Supplementary Information for

Deep Brain Stimulation in the subthalamic nucleus for Parkinson’s disease can restore dynamics of striatal networks

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This PDF file includes:
  - Supplementary text
  - Figs. S1 to S17 (not allowed for Brief Reports)
  - Tables S1 to S2 (not allowed for Brief Reports)
  - SI References
Supplementary Information Text

The supplementary text contains all the methods and details on the biophysical modeling.

Supplementary details

Below are the details directly referenced in the main document.

A. Additional results. The results provided below supplement the results provided in the main document.

A.1. Activity of isolated MSN network in baseline condition. In an isolated MSN network in baseline condition (Fig S1A), although there is no obvious synchrony in the MSN spiking activity (mean±SD of MSN firing rate: 1.46 ± 0.046 spk·s⁻¹) (Fig S1B), the spectrum of population activity shows a peak in the low beta frequency range (mean ± SD: 17.53 ± 2.77 Hz) (Fig S1C). Indeed, work from our lab (1) has shown that the MSN population can produce beta oscillations through an interaction between an inhibitory M-current and interneuronal GABAa inhibition.

A.2. Activity in core striatal model in baseline conditions. Our simulations for the core striatal model (Fig S1D-F) in baseline conditions show sparse gamma oscillations in FSI activity, where cells do not fire at every gamma cycle but produce gamma oscillations as a population. The FSI firing is sparse and does not show periodicity in spiking activity at the level of a single cell (mean±SD of FSI firing rate: 10.66 ± 0.061 spk·s⁻¹) (Fig S1E), but produces a peak at gamma frequencies (mean±SD: 58.63 ± 1.96 Hz) in the spectrum of population activity (Fig S1F). Work from our lab (2) has also shown that the FSIs are capable of intrinsically producing gamma oscillations due to their D-current, both at a population level and at the level of a single cell. We believe that this gamma oscillation generally plays a crucial role in suppressing beta oscillations in the striatum.

A.3. Effect of the FSI-MSN projection. We find that adding FSI inhibition onto MSNs (Fig S1D) changes the MSN population activity spectrum from one showing a peak of low beta-band activity (Fig S1C) in the case of an isolated MSN population activity to one without beta-band activity (Fig S1F). The change in MSN spectral properties, after adding FSI inhibition, is not a result of a decrease in MSN firing rate, but a change in the dynamics driving MSNs to spike under FSI inhibition. The average MSN spiking rate instead slightly increases from mean±SD: 1.46 ± 0.046 spk·s⁻¹ without inhibition to 1.88 ± 0.057 spk·s⁻¹ with FSI inhibition (Fig S1B,E). We believe that this increase is due to MSN rebound spiking from FSI inhibition: as we decreased FSI inhibition onto MSNs, by decreasing the maximal GABAa conductance of the FSI projections to MSNs, and that the FSI spiking activity increased (p<0.001, Welch’s t-test) from 0.66 ± 0.078 spk·s⁻¹ (Fig 1B), and that the FSI spiking activity increased (p<0.001, Welch’s t-test) from 10.66 ± 0.061 spk·s⁻¹ without STN input (Fig S1E) to 13.00 ± 0.067 spk·s⁻¹ with STN input (Fig 1B).

The increase in FSI excitability and firing rate is followed by a slight increase (p<0.001, Welch’s t-test) in FSI gamma frequency from 58.63Hz without STN input (Fig S1F) to 61.14 ± 2.27Hz with STN input (Fig S1C), consistent with the correlation between FSI oscillatory frequency and cell excitability (2, 3). The asynchrony of STN activity acts especially as a noise that further breaks any potential intrinsic FSI periodicity, thereby sustaining uncorrelated and irregular FSI firing. This irregularity, combined with a slight increase in FSI activity, leads to additional inhibition onto MSNs, lowering their spike rate.

A.4. Effect of adding GPe and STN in baseline conditions. On adding the GPe and STN populations, the spectra of population activity for MSNs and FSIs remain largely unchanged (comparing Fig S1F to Fig 1C). However, we observe that the MSN average firing rate decreased (p<0.001, Welch’s t-test) from around 1.84 ± 0.06 spk·s⁻¹ without inhibition to 1.21 ± 0.078 spk·s⁻¹ (Fig 1B), and that the FSI spiking activity increased (p<0.001, Welch’s t-test) from 10.66 ± 0.061 spk·s⁻¹ without STN input (Fig S1E) to 13.00 ± 0.067 spk·s⁻¹ with STN input (Fig 1B).

The increase in FSI excitability and firing rate is followed by a slight increase (p<0.001, Welch’s t-test) in FSI gamma frequency from 58.63Hz without STN input (Fig S1F) to 61.14 ± 2.27Hz with STN input (Fig S1C), consistent with the correlation between FSI oscillatory frequency and cell excitability (2, 3). The asynchrony of STN activity acts especially as a noise that further breaks any potential intrinsic FSI periodicity, thereby sustaining uncorrelated and irregular FSI firing. This irregularity, combined with a slight increase in FSI activity, leads to additional inhibition onto MSNs, lowering their spike rate.

A.5. Activity of isolated MSN network and core striatal model in PD. As shown in previous work (1), in the presence of higher cholinergic modulation, an isolated MSN network (Fig S4A) is capable of producing strong beta oscillations, as evidenced directly by MSN spiking activity (Fig S4B) with an average spike rate of 5.32 ± 0.04 spk·s⁻¹ and by the peak at the beta frequency 17.01 ± 0.47Hz in the spectrum of population activity (Fig S4C). Under parkinsonian conditions, in the presence of higher cholinergic modulation while providing additional D2 MSN excitability due to low levels of DA (Fig S5A), the spiking rate of MSNs is further increased to 7.66 ± 0.04 spk·s⁻¹ (Fig S5B) while retaining a prominent peak at beta frequencies (at 20.02 ± 0.77Hz, higher than the frequency due to only an increase in cholinergic tone: p<0.001, Welch’s t-test) in the spectrum of population activity (Fig S5C).

Similarly to our isolated MSN network, our core striatal model during PD (Fig S5D), comprised of MSNs and FSIs, is capable of producing a beta oscillation in MSNs, as weakly observed in the spiking activity (Fig S5E) and a peak at beta
frequencies (18.77 ± 2.07Hz) in the spectrum of population activity (Fig S5F). However, the MSN beta activity is more spread out along the spectrum (Fig S5F) due to the presence of FSI inhibition. Although FSI activity is weakened in the PD case compared to baseline condition, as apparent from the sparse spiking activity (Fig S5E) and the spectrum of population activity (Fig S5F) where the gamma oscillation is no longer present, it is still capable of partially inhibiting the beta oscillation present in MSNs, causing changes in the spectral content of MSN firings, compared to that of an isolated MSN network. This change is also followed by a decrease in MSN firing rate from 7.66 spk·s\(^{-1}\) in an isolated MSN network (Fig S5B) to 6.62 ± 0.21 spk·s\(^{-1}\) in an MSN network with FSI inhibition (Fig S5E).

A.6. Effect of adding GPe and STN in PD. After connecting the core striatal model to the STN and GPe, the beta frequency of the MSN activity (at 15.80Hz) decreased from that of the isolated MSN network (at 20.02Hz, p<0.001, Welch’s t-test) and that of the core striatal model (at 18.77Hz, p<0.001, Welch’s t-test), suggesting that FSI activity is partially pacing MSN activity to fire at a lower frequency due to synchronized and increased FSI inhibition. This increase in beta band power in MSNs is also accompanied by a decrease in firing rates to 4.85 ± 0.13 spk·s\(^{-1}\) (p<0.001, Welch’s t-test) (Fig 2B), a reduction likely due to the reduction in beta frequency despite the increase in beta activity in FSIs.

A.7. Causes of the increase in MSN excitability. It is the increase of excitability of the MSNs that generates beta activity in the striatum (Fig S6A), resulting from a combined effect of a decrease in M-current conductance \((g_M)\) (Fig S6B), an increase in background excitation \((I_{app})\) (Fig S6C) and a decrease in FSI GABA\(\alpha\) inhibition \((g_{FSI-MSN})\) (Fig S6D): separately restoring each of these changes decreases beta activity in the MSNs. The average MSN spiking rate decreases from 4.85 ± 0.16 spk·s\(^{-1}\) to 4.00 ± 0.10 spk·s\(^{-1}\) by restoring \(g_M\) (p<0.001, Welch’s t-test), to 4.14 ± 0.12 spk·s\(^{-1}\) by restoring \(I_{app}\) (p<0.001, Welch’s t-test) and to 4.73 ± 0.13 spk·s\(^{-1}\) by restoring \(g_{FSI-MSN}\) (p=0.0014<0.005, Welch’s t-test) (Fig S6A-D).

A.8. Resonance properties during PD. In PD, the MSN beta oscillation is synchronous enough to pattern the GPe at beta frequencies, as evidenced by the spiking activity (Fig 2B). The synchronous beta activity of GPe inhibits STN activity and, in turn, patterns it at beta frequencies, also evidenced by the spiking activity (Fig 2B). STN beta activity finally reaches the FSIs through the STN-FSI direct projections, and creates beta oscillations in the FSIs, weakly observed in spiking activity (Fig 2B) and more strongly in spectral properties (Fig 2C).

In baseline condition, the FSIs suppress, through their sparse gamma activity, the weak beta activity generated by the MSNs. However, if FSI activity is instead contaminated with beta activity, we expect the FSIs to become a conduit for beta-activity. The beta activity is strong enough during PD that it will entrain FSI activity, and the FSIs begin oscillating at beta frequencies instead of their preferred gamma. In such a setting, the MSNs will resonate to the FSI beta-inhibition due to their intrinsic and network dynamics, and beta activity is then amplified in MSNs and throughout the loop. This beta activity is strong enough that it will entrain FSI activity, and these begin oscillating at beta frequency contrary to their nature.

Particularly, in our simulations during PD, we find that the beta activity generated by MSNs is strong enough to reach STN through the GPe, as observed from spiking activity (Fig 2B) and population activity spectra (Fig 2C). The STN activity then patterns the FSIs at beta frequencies, and we observe resonance in the whole loop enabled by the FSIs: in the spectrum of MSN activity in the closed-loop system (Fig 2C), the power at the peak of beta-band activity (Fig 2C) is greater than that with STN input removed (p<0.001, Welch’s t-test) (Fig S5F) and (ii) the modal beta oscillation frequency is lower than that of an isolated MSN network (p<0.001, Welch’s t-test) (Fig S5C).

To further test the resonance property of the closed-loop system, we introduced direct exogenous beta activity into the MSNs during baseline condition. For high input amplitude, we observe resonance at the input frequency at the level of MSNs with the appearance of harmonics (Fig S7A). This resonance at high input amplitude appears in all four populations. As we decreased the input amplitude, the resonance at the level of MSNs weakens (Fig S7B) and ceases to exist (Fig S7C). More essentially, in baseline condition, we hypothesize that the closed-loop network has a capacity to dampen beta oscillations, because of the natural role of FSIs, instead of implementing positive feedback. To test this, we used a sustained high amplitude beta-activity as input into the MSNs for a predefined period and then removed that input. We find that the system returned from resonance to normal operation, in terms of spiking activity (Fig S8A) and spectral properties (Fig S8B).

A.9. Effect of exogenous input to STN. We find that an additional exogenous input into STN, if provided at the resonating frequency (15.8Hz) amplifies the existing beta oscillations throughout the loop, increasing the average MSN firing rate to 5.83 ± 0.12 spk·s\(^{-1}\) (p<0.001, Welch’s t-test) (Fig S9A,B). When the beta input frequency is not the resonating frequency (e.g., 17.5Hz or 20Hz instead of 15.8Hz), the input entrains the BG oscillations, and they lock to the frequency and phase of the input (Fig S9C-D).

A.10. Fixing stimulation intensity. We did not model the exact voltage value applied onto the axons, as it necessarily differs from the clinical parameter applied somatically. Instead, we assume that increasing the applied voltage at the level of the soma is equivalent to increasing the applied voltage at the level of the axon. The stimulation of the STN axons will induce AMPA currents in FSIs, via increases in the AMPA gating variables: the rate function for the open state of the AMPA receptor increases as the presynaptic axonal voltage increases, up to a maximum rate (See methods section below for more details). We thus fixed the applied voltage to the one that yields the maximum rate, and vary the remaining two parameters: stimulation frequency and pulse width.
A.11. FSI gamma frequency during DBS. As we vary the stimulation frequency, we find that the FSIs produce bursts at half of the stimulation frequency (Fig 3D). This linearity breaks down as we increase (e.g., above 150Hz) the stimulation frequency (Fig 3D). Indeed, inspecting the spectrum of FSI population activity, outside the 120-150Hz range, reveals a less pronounced peak around the half-frequency (Fig S11A). We hypothesize that the bursting dynamics of the D-current impose a limit on the bursting frequency. As such, while 135Hz is too high a frequency for the FSI bursts to be entrained at, the FSIs naturally follow a bursting at around 67.5Hz, firing at most every other cycle.

A.12. Effects of changing DBS frequency. DBS produces a sawtooth-shaped AMPA current at the stimulation frequency (Fig S11B). The stimulation frequency then dictates the period between the peaks of AMPA currents, but also changes the baseline of added excitation: the higher the frequency, the less time the current has to decay (Fig S11B). This current leads to fluctuations in the membrane potential of the FSIs (Fig S11C), and has an effect of increasing the overall excitability of the FSIs, as observed through an increase in FSI firing rate (Fig 3E). The increased firing rate of FSIs increases the amount of inhibition on MSNs, leading to a decrease in firing rate as the stimulation frequency is increased (Fig 3F).

A.13. Effects of changing DBS pulse width. Changing the pulse width, while fixing the stimulation frequency, modifies the duration in which the AMPA current rises before it decays again (Fig S11D), and thus modifies how much of an effect DBS stimulation has on FSI activity. Decreasing the pulse width decreases the level of excitation onto FSIs as observed through a decrease in firing rate (Fig S11E), leaving its inhibition onto MSNs ineffective for low values and allowing beta-activity to re-emerge. Indeed, we observe an increase in MSN average firing rate (Fig S11F) as the pulse width is decreased.

A.14. Effects of STN input on FSIs. The loss of DA during PD renders the FSIs unable to achieve a state similar to that of high DA levels during normal condition. This is due to two reasons. First, increasing the background excitation onto FSIs drives them at a theta/gamma at the level of a single cell. In PD, the FSIs lose the potential excitation received from high DA levels to change their firing pattern. Second, whether or not FSIs are able to synchronize is governed by how strong the gap junctions are with respect to external noise that the FSIs receive. The loss of DA severely reduces the electrical conductance of the gap junction (4) and compromises the ability of FSIs to synchronize at theta/gamma, especially in the presence of beta oscillations. DBS acts at these two levels, and effectively restores FSI synchrony by combining two effects. First, through HFS, DBS increases the level of FSI excitation to drive them at a theta/gamma oscillation at the level of a single cell. Indeed, we can observe gamma bursts in spiking activity (Fig 3B), and peaks at theta/gamma frequencies in the spectral properties of population activities (Fig 3C). Second, by additionally disconnecting the FSIs from STN, DBS reduces the amount of noise that reaches the FSIs from STN, allowing the weakened gap junctions to then synchronize FSI theta/gamma activity.

Specifically, STN provides noisy input to the FSIs, through its direct projections. In normal condition, the STN firing is tonic and asynchronous, providing the FSIs with noisy input that is uncorrelated among FSIs. However, the gap junctions of the FSIs, in normal conditions, are strong enough to overcome this noise, and achieve FSI synchrony at high DA levels. In parkinsonian conditions, STN is inputting beta activity into the FSIs, acting as noise with respect to desired synchronized theta/gamma oscillations. The electrical conductance of the gap junction, already weakened, leave the FSIs with little ability to synchronize in the presence of these beta oscillations. During PD, DBS dissociates STN axonal activity from STN somatic activity. The level of FSI synchrony is then controlled by how much the remaining background noise received by FSIs (which we modeled as cortical input) is uncorrelated/correlated among them.

A.15. Failure of FSIs to yield theta/gamma oscillations in PD without DBS. When we provide FSI-correlated noise, FSI excitation is too low to achieve theta/gamma oscillations at the level of a single cell as observed in spiking activity (Fig 4E), and FSI activity is strongly contaminated with beta activity instead as observed in spiking activity (Fig 4E) and spectral content (Fig 4F). We also cannot achieve synchronous firing (Fig 4G) under FSI-correlated noise, even if we artificially increase excitation to have each FSI at a theta/gamma individually, as evidenced through the spectrum (Fig 4H).

B. Comparison to alternate pathways from STN to FSIs and their role in DBS. There are multiple pathways for STN activity to reach FSIs. The STN-FSI projection may not be more important than these other pathways for normal function of the BG. However, in the context of DBS in STN as a treatment for PD, our work suggests that this STN-FSI projection is special. It remains to argue why other pathways would not work as well to restore normal BG dynamics.

There are two additional pathways to be considered: the GPe projection to FSIs (5, 6) and the cortical projections to FSIs (7, 8). We first discuss each separately and then discuss what is special about the STN-FSI projection.

Examining the GPe projection to FSIs. GPe receives projections from STN, and itself projects to striatum, preferentially affecting FSIs (6). The GPe neurons that project to STN also project to FSIs (5, 9), additionally suggesting DBS effects due to antidromic stimulation. To test the contribution of the GPe pathway, we extended our model to include additional projections GPe-FSI and STN-GPe, and simulated all the conditions considered in our work (Fig S15A), keeping the STN-FSI projection intact. Adding this GPe projection onto FSIs does add tonic inhibition onto FSIs, which can be countered by re-balancing the background excitation onto FSIs (which is usually assumed to encompass non-modeled constant excitation/inhibition onto the system, of which GPe inhibition onto FSIs was a part before incorporating it). When re-balancing FSI excitation and GPe excitation (due to the additional STN excitation coming from the added STN-GPe projection), our simulations show that the dynamics in normal, PD and DBS in PD conditions remain intact (Fig S15B-K). Minor changes in mean firing rates appear (Fig S15B,D,F; e.g., MSN firing rates are mean±SD: 0.99 ± 0.07 spk s⁻¹ in normal, 3.78 ± 0.14 spk s⁻¹ in PD and
During PD, FSIs need homogeneous background excitation to yield gamma bursts. If the cortical projecting cells are firing in PD conditions, we should expect these projections to provide beta activity to FSIs. Stimulating them will disrupt that beta activity. However, they can contribute to increasing FSI excitation and relieving cortical beta input onto FSIs, thereby aiding in restoring striatal dynamics during DBS in PD. This role is however different than that attributed to the STN-FSI projection, as described below.

**Examining the cortical projection to FSIs.** We had incorporated cortical input through background excitation onto FSIs. This cortical input increases in excitation and correlation among FSIs when normal conditions change from baseline to high levels of DA. This input thus has a role in aiding the transitions from sparse gamma oscillations in FSIs to theta/gamma oscillations. During DBS in PD these projections gain a more prominent role in enabling the transition between sparse gamma (Fig 3B-C) and theta/gamma oscillations (Fig 4A-D) (See results section on “DBS restores theta and gamma oscillations”). Indeed, in PD, DA levels can no longer enable such a transition. Thus, we believe that projections from cortex to FSIs play a crucial role in restoring natural striatal dynamics during DBS in PD. This role is different than the STN-FSI projections.

However, the stimulation pattern produces some heterogeneity in firing among STN cells that leaves the FSIs unable to deliver gamma bursts and synchronize well (Fig S17C,D). Thus, the dynamics observed at high DA levels are not restored under this scheme. In real network conditions, the effect of DBS on cortical cells might even be weaker:

1. It is unclear how entrained these cortical cells are by the DBS frequency, and how much of an increase in firing they would undergo, following either antidromic stimulation or direct stimulation through the CBT loop. These projections need to provide enough excitation to enable gamma oscillations in FSIs.
2. In PD conditions, we should expect these projections to provide beta activity to FSIs. Stimulating them will disrupt that beta activity. However, we expect FSIs to still be receiving beta input from other pathways. Thus, DBS would need to rely on shutting down additional pathways that amplify the beta activity in the BG loop, e.g., either through the STN-FSI or GPe-FSI projections.
3. During PD, FSIs need homogeneous background excitation to yield gamma bursts. If the cortical projecting cells are firing at high frequencies, our simulations (Fig S17C-D) suggest they may not provide the necessary homogeneous input pattern to FSIs enabling them to yield gamma bursts.

Our findings (Fig S17, combined with (1-3), indicate that such cortical projections cannot restore normal dynamics effectively. However, they can contribute to increasing FSI excitation and relieving cortical beta input onto FSIs, thereby aiding in restoring the necessary dynamics. Furthermore, if cortical projections substantially contribute to the beta activity present in FSIs, then blocking this input through stimulation becomes essential and necessary.

**The importance of the STN to FSI projections.** The STN-FSI projection is special in that it is (i) excitatory onto FSIs and (ii) monosynaptic from the stimulation site. It can then serve to raise the excitation of FSIs, and then convey homogeneity in input to FSIs to ensure adequate gamma bursts and synchrony. More importantly, applying DBS stimulation with both a cortical projection to FSI and STN/GPe pathway to FSIs present, but the STN-FSI projection absent, cannot recover the necessary dynamics, notably, the synchronous theta/gamma oscillations in FSIs that appear in normal conditions under high DA.

In sum, restoring striatal dynamics under DBS requires two effects: (1) Blocking the beta activity that reaches FSIs and (2) adequately exciting FSIs to restore their gamma dynamics (be it sparse or synchronized bursts). We find that neither the
projections from cortex to FSIs or the projections from GPe to FSIs can achieve effect (2) alone.

**Effect of alternate pathways on the expression of striatal dynamics.** The beta activity appearing in MSNs and the theta/gamma activity appearing in FSIs are generated by these cells’ intrinsic properties and currents. It is the inhibitory interaction of MSNs that result in beta dynamics(1), and the D-current dynamics in FSIs that can result in theta/gamma oscillations(2, 3). Therefore, input to the MSN/FSI populations, generated by the addition of the above considered alternate pathways, will not create these beta/gamma dynamics, but can either (1) allow them to be expressed by providing adequate excitation levels, (2) allow them to be removed by providing adequate inhibition levels and (3) can modulate their oscillatory frequency and phase-locking to input oscillations, by pushing the striatal dynamics to appear pre-maturely or post-maturely to their natural dynamics. When that modulation matches the oscillatory preference of the MSN and FSI populations, we get resonance and the frequencies in play are amplified. We then expect the GPe-FSI and cortex-FSI pathway to contribute additional beta dynamics to the BG loop in PD, but will not underlie the generation of striatal beta dynamics.

**These additional pathways can provide beta oscillations in PD.** Both cortical and GPe projections to FSIs can be strong conduits for beta activity to contaminate FSI dynamics and blocking that activity can be necessary. We expect DBS, through antidromic and orthodromic stimulation, to automatically alter activity and remove the beta input emanating from STN. It then prepares the conditions for the STN-FSI contribution in rectifying striatal dynamics. More generally, the therapeutic effects of DBS need to extend beyond rectifying striatal dynamics. These therapeutic effects can (partly) be due to striatal restoration, but there are also many additional mechanisms in play that can aid in restoring BG output dynamics as well as more downstream effects. Our core claim is that a mechanism that rectifies beta oscillations in the basal ganglia has to rectify a striatal source of the beta oscillation, and that can be achieved by the STN-FSI projection.

### C. Additional discussion details.

**C.1. Striatal oscillations.** Beta oscillations (10–13), gamma oscillations (7, 14) and theta oscillations (15, 16) are normally observed in a coordinated manner in striatal networks to drive behavior.

Beta oscillations are a robust, task-modulated feature of healthy striatum in humans (17, 18), monkeys (10, 12, 13, 19–21), bats (22) and rodents (11). They are also expressed in the membrane potential of MSNs in normal, non-parkinsonian rodents (23, 24) and MSN spike timing can be modulated in beta (13). They tend to appear through bursts (19, 21). The role of these bursts is thought to help switching among cell assemblies encoding motor programs (7, 25, 26). In our model, MSN beta bursts in normal conditions emerge due to disinhibition during FSI quiescence periods following FSI gamma bursts. It is surges of dopamine that increase FSI excitation and electrical coupling, pushing FSIs to produce synchronized gamma bursts, followed by quiescence. If dopamine is sustained at high levels long enough, we observe that these gamma bursts are nested in theta cycles (Fig 4A). More generally, in our model, a momentary disinhibition of MSNs due a decrease in FSI excitation can cause a surge of MSN beta activity in normal conditions. While this can naturally occur at a theta timescale under high DA levels, the decrease of FSI excitation can be due to other reasons, including quiescence following a random synchronized gamma burst in FSIs. Thus, the emergence of beta in MSNs in normal condition need not solely rely on the presence of theta dynamics in FSI, but only requires the absence (or weakening) of gamma dynamics in FSI.

Striatal gamma oscillations are considered to be generated through FSI activity (7, 27–30) and have been associated with the initiation and vigor of movement (31, 32). Gamma activity has been found to have a positive correlation with dopamine and locomotion (32–36) and to be anticorrelated in EEG and corticostratial LFP to beta power (32, 37, 38). Indeed, under high DA conditions, the gamma oscillations are nested within slow oscillations, leading to periodic gaps in FSI activity that allow MSN beta activity to emerge. We hypothesize that the FSI gamma bursts are necessary to terminate on-going motor programs, and initiate new programs by allowing for different MSN cell assemblies to activate, producing beta oscillations (2).

Theta oscillations are found in local field potentials recorded in the dorsal striatum (15, 39–41). These rhythms show phase amplitude coupling with gamma activity (40, 42), are thought to be orchestrated by FSI activity (15), and are modulated by dopaminergic activity and locomotion (15, 39). These rhythms are modulated during task performance (43), and arise particularly during navigation tasks where they coexist with the hippocampal theta rhythms (44, 45). The striatal theta is, however, considered to have a striatal origin (15) and its interaction with hippocampal rhythms can prove key in coordinating learning and memory (41, 46). These striatal theta rhythms can prove key in controlling of voluntary behavior at a theta time scale relevant to sequencing of behaviors.

**C.2. Existing computational work on DBS.** Work has shown that DBS can alter the input received by GPi to restore its functionality; this can be achieved by increasing regularity in GPs inputs which can reduce response variability in GPi neurons (47–49), or by the convergence of additional excitation from STN and inhibition from GPe that restore regular GPi firing (50), or more generally, through a mixture of responses caused by HFS converging in the GPi (51) regularizing GPi activity. It has also been proposed that DBS results in altered projection dynamics between BG nuclei, and then engage a mechanism of converging network-wide input onto the striatum, which then regularizes the activity in striatopallidal projections to the GPi to restore GPi function (52). The focus on normalization of basal ganglia output is to increase thalamic relay reliability, seen as essential to restore normal functioning of the BG-thalamo-cortical loop (53–55). The work (53) establishes how DBS can replace rhythmic inhibition (at tremor frequencies in the theta range) from GPi to the thalamus with regularized firing that, despite an increase in GPi inhibition frequency and amplitude, restores the responsiveness of thalamocortical cells to
sensorimotor input. The work (56) builds on the model in (53) and offers a detailed study of the effect of stimulation frequency on thalamic relay reliability.

C.3. On beta oscillations in the BG. Excessive beta oscillations extend beyond the striatum and are observed in several structures in the CBT loop (57) following dopamine depletion in rodent models of PD (30, 39, 58), in non-human primate models of PD (59, 60) and humans PD patients (61). The indirect pathway is particularly implicated in these abnormal dynamics (62), and this implication highlights a special participation of MSNs in beta generation in rodents (59, 62) and in non-human primates (63). While the literature had often reported increases in striatal firing rates connected to the increased beta activity (64), there has been recent contradictory results that report the absence of increased firing rates (65). Our modeling suggests that an excessive beta oscillation in the striatum cannot be produced by additional MSN synchrony alone, without enhanced excitability and therefore firing rates. However, our results do not rely on an excessive increase, as strong beta oscillations can be observed with only a 4- or 5-fold increase in firing rates.

Moreover, it has been reported (66) that MSNs do not display beta oscillations in parkinsonian conditions following dopamine depletion, contradicting findings and conclusions of other works (39, 67). However, (66) utilizes an MPTP intoxication procedures that leaves a parkinsonian non-human primate incapable of executing behavioral tasks. It is then uncertain whether or not MSN activity in such a state is altered compared to what is expected in regular parkinsonian conditions, where subjects are capable of tasks.

It has also been argued that the striatum cannot produce the beta oscillation by itself because blockade of striatum to GPe does not eliminate the beta (68). Instead, this study suggests that either the STN-GPe loop or the hyperdirect pathway are sources of beta in non-human primates. However, in (68), the blockade is confined to only a small region, targeting a small portion of the striatum to GPe projections, which we estimated from GPe size to be around 3%. This allows the rest of beta-producing striatal neurons to transmit beta downstream and engage the rest of the CBT loop, including STN, which our current study suggests can amplify beta throughout the indirect pathway loop via the STN-FSI connection pathway. In contrast to the above study, (69) suggests that either GPe or striatum or both may underlie beta generation in PD rodents, having ruled out both STN and cortex.

C.4. On the striatal origin of beta oscillations. Our previous work (1) suggests that networks of medium spiny neurons (MSNs) in striatum are capable of producing beta oscillations under normal conditions which become exaggerated in the parkinsonian state. Specifically, the beta oscillations will be exaggerated under conditions of high cholinergic tone or under conditions that tonically increase MSN excitation, such as loss of dopaminergic stimulation of D2 receptors. Consistent with our model findings, increasing the striatal cholinergic tone of normal mice produced robust, exaggerated beta oscillation in both the striatal local field potential and in cortex (1, 70, 71) as well as parkinsonian-like behavioral deficits (70). Exaggerated beta oscillations further emerge in the striatal LFP of parkinsonian rats (62, 72) and parkinsonian non-human primates (59, 67). Particularly, indirect pathway MSNs have been found to synchronize their spiking at beta frequency in the dopamine-depleted striatum of rats (62).

C.5. Additional effects for STN stimulation. DBS in STN will likely have direct effects on many connected and adjacent brain structures, with potential therapeutic effects. DBS in STN can excite the GPe, the GPi and the PPN (73) altering firing rates (74). In these sites, stimulation has also proven to improve parkinsonian symptoms (75–78). The GPe, in particular, has a normally high spiking rate, and STN stimulation may restore GPe functioning through a mechanism similar to what we observed for FSI, by increasing firing rates and countering the effect of beta-oscillation on GPe through high frequency oscillations. The GPe projects back to the striatum, targeting MSNs and FSI though both archypallidal and prototypical cells(5, 6, 66), which may prove to be a complementary route to restore striatal dynamics. HFS has also shown to result in antidromic activity (79–81), notably at the level of cortex through the hyperdirect pathway.

C.6. Correlated noise and beta synchrony. An increase of beta synchrony has been suggested by (82), resulting from periodic correlated cortical input to FSI. The beta synchrony in FSI is considered in (82) to be sustained by the FSI gap junctions. In our work, we have not modeled any mechanism that can generate beta oscillation in FSI from cortical connections; FSI, in our work, are entrained at beta by STN projections. Regardless, although further weakening gap junctions might lessen beta oscillations in PD, it would be at the expense of a deficit in re-establishing the theta/gamma oscillations.

C.7. Effect of DBS intensity and pulse-width. Gradually increasing stimulus intensity will result in oculomotor effects, autonomic effects, paresthesia, dystonic effects and speech impairment (83–86). These effects potentially emerge from a current spread to pyramidal tracts and other adjacent structures (87). We do not study such pathological conditions, and limit the voltage to therapeutics ranges.

Pulse-widths have conventionally ranged between 60µs and 450µs for DBS in STN (88), though recent research has been investigating the effect of shorter pulse-width (89). The choice of pulse-width additionally directly modulates the amount of excitation received by the FSI, and dictates the amount of time that the AMPA gates are open. Our model suggests that an increase in pulse-width while keeping a fixed amount of excitation requires a decrease in stimulus intensity. This relation has been observed clinically while modifying pulse-width with the goal of keeping clinical efficacy unchanged (83).
Model of neuron and dynamics

All neurons are modeled using a single compartment with Hodgkin-Huxley-type dynamics. The voltage change in each cell is described by:

\[ c_m \frac{dv}{dt} = - \sum I_{\text{membrane}} - \sum I_{\text{synaptic}} + I_{\text{app}} + I_{\text{noise}} \]  

[1]

The membrane capacitance \((c_m)\) is normalized to 1 \(\mu\text{F-cm}^{-2}\) for all neurons. All cells have a fast sodium current \((I_{Na})\), a fast potassium current \((I_K)\), a leak current \((I_L)\) for membrane currents \((I_{\text{membrane}})\). MSNs additionally have an M-current and FSIs additionally have a D-current (discussed in detail later). The synaptic currents \((I_{\text{synaptic}})\) depend on the connectivity, and are discussed in the section on network connectivity and synaptic currents. The applied current \((I_{\text{app}})\) is a constant that represents background excitation and the noise current \((I_{\text{noise}})\) corresponds to a gaussian noise.

Membrane currents and background excitation in baseline condition

The membrane currents are modeled using Hodgkin-Huxley-type conductance dynamics and formulated as:

\[ I = g(m^n h^k)(V - E_{\text{ion}}) \]  

[2]

Every membrane current has a constant maximal conductance \((g)\) and a constant reversal potential \((E_{\text{ion}})\). The activation \((m)\) and inactivation \((h)\) gating variables have \(n^\text{th}\) and \(k^\text{th}\) order kinetics with \(n, k \geq 0\). The dynamics of each gating variable evolves according to the kinetic equation (written here for the gating variable \(m\)):

\[ \frac{dm}{dt} = \frac{m_\infty - m}{\tau_m} \]  

[3]

The steady-state function \((m_\infty)\) and the time constant of decay \((\tau_m)\) can be formulated as rate functions for each opening \((\alpha_m)\) and closing \((\beta_m)\) of the ionic channel by using:

\[ m_\infty = \alpha_m / (\alpha_m + \beta_m) \quad \text{and} \quad \tau_m = 1 / (\alpha_m + \beta_m). \]  

[4]

The baseline excitation (modulated by dopamine and acetylcholine) and the sum of all excitatory and inhibitory exogenous inputs for a given neuron (e.g., from the cortex, thalamus and non-modeled input) is introduced into the model using a constant background excitation term \((I_{\text{app}})\). To account for variability in background excitation, we further introduce a Gaussian noise term \((I_{\text{noise}})\). The Gaussian noise has mean zero and standard deviation dependent on the neuronal cell type.

Striatal medium spiny neurons (MSN). Our model striatum consists of a network of medium spiny neurons (MSNs), which comprise about 95\% of the neurons in the rodent striatum (90). The membrane currents \((I_{\text{membrane}})\) of MSNs consist of a fast sodium current \((I_{Na})\), a fast potassium current \((I_K)\), a leak current \((I_L)\), and an M-current \((I_m)\) (91). We do not model MSN up and down states which are not prevalent in the awake state (92), the state being modeled, and therefore we do not include the Kir current in our model, which is active during the MSN down state.

Fast sodium current. The sodium current \((I_{Na})\) has three activation gates \((n=3)\) and only one inactivation gate \((k=1)\). The rate functions for the sodium current activation \((m)\) and inactivation \((h)\) variables are formulated as:

\[ \alpha_m = \frac{0.32(V + 54)}{1 - \exp[-(V + 54)/4]} \]  

[5]

\[ \beta_m = \frac{0.28(V + 27)}{\exp[(V + 27)/5] - 1} \]  

[6]

\[ \alpha_h = 0.128 \exp[-(V + 50)/18] \]  

[7]

\[ \beta_h = \frac{4}{1 + \exp[-(V + 27)/5]} \]  

[8]

The maximal conductance of the sodium current is \(g_{\text{Na}} = 100 \text{ mS-cm}^{-2}\). The sodium reversal potential is \(E_{Na} = 50\text{ mV}\).

Fast potassium current. The fast potassium current \((I_K)\) has four activation gates \((n = 4)\) and no inactivation gates \((k = 0)\). The rate functions of the activation gate are described by:

\[ \alpha_m = \frac{0.032(V + 52)}{1 - \exp[-(V + 52)/5]} \]  

[9]

\[ \beta_m = 0.5 \exp[-(V + 57)/40] \]  

[10]

The maximal fast potassium channel conductance is \(g_K = 80 \text{ mS-cm}^{-2}\). The reversal potential for potassium is \(E_K = -100\text{ mV}\).

Leak current. The leak current \((I_L)\) has no gating variables \((n = 0, k = 0)\). The maximal conductance of the leak channel is \(g_l = 0.1 \text{ mS-cm}^{-2}\). The leak channel reversal potential is \(E_L = -67\text{ mV}\).
**M-current.** The M-current ($I_M$) has one activation gate ($n = 1$) and no inactivation gate ($k = 0$). The rate functions for the M-current activation gate are described by:

\[
\alpha_m = \frac{Q_s 10^{-4}(V + 30)}{1 - \exp[-(V + 30)/9]} \quad [11] \\
\beta_m = -\frac{Q_s 10^{-4}(V + 30)}{1 - \exp[(V + 30)/9]} \quad [12]
\]

We use a $Q_{10}$ factor of 2.3 to scale the rate functions of the M-current since the original formulation of these kinetics described dynamics at 23°C (93). Thus, for a normal body temperature of 37°C, the M-current rate equations are scaled by $Q_s$, which is formulated as:

\[
Q_s = Q^{(37°C - 23°C)/10}_{10} = 3.209
\]

The maximal M-current conductance is $\bar{g}_m = 1.3 \text{ mS/cm}^2$ in baseline conditions.

**Applied current and noise.** The applied current ($I_{app}$) is set to 1.19 μA/cm$^2$, and the Gaussian noise ($I_{noise}$) has mean 0 and standard deviation 4√0.05 where 0.05ms corresponds to the time step of integration in our simulations.

**Striatal fast spiking interneurons (FSI).** Striatal fast spiking interneurons (FSIs) were modeled as in (3) and (2), using one compartment. The membrane currents ($I_{membrane}$) of FSIs consist of a fast sodium current ($I_{Na}$), a fast potassium current ($I_K$), a leak current ($I_L$), and a D-current ($I_D$). The formulation of these currents is taken from (2) that build upon previous models of striatal FSIs (3, 94).

**Fast sodium current.** The sodium current ($I_{Na}$) has three activation gates ($n=3$) and only one inactivation gate ($k=1$). The steady state functions for the sodium current activation ($m$) and inactivation ($h$) variables and their time constants are described by:

\[
m_\infty = \frac{1}{1 + \exp[-(V + 24)/11.5]} \quad [14] \\
h_\infty = \frac{1}{1 + \exp[(V + 58.3)/6.7]} \quad [15] \\
\tau_h = 0.5 + \frac{14}{1 + \exp[(V + 60)/12]} \quad [16]
\]

The time constant $\tau_m$ is assumed to be negligible (around 0ms) and thus we set $m = m_\infty$ (3). The maximal conductance of the sodium current is $g_{Na} = 112.5 \text{ mS/cm}^2$. The sodium reversal potential is $E_{Na} = 50\text{mV}$.

**Fast potassium current.** The potassium current ($I_K$) has two activation gates ($n=2$) and no inactivation gate ($k=0$). The steady state function for the potassium current activation ($n$) and its constant ($\tau_n$) are described by:

\[
n_\infty = \frac{1}{1 + \exp[-(V + 12.4)/6.8]} \quad [17] \\
\tau_n = (0.087 + \frac{11.4}{1 + \exp[(V + 14.6)/8.6]})(0.087 + \frac{11.4}{1 + \exp[-(V - 1.3)/18.7]}) \quad [18]
\]

The maximal conductance of the sodium current is $\bar{g}_K = 225 \text{ mS/cm}^2$. The potassium reversal potential is $E_{Na} = -90\text{mV}$.

**Leak current.** The leak current ($I_L$) has no gating variables ($n = 0, k = 0$). The maximal conductance of the leak channel is $g_L = 0.25 \text{ mS/cm}^2$. The leak channel reversal potential is $E_{L} = -70\text{mV}$.

**D-Current.** The fast-activating, slowly inactivating potassium D-current ($I_D$) is described mathematically as in (3) and has three activation gates ($n = 3$) and one inactivation ($k = 1$) gate. The steady state functions for the activation ($m$) and inactivation ($h$) variables and their time constants ($\tau_m$ and $\tau_h$), respectively) are described by:

\[
m_\infty = \frac{1}{1 + \exp[-(V + 50)/20]} \quad [19] \\
h_\infty = \frac{1}{1 + \exp[(V + 70)/6]} \quad [20] \\
\tau_m = 2\text{ms} \quad [21] \\
\tau_h = 150\text{ms} \quad [22]
\]

The maximal conductance of the D-current is 6 mS/cm$^2$.

**Applied current and noise.** The applied current ($I_{app}$) is set to 5.5 μA/cm$^2$, and the Gaussian noise ($I_{noise}$) has mean 0 and standard deviation 60√0.05 where 0.05ms corresponds to the time step of integration in our simulations.
We modeled the GABA<sub>a</sub> current (\(I_{membrane}\)) of STN and GPe neurons were then restricted to consist of a fast sodium current (\(I_{Na}\)), a fast potassium current (\(I_K\)) and a leak current (\(I_L\)). We set the parameters of these currents to be the same as those of MSNs, to not introduce new parameters.

To validate the robustness of these parameters, we additionally simulated the network in a set of modified parameters derived from (95), which effectively changes the maximal conductance of Na and K currents from 100 and 80 mS cm\(^{-2}\) to 37.5 and 45 mS cm\(^{-2}\) for STN neurons and 120 and 30 mS cm\(^{-2}\) for GPe neurons. Such changes will affect the excitation balance in the cell equations, and thus we increased \(I_{app}\) by 0.75 \(\mu\)A cm\(^{-2}\) for STN and decreased it by 0.5 \(\mu\)A cm\(^{-2}\) in GPe to rebalance the excitation levels. Our simulations with these parameters show no change in dynamics in any considered condition, keeping spectral and firing rates comparable to the original parameters (Fig S16A-F). Of course, these changes do affect the waveform of the action potential, which is not essential to our investigation.

**Applied current and noise.** The applied current (\(I_{app}\)) is set to 1.9 \(\mu\)A cm\(^{-2}\) for STN and 3.0 \(\mu\)A cm\(^{-2}\) for GPe, and the Gaussian noise (\(I_{noise}\)) has mean 0 and standard deviation 80\(\sqrt{\text{mV/0.05}}\) for both STN and GPe where 0.05ms corresponds to the time step of integration in our simulations. These values were chosen to give the GPe and STN populations appropriate baseline spike rates (~80Hz for GPe and ~17Hz for STN) and to mimic the largely asynchronous spiking seen under baseline conditions in these populations.

| \(C_m\) (\(\mu\)F cm\(^{-2}\)) | MSN | FSI | STN | GPe |
| --- | --- | --- | --- | --- |
| \(I_{app}\) (\(\mu\)A cm\(^{-2}\)) | 1.19 | 6.2 | 1.9 | 3 |
| \(g_{Na}\) (mS cm\(^{-2}\)) | 100 | 112.5 | 100 | 100 |
| \(g_K\) (mS cm\(^{-2}\)) | 80 | 225 | 80 | 80 |
| \(g_L\) (mS cm\(^{-2}\)) | 0.1 | 0.25 | 0.1 | 0.1 |
| \(g_M\) (mS cm\(^{-2}\)) | 1.3 | 6 |
| \(g_{il-cell}\) (mS cm\(^{-2}\)) | 0.15 |
| \(E_{Na}\) (mV) | 50 | 50 | 50 | 50 |
| \(E_K\) (mV) | -100 | -90 | -100 | -100 |
| \(E_L\) (mV) | -67 | -70 | -67 | -67 |

**Table S1. Parameters for membrane currents and background excitation in baseline condition for all four neuronal populations.**

**Network connectivity and synaptic currents in baseline condition**

Our network consists of 100 D2 MSNs, 50 FSIs, 40 STN cells and 80 GPe cells. We have a total of 6 types of projections between the populations, 5 inhibitory (MSN-MSN, FSI-MSN, FSI-FSI, MSN-GPe and GPe-STN) and 1 excitatory (STN-FSI). All inhibitory synapses were modeled using GABA<sub>a</sub> currents and all excitatory connections were modeled using AMPA currents. We modeled the GABA<sub>a</sub> current (\(I_{GABA-a}\)) using a Hodgkin-Huxley-type conductance:

\[
I_{GABA-a} = \bar{g}_{inh} s_{inh}(V - E_{inh})
\]  

[23]

of the gating variables from all pre-synaptic connections. The gating variable \(s_{inh}\) for inhibitory GABA<sub>a</sub> synaptic transmission is the sum:

\[
s_{inh} = \frac{1}{N} \sum_{k=1}^{N} S_{k \rightarrow j}
\]  

[24]

where \(N\) is the number of presynaptic neurons and \(S_{k \rightarrow j}\) describes the kinetics of the gating variable, for each pair of presynaptic neuron \(k\) and postsynaptic neuron \(j\), evolving according to:

\[
\frac{dS_{k \rightarrow j}}{dt} = g_{GABA-a}(V_k)(1 - S_{k \rightarrow j}) - \frac{S_{k \rightarrow j}}{\tau_{inh}}
\]  

[25]

Note that \(S_{k \rightarrow j}\) is a function of the presynaptic voltage \(V_k\), and its dynamics depend on the dynamics of the presynaptic neuron \(k\). The rate functions for the open state of the GABA<sub>a</sub> receptor (\(g_{GABA-a}(V_k)\)) is described by:

\[
g_{GABA-a}(V_k) = a(1 + \tanh(V_k/b))
\]  

[26]

for values of \(a\) and \(b\) that depend on the pre- and post-synaptic neuronal cell types and are provided in Table S2. The maximal conductance \(g_{inh}\) is scaled by the number of pre-synaptic neurons of a specific cell type. Excitatory AMPA synaptic currents use the same set of equations as for the GABA<sub>a</sub> current (eqns. 23 - 26) with the "GABA<sub>a</sub>" subscript replaced by "AMPA" and the "inh" subscript replaced by "exc". Parameters for all synaptic currents are provided in Table S2.
Table S2. Connectivity parameters in baseline condition. * We specified the conductances for the MSN-GPe and GPe-STN projection such that (i) the MSNs have a capability of inhibiting GPe and GPe neurons have a capability of inhibiting STN, and (ii) the firing rates are preserved, as found in the literature, for STN and GPe during the various conditions. The tonic activity in STN and GPe is driven by a high applied current in our model, and the conductances have to be adapted, within bounds as observed in the literature, to ensure that synaptics currents can overcome the set high applied excitation. The exact choice of the conductance does not influence our results, as long as (i) and (ii) are satisfied. ** This projection is understudied in the literature. We estimated the parameters from the findings in (100).

Remark regarding D1 and D2 MSNs. We do not include the D1 MSNs in the context of PD, since they are believed to be much less active in this diseased state and are canonically considered to not be part of our modeled loop going through the indirect pathway of the BG. We only introduce D1 MSNs to establish how DBS in STN restores striatal theta/gamma oscillations and theta-modulated beta bursts during PD. When D1 MSNs (N=100) are introduced, they received the same projection pattern as MSN-MSN projections and FSI-MSN projections. In this work, we assume that the D1 MSNs do not project to GPe and thereby do not alter BG loop dynamics.

Remark regarding the FSI-MSN projections. Each of the 100 D2 MSNs randomly receives projections from 15% of the full FSI population (N=50). Experimental findings show that MSN receives projections from local FSIs (within a 250µm radius) with probability 45% (98). We lower the connection probability to account for the ratio of MSNs:FSIs in our model network which is smaller than that found in vivo. While we can reduce the number of FSIs, we risk of losing heterogeneity in FSI responses. Instead, we will consider only a third of the FSIs to be local to an MSN and enforce the MSN to receive a projection from 45% of that third (which is equivalent to 15% of the FSI population). This will bring the number closer to experimental findings while keeping enough heterogeneity in responses.

Remark regarding FSI-FSI connectivity. FSIs were additionally connected by electrical connections via gap junctions. The electrical coupling for neuron j, has units in μA·cm⁻² and is formulated as:

$$I_{elec} = \frac{1}{N} \sum_{i} g_{elec}(V_{k} - V_{j})$$

with N equal to the number of FSIs neuron j is coupled to. This yields a change:

$$c_{m} \frac{dv}{dt} = -\sum I_{membrane} - \sum I_{synaptic} + \sum_{k} I_{elec} + I_{app}$$

The value of the gap junction conductance $g_{elec}$ depends on the level of dopamine, and is set in baseline condition to 0.15 mS·cm⁻². Each FSI was randomly electrically coupled to 33% of the remaining FSIs.

Remark regarding the STN-FSI projections. This projection is understudied in the literature. We estimated its parameters from the findings in (100), and we set the connectivity density from STN to FSI at 10%. We then tested the effects of having FSIs receive input from 50% and 90% percent of STN neurons. We did not observe a change in dynamics in any condition. Specifically, increasing the connectivity probability would increase the amount of homogeneity in the input. This increase in homogeneity will not cause significant changes in PD and PD+DBS conditions as beta oscillations and high frequency stimulation are already providing homogeneous input patterns irrespective of the connectivity probability, but may play a role in normal condition. This increase in homogeneity also does not appear to play an important role in altering the dynamics of FSIs as the background noise received by FSIs can mask this increase. It however reduces the amount of uncorrelated noise received by FSIs which can further aid FSIs in delivering synchronous theta/gamma oscillations.

Perturbations in parkinsonian conditions.

Parkinson’s disease was modeled starting from baseline condition and adding the following biophysical changes. The applied current ($I_{app}$) was increased to 1.25 μA·cm⁻² for MSNs (1) and decreased to 4.3 μA·cm⁻² for FSIs (2). The maximal conductance for the MSN-M-current was decreased to 1.2 mS·cm⁻² (1). The maximal conductance of the FSI-MSN projection was decreased by 20% to 0.48 mS·cm⁻², as a result of the increase in cholinergic tone (101). The maximal conductance of the FSI-FSI projection was also increased to 0.2. The value of the FSI electrical conductance $g_{elec}$ was also decreased to 0.075. The changes were extrapolated from (2), based on the changes in FSI parameters as a function of dopamine level. When modeled, D1 MSNs inherit the same parameters as D2 MSNs except for $I_{app}$ which is decreased to 1.13 in Parkinsonian conditions.
We expect the excitation of FSIs to be reduced in PD as DA has been found to excite FSIs in the striatum through in-vitro studies (4). Also, it has been found that acetylcholine (ACh) attenuates FSI inhibition of MSNs via presynaptic muscarinic receptors (101). We expect ACh to be high during PD states because DA tonically inhibits striatal ACh release under normal conditions (102). Indeed, it has been shown experimentally that antagonists of either D1 or D2 receptors, as well as loss of striatal dopamine in 6-OHDA rats, result in increased striatal levels of ACh (103). Thus, we expect DA depletion to further weaken FSI input to MSNs.

**Applying DBS in Parkinsonian conditions**

Applying DBS during parkinsonian condition was modeled by applying a high frequency voltage input, directly altering the rate function \( g_{AMPA}(V) \) for the open state of the AMPA receptor governing the AMPA synaptic current of FSIs coming from STN. In particular we have:

\[
g_{AMPA}(V) = 5(1 + \tanh((E + E_{HFS}P)/4))
\]

where \( E \) is set to \(-67\text{mV}\) that correspond to the resting potential of the neuron, \( E_{HFS} \) is a constant voltage amplitude and \( P \) corresponds to periodic pulses (modeled by a rectangular wave function of unit amplitude) with specified pulse-frequency (DBS frequency) and pulse-width (DBS pulse-width, dictating the duty cycle). For all voltages \( V \), we have \(-1 \leq \tanh(V) \leq 1\). The maximal \( E_{HFS} \) was chosen so that \( g_{AMPA}(V) \approx 0 \) as \( \tanh(E/4) \approx -1 \) during the off-cycle of the rectangular wave \( P \), and \( g_{AMPA}(V) \approx 10 \) as \( \tanh((E + E_{HFS})/4) \approx 1 \) during the on-cycle of the rectangular wave. Therefore, different choices for the value of \( E \) do not alter the behavior of the model as long as they are sufficiently negative.

**Alternate modeling of DBS in STN**

We directly incorporated high frequency stimulation into the presynaptic voltage at the AMPA receptor level, giving the DBS pulse-width direct control over the opening and closing of the channel. Instead, the AMPA receptors can be modeled to be driven by action potentials. We tested the effect of this modification and incorporated the DBS pulse directly into dynamics of the membrane potential of the soma, as our neurons consist of a single compartment. With such modifications, the effects of DBS depend on both the amplitude and the width of the pulse.

At a sufficiently high enough pulse amplitude compared to cell excitation (of pulse current amplitude of 100 \( \mu A\cdot cm^{-2} \)) and keeping pulse-width at 150us, axonal firing rates increased to mean\(\pm\)SD of 92.22 \( \pm \) 0.18 spk/s, and the dynamics observed in baseline condition are restored (Fig S17A,B ; MSN firing rate of mean\(\pm\)SD=1.34 \( \pm \) 0.05 spk/s). However, in this setting, the input to FSIs is heterogenous as the spike trains elicited at the STN axons are different from one STN axon to the other, and the FSIs admit different sets of pre-synaptic STN neurons. In this case, we do not recover theta/gamma oscillations under DBS as observed in normal conditions with high DA levels (Fig S17C,D). This is because a synchronous input to FSIs is crucial for the expression of theta/gamma in PD. To verify this, we removed all background noise in STN cells and were able to restore homogeneity in STN axonal responses as well as theta/gamma dynamics in FSIs.

In principle, it is possible to model HFS at the level of action potential instead of axonal AMPA receptor levels and obtain similar dynamics. This however leads to two issues: First, it is the ‘width’ of the action potential that will dictate the duration of opening of the AMPA channel, and the DBS pulse-width instead dictates how effective DBS is at initiating action potentials. Second, it will require introducing and tuning a new variable, the pulse-amplitude, that also dictates the level of DBS effectivenss in initiating action potentials. In such a situation, one can decrease the pulse-width, but would have to compensate by increasing the pulse amplitude to engage STN action potentials. By instead applying the DBS pulse width directly to presynaptic voltage of the AMPA receptor, we fix the effect of amplitude to the maximum and instead use the pulse-width to control the level of excitation received by the AMPA receptor. In reality, the axons are likely not receiving a square wave excitation and will likely be receiving a filtered version of the pulse, with a larger effective width. Furthermore, the width of an action potential is also much greater than the pulse-width clinically considered during DBS, and this can yield to a greater efficacy in keeping the AMPA receptors open.

While there can be variability with respect to which pulse-width value will be most effective, our model establishes that increasing pulse-width will increase axonal excitation, leading to increased FSI inhibition onto MSNs. This fact will hold regardless of whether we model it directly through AMPA receptors or via action potentials. We decided to model it through the AMPA receptor to avoid adding a new variable that dictates the effectiveness of DBS on STN somas, and what axonal firing rates this choice will lead to. We avoided adding such a variable as we have no principled means to validate it or interpreting its magnitude.

**High dopamine state and cortical input**

A high dopamine state during normal condition was modeled starting with the parameters in baseline condition and adding the following biophysical changes. The applied current \( I_{app} \) was decreased to 1.13 \( \mu A\cdot cm^{-2} \) for MSNs (expressing the D2-receptor) and increased to 8 \( \mu A\cdot cm^{-2} \) for FSIs. The maximal conductance of the FSI-FSI projection was also decreased to 0.05 mS\cdot cm^{-2}. The value of the FSI electrical conductance \( g_{elec} \) was also increased to 0.3 mS\cdot cm^{-2}.

A high dopamine state is coupled with increased correlated cortical activity that leads to correlated noise onto FSIs. The noise term \( (I_{noise}) \) for FSI neuron \( j \) is formulated as:

\[
I_{noise,j} = (1 - \lambda)X_j + \lambda Y
\]

where \( X_j \) is Gaussian random variable with mean 0 and standard deviation \( 60\sqrt{0.05} \) that is neuron specific and independent from that of the other neurons, and \( Y \) is Gaussian random variable with mean 0.4 and standard deviation \( 16\sqrt{0.05} \) that
is common to all FSIs. The parameter $\lambda$ is fixed between 0 and 1 and dictates the amount of correlation in the FSI noise. We modeled the baseline condition with only uncorrelated noise with $\lambda = 0$. We modeled the normal condition with high dopamine levels to consist primarily of correlated noise with $\lambda = 0.9$.

D1 MSNs are modeled in the same manner as D2 MSN but with $I_{app}$ increased to $1.23 \mu A \cdot cm^{-2}$ in normal conditions with high dopamine levels, and decreased to $1.13$ in Parkinsonian condition.

**Population activity and local field potentials**

Oscillations have been typically detected in local field potential (LFP) measurements reflecting aggregate population activity. We sought similar signals and dissected their spectral content. A striatal LFP will necessarily contain a mixture of MSN and FSI activity, with MSN activity accounting for most of the signal given the size of the FSI population compared to the MSNs. To assess the activity of the separate populations, we thus defined an aggregate signal for each.

Synaptic currents have been used in models of LFP, EEG, or MEG \((104–106)\). Therefore, per \((1)\), we model the aggregate population activity of MSN as the sum of all GABAa currents between MSNs. The MSN GABAa currents in our model reflect the spiking activity of MSNs, since each time an MSN spikes, it produces a GABAa current in other MSNs. Thus, our aggregate signal is tracking the population spiking activity of the MSNs. We are particularly interested in the population spiking activity of MSNs since this is the signal that will be transmitted to the output structure of the striatum, namely the GPe.

The FSIs also inhibit one another, and our aggregate signal consists of the GABAa synaptic currents between the FSIs. That aggregate signal should reflect the same spectral content as the sum of GABAa synaptic currents arising from the projections from FSIs to MSNs.

We have not modeled any connections between GPe or STN cells, and as such, the aggregate signals for GPe and STN were taken to be the sum of the membrane potentials of GPe and STN neurons, respectively.

To calculate the power spectral density of the LFP signal, we derive the discrete Fourier transform of the aggregate signal computed via the fast fourier transform implemented in Python SciPy. Power spectral density plots were constructed from simulations run for 5.5 seconds, while discarding the first 200ms of a simulation to ensure that the activity stabilized from the initial conditions.

**Statistics**

Plots of spiking activity and spectral content in all conditions were drawn from 5.5 second simulations. Statistics and statistical test were computed using Python 3. The results (e.g., averages and standard deviations) in each condition were based on 25 simulations. Parametric sweeps were based on 10 simulations per parameter value, unless otherwise indicted.

**Simulation methods**

Our network models were programmed in C++ and compiled using GNU g++. The differential equations were integrated using a fourth-order Runge Kutta algorithm. The integration time step was 0.05 ms. Model output is graphed and analyzed using Python 3.
Supplementary Figures
Fig. S1. Population dynamics in baseline condition, in the core striatal model. (A) Schematic illustrating the MSN network, unconnected to other populations. (B) Raster plot showing spiking activity of MSNs in baseline condition for the network in (A) (MSN firing rate: mean±SD=1.46 ± 0.046 spk·s⁻¹, N=25 simulations). (C) Graph showing the average (blue) and standard deviation (light blue) of the spectrum of MSN population activity, all in baseline condition for the network in (A) (N=25 simulations). (D) Schematic illustrating the core striatal model. (E) Raster plots showing spiking activity of MSN and FSI neurons, all in baseline condition for the network in (D). MSN firing rate: mean±SD=1.88 ± 0.057 spk·s⁻¹, N=25 simulations. FSI firing rate: mean±SD=10.66 ± 0.061 spk·s⁻¹, N=25 simulations. (F) Graph showing the average (blue) and standard deviation (light blue) of the spectra of MSN and FSI population activity, all in baseline condition for the network in (D) (N=25 simulations).
Fig. S2. Changes in MSN activity as a function of FSI inhibition. (A) Graphs showing the spectrum of MSN population activity and their average firing rate in the core striatal model during baseline condition with different maximal GABAa conductances for the FSI projections to MSNs (N=10 simulations for each value of maximal GABAa conductance). (B) Graphs showing the cross-correlation between the MSN population activity and the FSI population activity in the conditions of (A), plotted for a subset of the maximal GABAa conductances for the FSI to MSN projections. The x-axis represents the correlation time lag. (C) Graphs showing the autocorrelation of the MSN population activity as a function of time lag in the same conditions as (B).
**Fig. S3. Population dynamics for high levels of dopamine in the core striatal model** (A) Graph showing theta/gamma oscillations of an isolated FSI subjected to high excitation due to an increase of dopaminergic level in the Striatum. (B) Raster plot showing spiking activity of FSI neurons, in normal conditions with high level of DA, in the core striatal model comprising only FSIs and MSNs. (C) Graph showing the average (blue) and standard deviation (light blue) of the spectrum of FSI population activity, in normal conditions with high level of dopamine, in the core striatal model comprising only FSIs and MSNs. (D) (E) Graphs displaying population activity of MSN neurons, as in (B) and (C), for normal conditions with high level of dopamine, in the core striatal model. The raster plots show D1 and D2 MSN activity separately.
**Fig. S4.** Population dynamics of an MSN network during increase in cholinergic tone. (A) Schematic illustrating the parametric changes in the MSN network during high cholinergic tone from parameters in baseline condition. (B) Raster plot showing spiking activity of MSNs during high cholinergic tone condition for the network in (A) (MSN firing rate: mean±SD=5.32±0.037 spk·s⁻¹, N=25 simulations). (C) Graphs showing the average (blue) and standard deviation (light blue) of the spectrum of MSN population activity, during high cholinergic tone condition for the network in (A) (N=25 simulations).
Fig. S5. Population dynamics in PD, in the core striatal model. (A) Schematic illustrating the parametric changes in the MSN network during PD from parameters in baseline condition. (B) Raster plot showing spiking activity of MSNs during PD for the network in (A) (MSN firing rate: mean ± SD = 7.66 ± 0.04 spk·s⁻¹, N=25 simulations). (C) Graphs showing the average (blue) and standard deviation (light blue) of the spectrum of MSN population activity, during PD for the network in (A) (N=25 simulations). (D) Schematic illustrating the changes in the parameters of the biophysical model during PD, from baseline condition, in the core striatal model. (E) Raster plots showing spiking activity of MSN and FSI neurons, all in PD for the network in (D) (MSN firing rate: mean ± SD = 6.62 ± 0.21 spk·s⁻¹ N=25 simulations). (F) Graphs showing the average (blue) and standard deviation (light blue) of the spectra of MSN and FSI population activity, all in PD for the network in (D) (N=25 simulations).
Fig. S6. The effect of the biophysical perturbation in the MSN population on its activity during Parkinsonian conditions. (A) Left. Raster plot showing MSN spiking activity (MSN firing rate: mean±SD=4.85±0.13 spk·s⁻¹, N=25 simulations) during PD condition in the full network including FSIs, GPe and STN. Right. Graph showing the average (blue) and standard deviation (light blue) of the spectrum of MSN population activity during PD condition. (B) Similar to (A) but keeping the maximal conductance of the MSN M-currents intact during PD conditions (instead of decreasing it) (MSN firing rate: mean±SD=3.99±0.10 spk·s⁻¹, N=25 simulations). (C) Similar to (A) but keeping the background excitation onto MSNs intact during PD conditions (instead of increasing it) (MSN firing rate: mean±SD=4.14±0.13 spk·s⁻¹, N=25 simulations). (D) Similar to (A) but keeping the maximal conductance for the FSI projections to MSNs intact during PD conditions (instead of decreasing it) (MSN firing rate: mean±SD=4.73±0.13 spk·s⁻¹, N=25 simulations).
**Fig. S7. Beta activity in MSNs in baseline condition following exogenous beta-band input.** (A) Left. Raster plot showing MSN spiking activity in baseline condition and a full network, with a high amplitude exogenous sinusoidal input current (at beta frequency of 15.8 Hz) applied to the MSNs (MSN firing rate: mean±SD=3.24 ± 0.18 spk·s⁻¹, N=10 simulations). Right. Graphs showing the average (blue) and standard deviation (light blue) of the spectrum of MSN population activity, in baseline condition with a high amplitude exogenous sinusoidal input current applied to the MSNs. (B) Similar to (A) but decreasing the amplitude of the exogenous input into MSNs (MSN firing rate: mean±SD=1.85 ± 0.10 spk·s⁻¹, N=10 simulations). (C) Similar to (B) but further decreasing the amplitude of the exogenous input into MSNs (MSN firing rate: mean±SD=1.34 ± 0.07 spk·s⁻¹, N=10 simulations).
Fig. S8. Resonance properties of the closed-loop system. (A) Raster plots showing spiking activity of the four neuronal populations in baseline condition, where a high amplitude exogenous sinusoidal (15.8 Hz) input current is applied to MSNs for the first 2 seconds of the plots, and then removed for the remaining 2 seconds. (B) Graphs showing the spectrogram of population activity for the four neuronal population, in the same conditions as in (A), where beta input is applied to MSNs for the first 2 seconds and then removed for the remaining 2 seconds.
Fig. S9. The effect of exogenous beta activity in STN during PD condition. (A) Raster plot showing spiking activity of the four populations in PD condition while an exogenous sinusoidal input current (at beta frequency of 15.8 Hz) is applied to STN (MSN firing rate: mean ± SD = 5.83 ± 0.12 spk·s⁻¹, N=10 simulations). (B) Graphs showing the average (blue) and standard deviation (light blue) of the spectrum of population activity for each of the four populations, in PD condition while an exogenous sinusoidal input current is applied to STN (15.8 Hz) (N=10 simulations). (C) Same as (A) but with an input frequency of 17.5 Hz (MSN firing rate: mean ± SD = 5.23 ± 0.13 spk·s⁻¹, N=10 simulations). (D) Same as (B) but with an input frequency of 17.5 Hz (N=10 simulations). (E) Same as (A) but with an input frequency of 20 Hz (MSN firing rate: mean ± SD = 4.89 ± 0.05 spk·s⁻¹, N=10 simulations). (F) Same as (B) but with an input frequency of 20 Hz (N=10 simulations).
Fig. S10. The effect of exogenous beta activity in MSNs during PD condition. (A) Raster plot showing spiking activity of the four populations in PD condition while an exogenous sinusoidal input current (at beta frequency of 15.8 Hz) is applied to MSN (MSN firing rate: mean±SD=6.92 ± 0.19 spk·s^{-1}, N=10 simulations). (B) Graphs showing the average (blue) and standard deviation (light blue) of the spectrum of population activity for each of the four populations, in PD condition while an exogenous sinusoidal input current is applied to MSN (15.8 Hz) (N=10 simulations). (C) Same as (A) but with an input frequency of 17.5 Hz (MSN firing rate: mean±SD=6.69 ± 0.22 spk·s^{-1}, N=10 simulations). (D) Same as (B) but with an input frequency of 17.5 Hz (N=10 simulations). (E) Same as (A) but with an input frequency of 20 Hz (MSN firing rate: mean±SD=6.06 ± 0.19 spk·s^{-1}, N=10 simulations). (F) Same as (B) but with an input frequency of 20 Hz (N=10 simulations).
Fig. S11. Effect of DBS frequency and pulse width on FSI and MSN activity during PD. (A) Plot showing the spectrum of FSI population activity for different stimulation frequencies. (B) Top. Plot showing the STN AMPA current, input into FSIs, for different stimulation frequencies. Bottom. Close-up, of the top plot, on the minima of the AMPA current. (C) Plot showing example traces of FSI membrane potentials for different stimulation frequencies. (D) Plot showing the STN AMPA current, input into FSIs, for different pulse widths. (E) Graph showing the average FSI spiking rate (vertical error bars represent standard deviation. The coefficient of variation std/mean is small for the error bars to be visible.) as a function of DBS pulse width (N=10 simulations for each value of pulse width). (F) Graph showing the average MSN spiking rate (vertical error bars represent standard deviation. The coefficient of variation std/mean is small for the error bars to be visible.) as a function of DBS pulse width (N=10 simulations for each value of pulse width).
Fig. S12. The effect of DBS with low frequencies. (A) Raster plot showing spiking activity of MSNs and FSI in PD condition while DBS is applied with a simulation frequency of 65Hz (MSN firing rate: mean±SD=1.65±0.08 spk·s⁻¹, N=25 simulations). (B) Graphs showing the average (blue) and standard deviation (light blue) of the spectrum of population activity for MSNs and FSIs while DBS is applied with a stimulation frequency of 65Hz (N=25 simulations). (C) Same as (A), but with a stimulation frequency of 20Hz (MSN firing rate: mean±SD=5.57±0.23 spk·s⁻¹, N=25 simulations). (D) Same as (B), but with a stimulation frequency of 20Hz (N=25 simulations).
Fig. S13. Variations in MSN beta activity through changes in MSN excitability during PD condition. (A) Raster plots showing spiking activity of MSNs during PD while excitability is varied through the applied current ($I_{app}$), as a proxy for cortical/thalamic input. (B) Graphs showing the spectrogram of MSN population activity, in the same conditions as in (A). (C) Traces showing raw (black) and beta-band filtered (orange) population activity of MSNs, in the same conditions as in (A).
Fig. S14. The effect of DBS with low frequencies under correlated noise. (A) Raster plot showing spiking activity of FSI neurons, in PD during DBS at 65Hz under correlated noise condition. (B) Graph showing the average (blue) and standard deviation (light blue) of the spectrum of FSI population activity, in PD during DBS at 65Hz under correlated noise condition. (C), (D) Graphs displaying population activity of MSN neurons, as in (A) and (B), in PD during DBS at 65Hz under correlated noise. The raster plots show D1 and D2 MSN activity separately. (E) Graph showing the membrane potential of an example FSI neuron in PD during DBS at 130Hz under uncorrelated noise condition. (F) Same as (E) but during DBS at 130Hz under correlated noise condition. (G) Same as (E) but during DBS at 65Hz under uncorrelated noise condition. (H) Same as (E) but during DBS at 65Hz under correlated noise condition. (I) Graph showing the average FSI firing rate (bars representing standard deviation) as a function of DBS frequency (10 simulations per simulated frequency), under correlated noise condition. (J) Graph similar to (I) showing the average FSI theta band power as a function of DBS frequency. The theta band power is an average of the intensity (dB) of the spectrum in the frequency interval 4-8Hz. The baseline power considered to compute the intensity is the average power in the band less than 1Hz.
Fig. S15. The effect of adding STN-GPe and GPe-FSI projections in all conditions. (A) Schematic illustrating an extended network, including an STN-GPe excitatory projection and a GPe-FSI inhibitory projection. (B) Raster plot showing spiking activity in all populations during baseline conditions (MSN firing rate: mean $\pm$ SD = 0.99 $\pm$ 0.07 spk·s$^{-1}$, N=25 simulations). (C) Graphs showing the average (blue) and standard deviation (light blue) of the spectrum of all population activity during baseline conditions. (D) , (E) Plots similar to (B) and (C) during PD conditions (MSN firing rate: mean $\pm$ SD = 3.78 $\pm$ 0.14 spk·s$^{-1}$, N=25 simulations). (F) , (G) Plots similar to (B) and (C) during DBS in PD conditions (MSN firing rate: mean $\pm$ SD = 1.53 $\pm$ 0.08 spk·s$^{-1}$, N=25 simulations). STN somatic activity is not shown, as it is assumed shutdown and altered by DBS. (H) , (I) Plots similar to (B) and (C) shown for FSI activity under normal high DA conditions. (J) , (K) Plots similar to (H) and (I) under DBS in PD with correlated noise condition. All results are derived from N=25 simulations.
Fig. S16. Effect of altering STN and GPe membrane current parameters in normal and PD conditions. (A) Raster plot showing spiking activity in all populations during baseline conditions (MSN firing rate: mean±SD=1.13 ± 0.06 spks−1, N=25 simulations) (B) Graphs showing the average (blue) and standard deviation (light blue) of the spectrum of all population activity during baseline conditions. (C) Raster plot showing spiking activity in all populations during PD conditions (MSN firing rate: mean±SD=4.44 ± 0.03 spks−1, N=25 simulations) (D) Graphs showing the average (blue) and standard deviation (light blue) of the spectrum of all population activity during PD conditions. All results are derived from N=25 simulations.
Fig. S17. The effect of stimulating STN somas and not axons at the DBS frequency. (A) Raster plot showing spiking activity in MSN and FSI populations during DBS in PD, with stimulation applied to the somas instead of the axons (MSN firing rate: mean±SD=1.34 ± 0.05 spk·s⁻¹, N=25 simulations). (B) Graphs showing the average (blue) and standard deviation (light blue) of the spectrum of MSN and FSI population activity during the conditions in (A). (C) Raster plot showing spiking activity in MSN and FSI populations during DBS in PD with correlated noise, and with stimulation applied to the somas instead of the axons (MSN firing rate: mean±SD=1.62 ± 0.02 spk·s⁻¹, N=25 simulations) (D) Graphs showing the average (blue) and standard deviation (light blue) of the spectrum of MSN and FSI population activity during the conditions in (C).
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