indicate that the possibility of such a violation is not strongly supported, although it cannot be denied. Also separately, I have examined possible effects of dopamine that could be released by intrastriatal stimulation. The results suggest that such effects could potentially explain the observed slight difference in the PPR for cortical and intrastriatal stimulations in dMSNs, but likely not the much larger difference in iMSNs. In the following, I will discuss the limitations as well as the validity of my approach and present functional implications of the results of the present study.

Limitations and validity of my approach. In RESULTS, I have examined possible effects of dopamine potentially released in the striatum by intrastriatal stimulation on PPR. Along with dopamine, acetylcholine can also be released in the striatum by intrastriatal stimulation through activation of cholinergic fibers or interneurons (Tepper and Bolam 2004) and potentially affect PPR. Direct effects of acetylcholine on MSNs, however, are through muscarinic acetylcholine receptors (Oldenburg and Ding 2011) that are slow G protein-coupled receptors and thus not very likely to be able to provide the fast, strong inhibition on the response in iMSNs that is necessary to explain the observed differential PPR for cortical and intrastriatal stimulations (red lines in Fig. 10A). Fast nicotinic acetylcholine receptors exist at axon terminals of glutamatergic, dopaminergic, and fast-spiking (FS) GABAergic neurons (Koós and Tepper 2002; Zhou et al. 2002). However, these are also not very likely to provide fast, strong inhibition on the response in iMSNs for the following reasons: 1) effects on the glutamatergic terminals would be excitatory (facilitatory) rather than inhibitory, 2) effects through the dopaminergic terminals would be slow because they should eventually operate through G protein-coupled D1 or D2 receptors, and 3) effects through FS neurons would be stronger in dMSNs since FS neurons preferentially target
dMSNs over iMSNs (Gittis et al. 2010). Notably, the authors of the PPR experiments that I modeled (Ding et al. 2008) explicitly referred to acetylcholine, together with dopamine, as a potential contributor to the observed differential PPR for cortical and intrastriatal stimulations in iMSNs in their discussion, but a subsequent study by the same group that examined the effects of acetylcholine (Ding et al. 2010) did not report that they found evidence for it.

Other than dopamine and acetylcholine, a remaining possibility is that intrastriatal stimulation activates GABAergic interneurons (Wickens et al. 2007) or their fibers and that released GABA modulates the response to the subsequent glutamatergic input. However, this also seems not very likely to be able to fully explain the drastically differential PPR for cortical and intrastriatal stimulations in iMSNs: there are two major types of striatal GABAergic interneurons, FS cells and persistent low-threshold spiking (PLTS) cells, and the former cells appear to mediate the bulk of feedforward inhibition but preferentially target dMSNs over iMSNs (Gittis et al. 2010). Regarding GABA, there is a further possibility. A recent study (Tritsch et al. 2012) has shown that activation of dopaminergic fibers induces direct release of GABA from these fibers, resulting in rapid inhibition of MSNs, which can affect PPR with short interspike intervals. However, because such an effect has been shown to be comparable between dMSNs and iMSNs (Tritsch et al. 2012), it would not be able to fully explain the dramatic difference in PPR for cortical and intrastriatal stimulations only in iMSNs.

A factor that was not considered in the model of the present study is the possible effect of thalamostriatal fibers, which could be activated by intrastriatal stimulation but not by cortical stimulation. In the experimental study of PPR (Ding et al. 2008) that I modeled, the authors also conducted cortical and thalamic stimulations using horizontal slices and found that although PPR for cortical stimulation is facilitatory for both dMSNs and iMSNs, PPR for thalamic stimulation is depressive for both types of MSNs. This raised a possibility that the observed differential PPR for intrastriatal stimulation for dMSNs and iMSNs could be explained if thalamostriatal axons innervating iMSNs have a lower electrical threshold. However, the authors mentioned that grading the intrastriatal stimulation intensity did not systematically change PPR properties, questioning the validity of such an explanation. They also mentioned that in the experiments using horizontal slices, thalamic stimulus intensity was on average 1.5 times that of the cortical stimulus intensity. This might indicate that corticostraiatal axons can be activated more easily than thalamostriatal axons and could then justify the nonincorporation of the effects of thalamic inputs in the modeling of the present study. In fact, a different group has also examined PPR for cortical and thalamic stimulations using very similar horizontal slices (Smeal et al. 2007), but they found that PPR for thalamic stimulation was more facilitatory than that for cortical stimulation, opposite to the results of Ding et al. (2008); the reason for this discrepancy remains unresolved, but it could be due to heterogeneity of thalamostriatal fibers (Ding et al. 2008). Besides the issue of thalamostriatal fibers, effects of possible release of neuromodulators/GABA in the striatum by activation of interneurons/fibers by cortical stimulation also are not considered in the present study (only release of them by intrastriatal stimulation has been considered, as described above).

Although it remains elusive exactly how thalamic inputs, as well as neuromodulators and GABA in the striatum, affect striatal PPR, there is a study whose results appear to support the main argument of the present study that the differential PPR for cortical and intrastriatal stimulations come at least partially from different compositions of activated corticostriatal fibers. Specifically, in a study that examined PPR of corticostriatal synapses by stimulating the corpus callosum in coronal slices (in mice) (André et al. 2011), PPR in dMSNs appeared to be more facilitatory than PPR in iMSNs when interspike interval was 25, 50, or 100 ms, although there was no direct comparison (presumably because it was not the theme of that study) and such a difference apparently existed at 1.5 mo but not at 12 mo. This result appears to be at odds with the cortical stimulation experiment that was modeled in this study (Ding et al. 2008) (Fig. 1A, top), in which PPR was comparable in dMSNs and iMSNs, or even apparently a bit more facilitatory in iMSNs than in dMSNs, although the difference was not significant. Stimulation of the corpus callosum would primarily recruit corticostriatal fibers from contralateral IT cells, although it could also activate axons from ipsilateral IT cells via an axon reflex as well as PT axons (pyramidal tract) passing nearby. The fact that PPR for callosal stimulation appears to be more facilitatory in dMSNs than in iMSNs seems to be in line with the prediction of the present study that IT→dMSN synapses are more facilitatory than IT→iMSN synapses. Moreover, the same group also has examined PPR of corticostriatal synapses in a different study (Cepeda et al. 2008), but there they stimulated not only the corpus callosum but also the cortex (deeper cortical layers) by using a bipolar electrode. Intriguingly, in that study, PPR was more facilitatory in iMSNs than in dMSNs, seemingly opposite to the above-mentioned study (André et al. 2011). Given that additional stimulation of the cortical deep layers would increase the ratio of PT axons in the activated corticostriatal fibers, this result also seems to be in line with the prediction of the present study that PT→iMSN synapses are more facilitatory than PT→dMSN synapses.

Eventually, the predictions of the present study about connection type-dependent short-term plasticity need to be tested in experiments. It may not be so straightforward, however, to examine short-term plasticity in realistic conditions by using optical stimulation such as the one used in the study that I have referred to (Kress et al. 2013). Specifically, such stimulation, if strong, would synchronously activate a large number of synapses on the MSNs’ dendritic branches. It could then cause highly nonlinear dendritic events such as plateau potential (Plotkin et al. 2011) or saturation, and thereby it could be difficult to accurately measure PPR in the soma. I examined whether such difficulty can indeed appear by using an existing multicompartiment spiking neuron model of MSNs in the nucleus accumbens in the NEURON simulation environment (Wolfl et al. 2005). Specifically, I compared response to repetitive synaptic inputs with increasing conductance in three cases: 1) inputs to four different primary dendritic branches, 2) inputs to four different tertiary dendritic branches, and 3) inputs to the same single tertiary dendritic branch (see MATERIALS AND METHODS for details). As a result (Fig. 11), whereas changes in the EPSC response...
amplitude in case 1 faithfully reflect the increase in synaptic conductance, changes in the EPSC amplitude in case 2 are milder, and those in case 3 are even less, indicating a possible appearance of such a difficulty due to dendritic nonlinearity in examination of PPR as raised above. On the other hand, if the magnitude of repetitive optical stimulation is weak, a small number of synapses that are randomly selected at each stimulation would be activated, and thereby it would again be difficult to accurately measure PPR. Thus exploration of appropriate conditions would be not easy, and sophisticated methods are expected to be developed.

Functional implications: corticostriatal temporal difference hypothesis. The corticostriatal system is thought to be crucially involved in reward/reinforcement learning, action selection,
and motor control. Recently, a hypothesis on the specific roles of the corticostriatal system in these cognitive functions was proposed (Morita et al. 2012, 2013). According to this hypothesis, referred to as the corticostriatal temporal difference (TD) hypothesis (Fig. 12A), IT cells represent the current action or state of the animal, whereas PT cells represent the previous action/state, by virtue of the unidirectional projections from IT cells to PT cells (Morishima and Kawaguchi 2006) and the strong recurrent excitation among PT cells (Morishima et al. 2011), which presumably maintains PT cells’ activity for a certain time. Given that IT cells preferentially activate dMSNs, whereas PT cells predominantly recruit iMSNs, as suggested by the anatomical studies (Lei et al. 2004; Reiner et al. 2010) (whether this is indeed the case is the target of the present study), and also that the value of actions/states is represented in the striatum (Doya 2000; Kawagoe et al. 2004; Samejima et al. 2005), dMSNs and iMSNs presumably represent the values of the current action/state and the previous action/state, respectively. Since dMSNs and iMSNs would potentially cause net positive and negative impacts on the activity of midbrain dopamine neurons via the output nuclei of the basal ganglia, respectively, the difference of the values of the current and previous actions/states, which is the core of the reward prediction error (RPE) defined in the reinforcement learning theory (called the TD error; Sutton and Barto 1998), can be computed in the dopamine neurons, providing a possible mechanistic account for the suggested dopaminergic representation of RPE (Montague et al. 1996; Schultz et al. 1997). Along with being involved in the computation of RPE in such a way, dMSNs and iMSNs are hypothesized to also engage in execution (initiation) and termination of action through disinhibition and reinhibition of the thalamocortical feedback inputs, respectively, as has been suggested (Nambu 2008), with the layer 1-prefering (Kuramoto et al. 2009) thalamocortical inputs presumably targeting the extensively branched tuft dendrites of PT cells and triggering/boosting PT cells’ output to the pyramidal tract (or other cortical areas) to initiate an action (or action plan) (Morita et al. 2012, 2013). A critical assumption of this corticostriatal TD hypothesis is, as described above, the preferential activation of dMSNs and iMSNs by IT cells and PT cells, respectively. This assumption was originally made based solely on the anatomical connection preferences (Lei et al. 2004; Reiner et al. 2010), and its validity has been questioned by the optogenetic study (Kress et al. 2013). The results of the present work indicate that, in reality, IT→dMSN and PT→iMSN preferences would not appear in the responses to the initial inputs, as shown by the optogenetic study, but would then become prominent in the responses to repetitive inputs by virtue of the combination of the anatomical connection preferences and the connection type-dependent short-term synaptic plasticity (Figs. 3C, 4D, and 6E).

What are, then, the functional roles of IT→dMSN and PT→iMSN inputs, which presumably have rather strong impacts at the beginning but then decay with time? In fact, the corticostriatal TD hypothesis (Morita et al. 2012, 2013) posits that not only the presumably major IT→dMSN and PT→iMSN pathways but also the IT→iMSN and PT→dMSN pathways have important functional roles. Specifically, the IT→iMSN pathway has been suggested to be possibly involved in the temporal discount of future rewards (Morita et al. 2012), and
the PT inputs to dMSNs have been proposed to cause dendritic activation that works as a marker for the induction of dopamine-dependent synaptic plasticity (Morita et al. 2013). Here I extend the latter proposal on the basis of results of the present study.

It has been empirically indicated (Roesch et al. 2007) that the dopamine neurons in the ventral tegmental area (VTA) encode a particular form of RPE defined in one of the popular algorithms of reinforcement learning called Q-

\[
R(t) = R(t_{i-1}) + Q(A(t_i)) - Q(A(t_{i-1}))
\]

\[
R(t) = R(t_{i-1}) + Q(A(t_i)) - Q(A(t_{i-1}))
\]

\[
R(t) = R(t_{i-1}) + Q(A(t_i)) - Q(A(t_{i-1}))
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\[
R(t) = R(t_{i-1}) + Q(A(t_i)) - Q(A(t_{i-1}))
\]
learning (Watkins 1989). The RPE for Q-learning contains a term representing the maximum of the values (future reward expectations) of possible actions, regardless of whether that maximum-valued action is actually selected or not. Specifically, when there are two possible actions $A_1$ and $A_2$ at a given time point (time $t_i$), RPE for Q-learning at that time point amounts to $R(t_{i-1}) + \gamma \max\{Q(A_1), Q(A_2)\} - Q(A(t_{i-1}))$, where $R(t_{i-1})$ and $Q(A(t_{i-1}))$ are reward obtained at $t_{i-1}$ (if any) and the value of the action selected/executed at the previous time point ($t_{i-2}$), respectively, and $\gamma$ is the degree of temporal discount of future rewards, called the time discount factor. Given that the VTA dopamine neurons encode this RPE as suggested, the quantity $\max\{Q(A_1), Q(A_2)\}$ should be calculated in some neural structure that causes positive impacts on the activity of the dopamine neurons. In this regard, the previous study (Morita et al. 2013) proposed that the “max” operation could be implemented in the IT→dMSN pathway: subpopulations of dMSNs representing the values of different possible actions presumably compete through feedforward (and possibly also recurrent) inhibition, and the one corresponding to the maximum-valued action presumably wins. For example, when there are two possible actions $A_1$ and $A_2$, and if $Q(A_2)$ is larger than $Q(A_1)$, the dMSN subpopulation representing $Q(A_2)$ wins the competition (presumably after a brief transient period) and the dopamine neurons receive “+Q(A_2)” from those dMSNs (Fig. 12B, left). In Q-learning (as well as in other reinforcement learning algorithms), action is assumed to be selected probabilistically, or in other words, in a “soft-max” manner, and thus the maximum-valued action ($A_2$ in our example) is selected with the highest probability, but not always. Such soft-max action selection has been proposed (Morita et al. 2013) to be implemented by competitive neural dynamics among PT cells, which receive thalamic inputs conveying (transient) value signals from dMSNs (Fig. 12B, left and middle). Now assume that not the maximum-valued action ($A_2$ but instead the other action ($A_1$) is selected and executed (Fig. 12B, middle). At the next time point (time $t_i$), RPE then amounts to $R(t_i) + \gamma \max\{\text{values of possible actions}\} - Q(A_1)$, and crucially, the value of the selected/executed action [i.e., $Q(A_1)$], rather than $Q(A_2)$, needs to be updated according to this RPE (so that Q-learning is correctly implemented). Given that RPE is encoded by dopamine and $Q(A_1)$ is stored in the strength of the synaptic connections between cortical (IT and PT) cells and MSNs corresponding to $A_1$, such an update is expected to be implemented by dopamine-dependent plasticity (c.f., Reynolds et al. 2001) of these synapses (purple dotted circles in Fig. 12B, right).

The emerging question is how plasticity can be induced specifically at the synapses between $A_1$-corresponding IT cells and dMSNs and not at those between $A_2$-corresponding IT cells and dMSNs, despite that not $A_1$ but $A_2$ was the maximum-valued action so that dMSNs corresponding to $A_2$ presumably became the winner (i.e., only their activity survived after the transient period) (Fig. 12, left): activity-dependent intracellular mechanism (e.g., calcium accumulation) is unlikely to be able to operate as a marker for plasticity induction, because such a mechanism would incorrectly mark dMSNs corresponding to $A_2$ that were maximally activated. For this issue, it has been proposed (Morita et al. 2013) that inputs from $A_1$-corresponding PT cells to $A_1$-corresponding dMSNs (red oblique line in Fig. 12B, middle) can be a marker for plasticity induction, given that such specific PT→dMSN projections between cells corresponding to the same action are formed (possibly through self-organization). There is, however, a concern that if such PT→dMSN inputs are strong enough to operate as a marker for plasticity induction, these inputs may also cause considerable impacts on the activity of downstream dopamine neurons, counteracting the impacts of the PT→iMSNs pathway and thereby interfering with the calculation of RPE. Here is the point where the results of the present study provide a possible solution. Specifically, given that the impact of PT inputs on dMSNs is initially strong, as shown by the optogenetic study (Kress et al. 2013), and subsequently decays as suggested by the present work (Figs. 3Ce, 4D, 6E, and Fig. 12B, bottom), such inputs might be able to efficiently cause dendritic activation for plasticity induction (c.f., Golding et al. 2002; Surmeier et al. 2011) without inducing much axosomatic spiking activity so that the computation of RPE is hardly affected. Notably, this proposed mechanism can also work well in the case where selected action matches the maximum-valued one, or where the circuit implements other reinforcement learning algorithms such as SARS (Rummery and Niranjan 1994), as empirically suggested from the observed activity pattern of dopamine neurons in the substantia nigra pars compacta (SNc) (Morris et al. 2006), or expected SARS learning (van Seijen et al. 2009). A prediction of this proposed mechanism is that for dopamine-dependent plasticity induction in dMSNs, there should be a time lag between glutamatergic inputs and dopaminergic inputs corresponding to the duration necessary for depression of PT→dMSN inputs and facilitation of PT→iMSN inputs (at the minimum). It is also predicted that plasticity induction in iMSNs should be quite different from that in dMSNs even if they similarly implement RPE-dependent update of action value (of the same sign) as assumed in the corticostriatal TD hypothesis (Morita et al. 2012, 2013).

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

K.M. conception and design of research; K.M. performed experiments; K.M. analyzed data; K.M. interpreted results of experiments; K.M. prepared figures; K.M. drafted manuscript; K.M. edited and revised manuscript; K.M. approved final version of manuscript.
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