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Beta-Band Oscillations without Segregated Pathways: the opposing Roles of D2 and D5 Receptors in the Basal Ganglia

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1 **Abstract**

2 The timescales of the dynamics of a system depend on the combination of the timescales of its components
3 and of its transmission delays. Parkinson's disease is characterized by the death of dopaminergic neurons
4 and the emergence of strong β -band (15-35Hz) oscillations throughout the basal ganglia nuclei. Here we
5 combine experimental stimulation data from ten studies, that reveal the timing of excitatory and inhibitory
6 events in the basal ganglia circuit, to estimate its set of transmission delays. In doing so, we reveal possible
7 inconsistencies in the existing data, calling for replications, and we propose two possible sets of transmission
8 delays.

9 We then integrate these delays in a model of the primate basal ganglia, that does not rely on direct and
10 indirect pathways' segregation, and show that, while much attention has been given to the role of the striatal
11 dopaminergic receptors in Parkinson's disease symptoms, extrastriatal dopaminergic depletion in the external
12 part of the globus pallidus and in the subthalamic nucleus is sufficient to generate β -band oscillations in the
13 high part of the band. More specifically, we show that that D2 and D5 dopamine receptors in these nuclei
14 play opposing roles in the emergence of β -band oscillations, thereby explaining how completely deactivating
15 D5 receptors in the subthalamic nucleus can, paradoxically, cancel oscillations.

1 Introduction

Along with bradykinesia, hypokinesia, akinesia and resting tremor, one of the major hallmarks of Parkinson's Disease (PD) is the aberrant β -band (15-35 Hz) oscillatory activity recorded in several nuclei of the Basal Ganglia (Marsden, 1984, 1989, Berardelli et al., 1996, Samii et al., 2004, Berardelli et al., 2001, Mazzoni et al., 2012). Specifically, stronger than normal β -band power has consistently been revealed in EEG and MEG recordings from PD patients and in primate models of PD (Oswal et al., 2013), and is also found in electro-physiological recordings in the sub-thalamic nucleus (STN) and globus pallidus (GP) (Filion and Tremblay, 1991, Nini et al., 1995, Levy et al., 2000, Brown et al., 2001, Kühn et al., 2006, Weinberger et al., 2009). Remarkably, the fact that β -band activity can be restored to normal levels by administration of the DA precursor L-dopa (Brown and Marsden, 1999, Doyle et al., 2005), shows that DA and the intensity of neural activity in the β -band are intimately related (Oswal et al., 2013). However, the specifics of their relationship remain elusive. Traditionally, a change in the balance between the direct and indirect pathways of the basal ganglia (BG) (Albin et al., 1989, Gurney et al., 2001, Frank et al., 2004, Frank, 2005) has been considered to be the origin of the anti-kinetic PD symptoms, later extending to encompass the generation of abnormal oscillations (Humphries et al., 2006, Van Albada and Robinson, 2009, Van Albada et al., 2009, Tsirogiannis et al., 2010, Kumar et al., 2011, Lindahl and Hellgren Kotaleski, 2016).

Although frequent in the computational literature, there is growing experimental evidence suggesting this hypothesis might need partial revision (referred to as the second problem on the basal ganglia, in Nambu, 2008). Specifically, in order to cause this imbalance, striatal medium spiny neurons (MSN) would have to be organized into independent populations that express either D1 or D2 receptors, each then respectively projecting to the internal or external segments of the globus pallidus (GPi/GPe). While striatal pathways may indeed be segregated in mice (e.g., Valjent et al. 2009, but see also Cazorla et al. 2014), tracing studies in monkeys (Parent et al., 1995, Lévesque and Parent, 2005) and rats (Kawaguchi et al., 1990, Wu et al., 2000, Fujiyama et al., 2011) have consistently shown that the majority of MSN projects both to the GPe and GPi.

Thus, at least for monkeys, and possibly for rats, there is considerable anatomical evidence that casts a doubt on the position that these pathways act and interact independently, and that consequently their functional imbalance is the cause of β -band oscillations in the BG. Alternatively, stronger than normal β -band oscillations have also been linked to an imbalance of extra-striate DA receptors (Benazzouz et al., 2014), which are present across all basal ganglia nuclei (Rommelfanger and Wichmann, 2010) and are equally affected by DA loss. However, their roles are still not fully understood.

46 In this study we test the hypothesis that extra-striate DA receptors are sufficient to set the basal ganglia
47 in an oscillatory regime under dopamine depletion, by means of a computational model. To do so we use
48 an existing BG model of the macaque monkey (Liénard and Girard, 2014, see Fig. 1) that we extend with
49 transmission delays as realistic as possible, so as to properly estimate the frequency of these oscillations.
50 The estimation of these delays is based on ten studies (Yoshida et al., 1993, Nambu et al., 2000, Turner and
51 DeLong, 2000, Nambu et al., 2002, Kita et al., 2004, 2006, Tachibana et al., 2008, Iwamuro et al., 2009, 2017,
52 Polyakova et al., 2020) that provide the latency of the excitatory and inhibitory events in all the BG following
53 stimulations applied in the cortex, the striatum, the subthalamic nucleus or the external globus pallidus. The
54 combination of all these data reveal some possibly contradictory measurements, leading us to use two sets of
55 delays. The first one is the best possible compromise that can be established when trying to satisfy all the
56 –possibly contradictory– constraints, while the second one is obtained by removing the data from a single
57 study, so as to minimize experimental data incompatibilities.

58 Using both sets of delays with the Liénard and Girard (2014) model, we simulated the effect of a gradual
59 DA depletion on the dynamics of the neural circuitry by varying the only two free parameters of the model.
60 Our main result shows that as the level of DA transits below a critical boundary, the STN-GPe network starts
61 oscillating within the high part of the β -band. Specifically, our model of the BG shows that D2 dopamine
62 receptors in the STN and the GPe, and D5 dopamine receptors in the STN, play opposing roles for the
63 emergence of β -band oscillations, and are the simplest cause for this phenomenon. The robustness and
64 simplicity of our predictions strongly support abnormal activity of extra-striate dopamine receptors as the
65 cause of parkinsonian oscillations, and that their frequency is set by the axonal transmission delays of the
66 STN-GPe loop.

67 **2 Results**

68 **Transmission Delays in the primate Basal Ganglia**

69 The method we used to estimate the delays between nuclei was based on an exhaustive search, tailored to
70 reproduce the timings recorded during stimulation experiments. All delay combinations were evaluated (taking
71 delay values in the 1-12 ms interval), the latency of an experimentally measured inhibitory or excitatory
72 event was simply compared to the sum of the transmission delays and neural processing time in all the
73 possible pathways, and resulted in a score dependent on the difference between the measurement and the
74 closest pathway prediction (for more details, see section 4.1). This operation yielded a first set of best

| Connection | A | B | C | D | E | F | G | H | Cmpr | Antdrm | NoPlkv |
|------------|-----|---|---|-----|-----|-----|-----|-----|-----------|----------|------------|
| Ctx → Str | 6 | 2 | 4 | N/A | N/A | N/A | 2.5 | N/A | 6 | 9 | 9 |
| Ctx → STN | 5 | 1 | 1 | N/A | N/A | 5.5 | 2.5 | N/A | 4 | 4 | 4 |
| Str → GPe | N/A | 1 | 3 | N/A | N/A | N/A | 7 | N/A | 8 | 4 | 6 |
| Str → GPi | 10 | 1 | 3 | N/A | N/A | N/A | 7 | N/A | 11 | 8 | 8 |
| STN → GPe | N/A | 1 | 1 | 6 | 5 | 6 | 2 | 5 | 9 | 4 | 2 |
| STN → GPi | 5 | 1 | 1 | N/A | N/A | N/A | 4.5 | N/A | 4 | 4 | 4 |
| GPe → STN | N/A | 1 | 1 | 6 | 5 | 6 | 1 | 5 | 1 | 2 | 7 |
| GPe → GPi | N/A | 1 | 1 | N/A | N/A | N/A | 3 | N/A | 1 | 4 | 3/4 |

^A:Leblois et al. (2006a) ^B:Van Albada and Robinson (2009) ^C:Tsirogiannis et al. (2010) ^D:Holgado et al. (2010)
^E:Kumar et al. (2011) ^F:Pavlidis et al. (2015) ^G:Lindahl and Hellgren Kotaleski (2016) ^H:Shouno et al. (2017)

Table 1: Axonal delays in ms from previous computational studies of the primate BG and obtained with our model and fitting method. N/A (not applicable) indicates connections excluded from a given model. Cmpr: compromise solution; Antdrm: solution with antidromic Str → Ctx activations; No-Plkv: solution without the data from Polyakova et al. (2020), see text for more details

75 fitting axonal delays shown in Table 1, in the column labelled *Cmpr*. The first observation deriving from the
76 comparison of the predicted excitation and inhibition events with the data gathered from the experimental
77 stimulation studies (fig. 2, top row), is that this set of delays predicts an unreported inhibitory event in the
78 STN, after a cortical stimulation. This early inhibition however happens 18 ms after stimulation, only 1 ms
79 before the expected late excitation event, and could therefore be masked by the latter and be experimentally
80 undetectable. Indeed, inhibitory events are detected when the firing rate drops below the mean firing rate
81 minus 1.5 standard deviation, for at least two consecutive 1 ms bins (Polyakova et al., 2020).

82 We can observe that the set of event timings reported in Polyakova et al. (2020) has some specificities that
83 impose strong constraints on the results of our search (see Table 2): in this work only were measured event
84 latencies in the STN, caused by striatal and GPe stimulations. In particular, GPe stimulations elicited an
85 extremely fast (as it could begin immediately after the stimulation artifact) *early inhibition* effect, and striatal
86 stimulations elicited an *early excitation*, after 4.6 ms on average. The first effect can be mediated by the direct
87 GPe → STN connection, and indeed such a fast inhibition could not reasonably be the result of a polysynaptic
88 pathway. This thus forces the delay of this projection to take the minimal possible value considered, 1 ms.
89 Using such a short delay here has of course repercussions on a number the latencies of the excitatory and
90 inhibitory events predicted by the model (fig. 2, top). Those, whose pathway use this projection, tend to be

91 in the lower ranges: either close to the average minus one standard deviation (Ctx \rightarrow GPi late excitation,
92 Str \rightarrow STN inhibition, Str \rightarrow GPe excitation, GPe \rightarrow GPi excitation) or even lower (Str \rightarrow GPi excitation).

93 The second effect, i.e. the STN excitation following a striatal stimulation in less than 5 ms, seems to be
94 in contradiction with previous data. The shortest pathway supporting this effect within the basal ganglia is
95 the Str \rightarrow GPe \rightarrow STN one. But the results of Kita et al. (2006) and Yoshida et al. (1993) suggest that the
96 Str \rightarrow GPe pathway has an average latency of 10ms, implying that the Str \rightarrow GPe \rightarrow STN pathway should
97 be longer than that, and are thus not compatible with a twice smaller total latency. A pathway through the
98 thalamus, not included in the search we performed, would not solve the apparent contradiction: it would be
99 a Str \rightarrow GPi \rightarrow Th \rightarrow STN pathway, that goes through the Str \rightarrow GPi connection, whose latency (Kita et al.,
100 2006, Yoshida et al., 1993) is also larger than 10 ms.

101 This first set of delays thus appears to be the best possible compromise (*Cmpr* column in Table 1) to
102 reconcile these two new short-latency events presented in (Polyakova et al., 2020) with the previously available
103 data, but is yet not fully satisfactory.

104 One possibility, to solve the apparent contradiction concerning the early Str \rightarrow STN excitation, would
105 be to find another pathway to handle this effect. We explored the possibility that this observation would
106 result from an antidromic activation of the cortex, that would then excite the STN. Including this new
107 pathway in the search resulted in the *Antdrm* set of delays (Table 1 and Fig. 2, middle). This second set of
108 delays now predicts an early Ctx \rightarrow STN inhibition that should be detectable, as it happens 5 ms before the
109 documented late excitation. Moreover, while using this antidromic pathway allows the Str \rightarrow STN excitatory
110 event latency to fit nicely in the expected interval, it is also recruited to explain the Str \rightarrow STN inhibitory
111 event, the Str \rightarrow GPe excitatory event and the Str \rightarrow GPi excitatory event, causing these latencies to become
112 quite low (almost two standard deviations away from the averages documented in the experimental data).
113 The introduction of this hypothesis of an antidromic activation is thus not satisfactory, as it solves some
114 problems but simultaneously introduces new ones.

115 Finally, we searched what would be the best set of transmission delays if we discarded the data from
116 (Polyakova et al., 2020). The resulting set (*NoPlkv* column in Table 1) also predicts a detectable inhibitory
117 event in the STN after cortical stimulation, as it happens 9 ms before the late excitatory event. The other
118 limitations of this third set of delays are: the conjunction of a Ctx \rightarrow STN late excitation latency that is a
119 bit too large, while the following final inhibition is a bit too low; Str \rightarrow GPe and \rightarrow GPi excitation latencies
120 that are also in the lower range. On this restricted set of data, it scores better than the *Cmpr* set, but is also
121 not fully satisfactory.

122 As such, in the remainder of the article, we will both use the *Cmpr* and the *NoPlkv* sets, and thus
123 duplicate all simulations.

124 Many previous computational studies assumed the STN \rightarrow GPe and GPe \rightarrow STN axonal delays to be
125 similar or equal (Table 1). By contrast, all our candidate explanations yield largely different delays for these
126 projections in the three considered delay sets. Surprisingly, the *Cmpr* set and the *NoPlkv* set have opposite
127 tendencies: the STN \rightarrow GPe is the slowest projection (9 ms) according to the *Cmpr* set, while it is the
128 GPe \rightarrow STN (7 ms) according to the *NoPlkv* one.

129 An intuitive explanation for the imbalance of these two delays inside the same loop may be gained by
130 observing the timing of the early excitation of GPe after cortical stimulation (recorded after roughly 9 ms
131 in Nambu et al., 2000, Kita et al., 2004, cf. Table 3). The quick early excitation of GPe is most likely to
132 be conveyed through the Ctx \rightarrow STN \rightarrow GPe pathway, since the alternative pathway Ctx \rightarrow Str \rightarrow GPe
133 \rightarrow STN \rightarrow GPe involves several other loops and is incompatible with other timings. Furthermore, given that
134 the Ctx \rightarrow STN connection conveys excitatory events in about 6 to 7 ms (Nambu et al., 2000, Iwamuro et al.,
135 2009, 2017, Polyakova et al., 2020), the STN \rightarrow GPe connection delay has to be around 2 to 3 ms. Intuitively,
136 such a quick STN \rightarrow GPe connection implies a slow GPe \rightarrow STN connection in order to satisfy the other
137 timing constraints within the basal ganglia (Table 3 and 2). For example, the Ctx \rightarrow GPe, the Str \rightarrow GPe,
138 the Str \rightarrow GPi and GPe \rightarrow GPi late excitatory events all transit through the STN \leftrightarrow GPe loop. This is
139 indeed what the *NoPlkv* set predicts. Mechanistically, this delay imbalance is consistent with the potential
140 myelination of glutamatergic STN axons. Corroborative with the *NoPlkv* set, evidence of the existence of
141 STN axons myelination has been reported in monkey and rat studies (Yelnik and Percheron, 1979, Koshimizu
142 et al., 2013). Incidentally, a detailed computational study of STN neurons has shown that their myelination
143 may mediate the therapeutic effects of deep brain stimulation (Bellinger et al., 2008). On the contrary, and
144 as previously mentioned, the *Cmpr* set is heavily constrained by the minimal GPe \rightarrow STN latency required
145 by the (Polyakova et al., 2020) data, such that the STN \rightarrow GPe delay is used to compensate and prolong the
146 duration of the transit of the signals inside the STN \leftrightarrow GPe loop.

147 **Conditions for the Emergence of β -Band Oscillations**

148 We simulated the effect of extra-striatal DA depletion on both the pre-synaptic D2-like receptors in the GPe
149 and the STN, and the post-synaptic D5 receptors in the STN (See Eqs. 10 and 11), while incorporating the
150 axonal delays described in the previous section. Our results show that an increase of the PSP amplitude
151 in the GPe and the STN and a not too strong increase of the mean threshold between resting and firing

152 rates in the GPe and the STN generate an oscillatory regime for both sets of delays (dark-blue regions of
153 the parameter exploration matrices of Figs. 3A and 4A). This oscillatory regime affects all the simulated
154 populations (fig. 5), and because of the fundamental differences in the transmission delays in the STN \leftrightarrow GPe
155 loop for the two considered sets of delays, the STN peak activity precedes the GPe one (fig. 5, "GPe & STN"
156 panels) with a longer duration with the *Cmpr* one (11 ms) than with the *NoPlkv* one (3 ms). The frequency
157 of these oscillations are in the upper β -band, with an average frequency of 32Hz for the *Cmpr* set of delays,
158 and 35Hz for the *NoPlkv* one (panels B of figs. 3 and 4). It is interesting to note that in the normal regime of
159 operation (power spectra in figs. 3C and 4C), the tendency of the model to favour these frequencies is already
160 visible.

161 The conditions of generation of a high- β oscillatory behaviour in the STN and the GPe, when simulating
162 extra-striate dopaminergic depletion, require a trade-off between the facilitation of the PSP, driven by the D2
163 receptors and the weakening of the STN excitability by the D5 receptors.

164 It is worth noting that although our simulations also reported oscillatory activity following DA depletion
165 in other nuclei such as the GPi and Striatum, including MSN and FSI cells (Fig. 5), these oscillations did not
166 originate locally. Replacing the simulated pallido-striatal and subthalamo-striatal activities with synthetic
167 signals mimicking the baseline obtained in the normal condition, cleared the striatal oscillatory activity (figs. 6
168 and 7, "no feedback to striatum" panels), thus confirming the GPe \leftrightarrow STN origin of the oscillations. By
169 contrast, if the GPe \rightarrow FSI connection remained active (see Fig. 6 and 7, "GPE \rightarrow FSI enabled" panels), the
170 oscillations re-emerged in the Striatum. Note also that keeping this feedback connection active, and thus the
171 MSN \rightarrow GPe \rightarrow FSI \rightarrow MSN loop, increased the amplitude of the oscillations in the GPe and the GPi. The
172 GPi provides no input to other basal ganglia nuclei, and thus cannot be involved in the observed emergence
173 of oscillations. In conclusion, oscillatory activity in the Striatum and GPi does not originate locally, but is
174 conveyed from the phase-locked oscillatory activity of the GPe \leftrightarrow STN loop.

175 The frequency of the oscillations depended essentially on the projection delays between the GPe and
176 the STN. We explored, for both sets of delays, the changes on oscillation frequency caused by all possible
177 variations of the GPe \rightarrow STN and the STN \rightarrow GPe delays between 1 and 13ms (Fig. 8), while keeping the
178 rest identical: the sum of these delays clearly defines the oscillation frequency.

179 **3 Discussion**

180 This study has proposed a simple method to combine the existing stimulation experiments used to measure
181 the latency of excitatory and inhibitory events in the basal ganglia, so as to estimate the transmission delays
182 in the various connections of the circuit. This method highlighted some apparent contradictions in the
183 experimental data concerning the GPe to STN projection, which led us to propose two sets of delays, a first
184 one providing the best possible compromise resulting from this data, and a second one ignoring the measures
185 obtained in the Polyakova et al. (2020) study that introduced the potential contradiction (columns *Cmpr*
186 and *NoPlkv* in table 1, respectively).

187 We have also shown that specific changes of biophysical properties within the GPe-STN loop are sufficient
188 to trigger oscillations in the high β -band. These predictions resulted from the introduction of these sets
189 of delays within a computational model of the macaque monkey basal ganglia, fitted from over a hundred
190 independent anatomical and physiological experimental data in macaque monkeys (Li enard and Girard, 2014).
191 Although this model contains numerous parameters, it is important to notice that these were optimized
192 to fit to healthy non-human primate data. By contrast, the results and predictions of this study result
193 from varying two free parameters only, which model the process of DA depletion in GPe and STN: the D2
194 PSP amplification and D5 firing threshold increase (Figs. 3 and 4). A first prediction of our model is that
195 extra-striate D2 receptors (in the GPe and the STN) and D5 receptors (in the STN) play opposing roles in
196 the generation of β -band oscillations when DA decreases: D2 receptors cause them to appear and gradually
197 increase their intensity, and D5 receptors attenuate them. A second prediction is that decreasing the STN
198 D5 receptor activity beyond its constitutive activity (i.e. degrade the D5 receptors normal behaviour even
199 stronger than with DA depletion) would shift the dynamics of the system towards a steady state with no
200 oscillations (see Fig. 3 and 4, shift from the dark-blue to the light-blue area along the STN θ offset axis).
201 This is consistent with observations by Chetrit et al. (2013), who showed that diminishing the D5 receptor
202 constitutive activity in the STN of 6-OHDA PD rats did cancel abnormal neuronal activity and reversed motor
203 impairment. Finally, the oscillatory activity reported in other nuclei (e.g. within the FSI-MSN circuitry)
204 does not originate locally, but is rather relayed by projections from the GPe/STN loop (figs. 6 and 7).

205 **Axonal delays**

206 Numerous stimulation studies participated in characterizing transmission delays across different neuronal
207 groups of the BG circuitry (Yoshida et al., 1993, Turner and DeLong, 2000, Nambu et al., 2000, 2002, Kita

208 et al., 2004, 2005, 2006, Tachibana et al., 2008, Iwamuro et al., 2009, 2017, Polyakova et al., 2020), to the
209 best of our knowledge, this work is the first to combine these experimental studies by computational means
210 in order to determine the set of delays that could be compatible with all of them. In a review dedicated
211 to the GPe, Jaeger and Kita (2011) proposed in their Fig. 1 a summary of the results obtained by the
212 then-available stimulation studies, in which a set of transmission delays was proposed to explain the latencies
213 of excitatory and inhibitory events (panel A of their fig. 1). The details of the method used to propose this
214 set of delays was unfortunately not documented in the main text. We have evaluated the score of this set
215 with our method (Fig. 9), it clearly performs worse than the sets reported in this manuscript. In particular,
216 it tends to underestimate the latency of all the late effects. Interestingly, this set of delays also predicts an
217 early inhibition in the STN after cortical stimulation (with a 10 ms latency), before the late excitation and
218 the final inhibition. In the panel B of their Fig. 1, they suggest that this inhibition would be sufficient to
219 stop the STN early excitation, but may not be strong enough to generate an inhibitory event *per se* (i.e. a
220 decrease of the activity below the baseline, strong enough and long enough to be categorised as an inhibitory
221 event), explaining why its is not reported in experimental studies.

222 As mentioned above, the results from (Polyakova et al., 2020) raise questions that require further
223 investigation on both the experimental and the modeling sides. First, the extremely short transmission
224 delay from the GPe to the STN (1 ms) measured in this study imposes, in order to stay as much as possible
225 coherent with the rest of the data, a STN to GPe delay (9 ms) that is much larger than what suggests the
226 Nambu et al. (2000) direct measure (5.5 ± 2.3 ms). Second, the 5 ms delay between a striatal stimulation
227 and an excitatory event in the STN does not appear to be compatible with the most obvious and shortest
228 pathways for its transmission (Str \rightarrow GPe \rightarrow STN or Str \rightarrow GPi \rightarrow Th \rightarrow STN), as they recruit projections
229 whose transmission delay is at least 10 ms (Str \rightarrow GPe or Str \rightarrow GPi). However, the apparent inconsistency
230 of these measures may purely result from the limitations of our methodology: we adopted a very crude way
231 of estimating the total duration of the transmission of a stimulation along a pathway (summing transmission
232 delays with a neural processing delay common to all BG neural populations), which does not honour the real
233 complexity of the dynamics of the basal ganglia neural circuit, and we cannot also exclude the possibility that
234 we neglected possible alternate transmission pathways, especially those that would transit outside the basal
235 ganglia proper. A more subtle approach to model these phenomena may thus help solving these paradoxes.
236 Nevertheless, an experimental replication of the STN recordings following striatal and GPe stimulations
237 would be quite useful to ascertain that the sources of these potential inconsistency come from the model.

238 **Striatal and extra-striatal contributions to pathology**

239 Our results suggest that β -band oscillations may arise in the BG circuitry when DA is scarce, irrespective of
240 the effect of DA depletion onto DA receptors in the MSN and the FSI in the Striatum, which our model
241 deliberately excludes. Although the extent to which Striatal cells contribute to these oscillations remains
242 to be addressed, our results show that the direct/indirect pathway segregation may be neither central nor
243 necessary to understand the PD oscillatory phenomena in primates.

244 By removing our focus from the segregation of striatal D1/D2 receptors, we implicitly assumed that the
245 excitatory and inhibitory effects of DA in the striatum cancel each other, yielding no effect on MSN firing rate
246 in average. Consistently with this, electrophysiological studies in primates reported no change in the striatal
247 firing rate after MPTP injection (Goldberg et al., 2002). Furthermore, the modification of the distribution of
248 the firing rates in the MSN population (decreased activity in D1 neurons, increased activity in D2 ones) would
249 exert little influence on the STN \leftrightarrow GPe loop, as a consequence of the massively collateralized striato-fugal
250 projection in primates (Parent et al., 1995, Lévesque and Parent, 2005, Nadjar et al., 2006).

251 Finally, we did not model the effect of DA depletion on the GPi, first, because experimental data on
252 the effects of such depletion is incomplete and contradictory effects have been reported (Rommelfanger
253 and Wichmann, 2010), and second, because the GPi projects only outside the modeled BG circuitry, and
254 thus cannot participate in the local generation of oscillations. Should the model be extended to encompass
255 the cortico-baso-thalamo loops, the GPi would become a central actor of these loops, and as such would
256 participate actively in their dynamics. Modeling GPi DA receptor would then become essential to determine
257 the effects of DA depletion across the circuit.

258 The expression of D5 receptors in the GPe, similar to what is found in the STN, and their effect on
259 neural activity is unclear (Rommelfanger and Wichmann, 2010). Thus, for the sake of completeness, we
260 simulated the same increase of the firing threshold in the GPe as in the STN. Adding that modulation only
261 marginally modifies the reported boundaries of the oscillation region in the parameter space (fig. 10, A and
262 C). Indeed, isolating the effect of these putative GPe receptors by removing the D5 modulation in the STN
263 revealed that increasing the firing threshold of the GPe does not really affect the emergence of oscillations.
264 This suggests that cancelling the constitutive activity of D5 receptors in the GPe should not replicate the
265 electrophysiological and motor observations Chetrit et al. (2013) obtained in the STN.

266 A clear limitation of the model is that the oscillations it generates are in the highest part of the β -band,
267 while MPTP monkeys rather exhibit oscillations in the lower range (Tachibana et al., 2011). This may result

268 from a number of simplifications of our model. First, the dynamics of the simulated neural populations
269 depend exclusively on the dynamics of the post-synaptic potentials at the synaptic level, no other internal
270 dynamics of the neuron itself is simulated, that could dampen the oscillations. Second, no synaptic adaptation
271 mechanisms were included, while (Shouno et al., 2017) suggest that short-term facilitation and depression
272 participate in the GPe-STN loop behaviour. Investigating whether these simplifications are sufficient to
273 explain this discrepancy is the matter of future work.

274 Theories of β -band Oscillations

275 There are several theories for the origin of β -band oscillations in the BG: the *striatal origin theory*, based
276 on the hypothesis of changes of intrinsic properties of striatal MSNs (McCarthy et al., 2011); the *striatal*
277 *inhibition theory* on the increased striatal inhibition by means of the D2 neurons on the GPe-STN loop
278 (Kumar et al., 2011, Lindahl and Hellgren Kotaleski, 2016); and the *FSI loop theory*, which posits that (in
279 mice) the GPe to Striatum feedback projection (through the FSI) is the cause of the oscillations (Corbit
280 et al., 2016). When it comes to explain primate data, these theories have been nevertheless challenged by
281 experimental evidence showing that the GPe still exhibits oscillatory behaviour after having severed its
282 inhibitory inputs from MSN (Tachibana et al., 2011), and by the absence of segregated striato-fugal pathways.
283 Concerning the *FSI loop theory*, our results show that, in primates, the role of the MSN-GPe-FSI loop is
284 consistent with a relay transferring GPe-STN oscillations back to the striatum (see Figs. 6 and 7), and
285 that it is unlikely to be a source. Additionally, Van Albada and Robinson (2009), Van Albada et al. (2009)
286 introduced the hypothesis of the *thalamo-cortical loop* being the primary cause of oscillation. Again, this
287 hypothesis seems unlikely, as (1) it requires the segregation of direct/indirect pathways which is non-existent
288 or partial in primates, and (2) it is severely constrained by long intrinsic delays, which are more suitable to
289 sustain θ than β -band oscillations (Leblois et al., 2006b). Finally, Pavlides et al. (2015) showed that it is
290 possible for a properly parametrized cortico-basal model encompassing three loops (the STN \leftrightarrow GPe, the
291 intra-cortical and the cortico-basal) to contribute to the emergence of β oscillations, without any of them
292 being capable of autonomously sustaining them.

293 By contrast to the aforementioned hypotheses and models show that the STN \leftrightarrow GPe loop of primates
294 is ready to oscillate autonomously in the β -band by simply increasing the coupling between both nuclei.
295 Furthermore, although previous research had already hinted this loop to be the source of sustained β -band
296 oscillations (Gillies et al., 2002, Terman et al., 2002), we are first to pinpoint the opposing roles of D2 and D5
297 extrastriate receptors in the emergence of these oscillations.

298 Together with our results, three other independent studies had suggested the GPe-STN loop to be crucial
299 to generate oscillations in the β -band. However, they exhibit some degree of inconsistency with experimental
300 data, either in their assumptions or in their implementation, or rely on additional mechanisms not required
301 in our parsimonious model. First, Tsirogiannis et al. (2010) used unrealistic brief transmission delays (1 ms
302 for both GPe \rightarrow STN and STN \rightarrow GPe connections, cf. Table 1), assumed PD to influence the time-course
303 of post-synaptic potentials, and relied on the existence of segregated direct/indirect pathways. Likewise,
304 Nevado Holgado et al. (2010) stressed the importance of the transmission delays in this loop to set the
305 oscillation frequency. However, they assumed PD to yield an unrealistically strong change of synaptic strength
306 (two-fold increase for GPe \rightarrow GPe, almost four-fold for cortex \rightarrow STN, almost ten-fold for striatum \rightarrow GPe and
307 GPe \rightarrow STN). Finally, in their recent spiking model, Shouno et al. (2017) showed that STN-GPe oscillations
308 could emerge if post-inhibitory rebound excitation at the STN level and short-term plasticity in both STN
309 and GPe were introduced. Our model shows that these mechanisms are nevertheless not required.

310 Humphries et al. (2006) have shown that GPe-STN oscillations in rats would yield γ -band and slow
311 (< 1 Hz) oscillations. To assess the generality of our hypothesis, we transferred the delays of Humphries et al.
312 (2006) to our primate model, as to test whether the predicted frequency of our model would also match data
313 obtained experimentally on that species. Interestingly, when changing the transmission delays of our model
314 to those of the rodent literature (namely 4ms for GPe \rightarrow STN and 2ms for STN \rightarrow GPe), our predicted
315 oscillation frequency shifted to 44 Hz (Fig. 8), a value reasonably close to those recorded in rats (53-55 Hz).
316 Although cautiously, this may suggest a common principle of oscillation across both species. Note however
317 that experimental results tend to suggest that the mechanisms of abnormal oscillations in PD models can be
318 different from one species to another: the involvement of the STN reported in monkeys (Tachibana et al.,
319 2011) hasn't been found in mice (de la Crompe et al., 2020).

320 4 Methods

321 4.1 Characterization of Delays between Primate Basal Ganglia Nuclei

322 For our model to make sensible predictions about the naturally occurring frequencies of oscillation across
323 basal ganglia nuclei, it was first required to establish the typical transmission delays across them for the case
324 of the macaque brain, which are not directly available. Instead, we had to derive them from the latencies
325 between excitatory and inhibitory events recorded during stimulation studies (Yoshida et al., 1993, Turner
326 and DeLong, 2000, Nambu et al., 2000, 2002, Kita et al., 2004, 2006, Tachibana et al., 2008, Iwamuro et al.,

2009, 2017, Polyakova et al., 2020). Therefore, it was first necessary to develop a methodology to properly identify the combinations of pathways and transmission delays involved in each experimental data set (see Tables 2, 3 and 4), so as to extract the specific delays across basal ganglia nuclei.

To that end, we considered all known connections within the BG (Fig. 11A), with the exception of the sparse projections from STN to Striatum and from GPe to Striatum (Jaeger and Kita, 2011). Indeed, STN stimulation fails to elicit MSN activity (Kita et al., 2005); and although cortical stimulation elicits MSN overactivity, this is not followed by a noticeable second excitation which would have signaled a rebound mediated by the STN (Nambu et al., 2002). Also, if the GPe to Striatum projection were functionally active in stimulation studies, we would expect the subsequent inhibition of the GPe to cause MSN overactivity, an event which has not been observed experimentally (Nambu et al., 2002). Notice that the resulting simplification of the BG connectivity graph is also in line with the results of our previous study (Liénard and Girard, 2014) which showed that the influence of these pathways on the striatum could only be potent if they targeted the FSI. Hence, they could only influence the MSN by silencing them through interneurons, and as MSN are already mostly silent at rest, this should not have observable consequences on the other nuclei.

To match the timings between excitatory and inhibitory events reported in the literature, we first deployed the graph of the projections potentially involved into series of candidate pathways (Fig. 11 discussed in next section). We further trimmed down the number of pathways by excluding highly recurrent ones as to lower the computational complexity of the search. We limit in particular the number of iterations through the STN↔GPe loop to two, as more iterations would result in latencies that are too long; other exclusions are discussed in details in section 4.1.1. The resulting set of candidate pathways that are summarized along with the experimental timing references in Tables 2, 3 and 4. Note that some of the studies we include here stimulated different cortical areas, for example Nambu et al. (2000) stimulated the primary motor area (M1) as well as the supplementary motor area (SMA). In such cases, we rely on the shortest latency reported per study.

We then perform an exhaustive exploration of the space of axonal delays to find the best fit. In order to achieve this, we compute the time that would be needed by each pathway in a simplified model to match to the experimentally recorded delay, and score the fit of the quickest pathway with experimental data. To aid the optimization process, all delays were constrained to assume biologically plausible values (1-12 ms). Our exhaustive search to find the optimal fit thus implied the evaluation of all the 12^8 (≈ 430 million) possible combinations. Each combination was assigned a score dependent on the amount of experimental data it was able to replicate.

| Stim. | Rec. | Response | Candidate pathways | Latency (ms) |
|------------|---|---|-------------------------|-------------------------|
| Str | GPe | inhibition | Str → GPe | 10.5 ± 3.2 ^A |
| | | | | 10.4 ± 7.4 ^B |
| | excitation | Str → GPe → STN → GPe | 26.5 ± 6.7 ^A | |
| | | (Ctx ← Str antidromic); Ctx → STN → GPe | | |
| | GPi | inhibition | Str → GPi | 13.1 ± 3.5 ^A |
| | | | | 10.4 ± 7.4 ^B |
| excitation | Str → GPe → STN → GPi | 27.5 ± 6.7 ^A | | |
| | (Ctx ← Str antidromic); Ctx → STN → GPi | | | |
| STN | excitation | Str → GPe → STN | 4.6 ± 2.4 ^C | |
| | | (Ctx ← Str antidromic); Ctx → STN | | |
| inhibition | Str → GPe → STN → GPe → STN | 37.8 ± 14.6 ^C | | |
| | (Ctx ← Str antidromic); Ctx → STN → GPe → STN | | | |
| STN | GPe | excitation | STN → GPe | 5.5 ± 2.3 ^D |
| | GPi | excitation | STN → GPi | 4.7 ± 1.9 ^D |
| GPe | GPi | inhibition | GPe → GPi | 4.6 ± 1.6 ^E |
| | | | GPe → STN → GPi | |
| | excitation | GPe → STN → GPe → GPi | 21.4 ± 8.6 ^E | |
| | | GPe → STN → GPe → STN → GPi | | |
| STN | inhibition | GPe → STN | 2.0 ± 2.0 ^C | |
| | | excitation | GPe → STN → GPe → STN | 12.7 ± 4.1 ^C |

^A:Kita et al. (2006) ^B:Yoshida et al. (1993) ^C:Polyakova et al. (2020) ^D:Nambu et al. (2000) ^E:Tachibana et al. (2008)

Table 2: Summary of the candidate pathways and reference data in ms (Part 1). The column "Stim." indicates the location of the stimulation; "Rec." indicates the location of the recording; "Response" indicates the type of response recorded; the candidate pathways along the quantitative data expressed as mean±SD constitute the remainder of the table. In the case of striatal stimulation, we also consider pathways involving antidromic excitation of cortical axons, noted as "Ctx ← Str antidromic" (see methods for details).

| Stim. | Rec. | Response | Candidate pathways | Latency (ms) | |
|-------|------|------------|---|--|--|
| Ctx | Str | excitation | Ctx → Str | 10.2 ± 2.5^A 8.5 ± 5.9^B | |
| | | | early exc. | Ctx → STN | 5.8 ± 4.5^C 7.0 ± 1.7^D 6.7 ± 1.8^E 5.4 ± 1.4^F |
| | STN | late exc. | Ctx → Str → GPe → STN | 19.8 ± 5.3^C | |
| | | | Ctx → STN → GPe → STN → GPe → STN | 16.7 ± 2.8^D 17.8 ± 3.8^E 16.8 ± 4.1^F | |
| | | | final inhibition | Ctx → Str → GPe → STN → GPe → STN | 32.3 ± 11.8^C |
| | | | Ctx → STN → GPe → STN | | |
| | GPe | early exc. | Ctx → Str → GPe → STN → GPe | 9.2 ± 3.8^C | |
| | | | Ctx → STN → GPe | 8.7 ± 1.3^G 9.2 ± 2.0^E | |
| | | | inhibition | Ctx → Str → GPe | 16.9 ± 4.4^C |
| | | late exc. | Ctx → STN → GPe | 16.9 ± 2.0^G 24.6 ± 5.1^H 16.7 ± 3.0^E | |
| | | | Ctx → Str → GPe → STN → GPe | 25.8 ± 2.6^C | |
| | | | Ctx → STN → GPe → STN → GPe → STN → GPe | 30.8 ± 1.9^G 28.1 ± 4.4^E | |

^A:Nambu et al. (2002) ^B:Turner and DeLong (2000) ^C:Nambu et al. (2000) ^D:Iwamuro et al. (2009) ^E:Iwamuro et al. (2017)
^F:Polyakova et al. (2020) ^G:Kita et al. (2004) ^H:Yoshida et al. (1993)

Table 3: Summary of the candidate pathways and reference data (Part 2). See Table 2 for notations.

| Stim. | Rec. | Response | Candidate pathways | Latency (ms) |
|-------|------|------------|---|------------------|
| | | | Ctx → Str → GPe → STN → GPi | 7.8 ± 2.4^A |
| | | early exc. | Ctx → STN → GPi | 9.2 ± 2.2^B |
| | | | Ctx → STN → GPe → STN → GPe → GPi | 10.0 ± 2.6^C |
| | | | | 20.9 ± 5.0^A |
| | | | | 19.4 ± 3.0^B |
| Ctx | GPi | inhibition | Ctx → Str → GPi | 19.4 ± 4.6^C |
| | | | | 24.6 ± 5.1^D |
| | | | Ctx → Str → GPe → STN → GPi | 29.9 ± 6.5^A |
| | | late exc. | Ctx → STN → GPi | 32.6 ± 8.7^B |
| | | | Ctx → STN → GPe → STN → GPe → GPi | 28.2 ± 5.2^C |
| | | | Ctx → STN → GPe → STN → GPe → STN → GPi | |

^A:Nambu et al. (2000) ^B:Tachibana et al. (2008) ^C:Iwamuro et al. (2017) ^D:Yoshida et al. (1993)

Table 4: Summary of the candidate pathways and reference data (Part 3). See Table 2 for notations.

358 4.1.1 Pathways involved in the stimulation experiments

359 Stimulations in the cortex, Str, STN or GPe result in an intricate superposition of excitatory and inhibitory
360 effects that could be supported by a multitude of different pathways. We could however simplify the connection
361 graph to rule out several pathways. We will successively review the different stimulation locations, the
362 excitatory or inhibitory responses that they cause and the pathways that could be mediating these responses
363 (Fig 11A).

364 First we considered the case of the striatal stimulation (Fig. 11B). Following this stimulation, GPe and
365 GPi neurons are first inhibited, then excited (Kita et al., 2006). The artificial blockade of STN eliminates the
366 excitation but does not affect the inhibition (Kita et al., 2006), hence the STN is required for the excitation.
367 The excitation can thus not possibly be mediated by the (Str → GPe → GPi) chain because it does not
368 involve the required STN, so we can rule out pathway number 1 of Fig. 11B. Furthermore, the artificial
369 blockade of STN does not change the timing of the inhibition, so we can also rule out the pathways number 2
370 and 3 of Fig. 11B because the chains (Str → GPe → STN → GPe → GPi) and (Str → GPe → STN → GPe
371 → STN → GPe → GPi) involve the STN and result in an inhibition of GPi.

372 Next we considered a stimulation in the STN (Fig. 11C). Following this, more than 80% of the responding

373 neurons in the globus pallidus are excited (Nambu et al., 2000). As this excitation is not followed by an
374 observable inhibition, we can rule out the pathways numbered 1, 2 and 3 of Fig. 11C because they would lead
375 to an underactivity either in GPe or GPi.

376 We then considered the GPe stimulation (Fig. 11D). In this experiment, only half of the GPi neurons
377 show an early excitation occurring fast (3.4 ± 0.9 ms), and they all show later an inhibition that is followed
378 by an excitation (Tachibana et al., 2008). This early excitation can hardly be explained by the basal ganglia
379 pathways, because the chains finishing earliest in the GPi, i.e. (GPe \rightarrow STN \rightarrow GPi) and (GPe \rightarrow GPi),
380 result in an inhibition. The (GPe \rightarrow Str \rightarrow GPi) chain could possibly account for this early excitation,
381 however we did not include the GPe \rightarrow MSN pathway as it does not seem to be involved in these stimulation
382 experiments (c.f. the beginning of this section), and furthermore the latency of this excitation is clearly
383 too fast to be mediated through the slow Str \rightarrow GPi connection. Finally, as discussed in Tachibana et al.
384 (2008), the early excitation could be mediated by STN axons targeting both the GPe and GPi. As this does
385 account for the fact that only half of GPi neurons respond and as other pathways can not plausibly explain
386 an early excitation that is this fast, we will not consider further this early excitation. We can also rule out
387 the pathways numbered 1 and 2 because they suppose a late inhibition following the reported inhibition and
388 excitation in GPi, and Tachibana et al. (2008) did not report such a late inhibition.

389 Finally, Fig. 11E-F illustrates the case of the *cortical stimulation*. This stimulation leads to three
390 distinct temporal responses in STN, GPe and GPi (Nambu et al., 2000): an early excitation followed by an
391 inhibition, and finally a late excitation. To understand the possible timecourses of this cortical stimulation,
392 we subdivided it according to the chains beginning with the direct striatal excitation (Fig. 11E) and with
393 the direct subthalamic excitation (Fig. 11F). After the artificial blockade of activity in the STN, Nambu
394 et al. (2000) reported that the GPi does not exhibit the early or late excitation. We can thus deduce that the
395 STN is required for these excitations, so we can rule out the pathway 1 of Fig. 11E corresponding to the
396 chain (Ctx \rightarrow Str \rightarrow GPe \rightarrow GPi) because the STN is not involved in it. Nambu et al. (2000) also reports
397 that after STN blockade, the GPi exhibits the same inhibition, so we deduce that the STN is not part of
398 the chains leading to an inhibition in GPi and rule out the pathways 2 to 6, corresponding to the chains
399 involving the STN and resulting in an underactivity in GPi. No late inhibition has been reported in Nambu
400 et al. (2000), so the pattern of activity "-" then "+" then "-" in the STN is not plausible. We hence rule out
401 the pathway 7.

402 4.1.2 Optimization of inter-nuclei delays

403 To compute the time t needed for the stimulation in "nucleus 1" to flow over a given chain (nucleus 1
404 \rightarrow nucleus 2 \rightarrow ... \rightarrow nucleus n) and to be eventually recorded in "nucleus n ", we use a simple formula:

$$t = \Phi + \sum_{i=1}^{n-1} (\delta_{i \rightarrow i+1} + \xi) \quad (1)$$

405 with $\delta_{i \rightarrow i+1}$ the axonal delay between nuclei i and $i + 1$, Φ the time needed for the stimulation to be
406 effective in nucleus 1 and ξ the time needed to any nucleus to change their firing rate when receiving the
407 stimulation. The time required for the stimulation to be effectively eliciting action potentials is very small, so
408 we set $\Phi = 1$ ms (a value of $\Phi = 0$ ms was also considered and led to similar results). The time required
409 for the action potential once at the synapse level to be captured by the postsynaptic neuron and to change
410 its potential was considered to be $\xi = 1$ ms, equal for all populations for the sake of simplicity. This latter
411 constant is justified from the shape of the change of intensity after a spike mediated by either AMPA or
412 GABA_A, because it is already significant after 1 ms (Destexhe et al., 1998) and is in line with the alpha
413 functions that we used in the BCBG model (Liénard and Girard, 2014).

414 While most pathways modeled involve successive action potentials, we also test separately the existence of
415 cortical antidromic activation of pyramidal tract neurons at striatal stimulation sites. Indeed, such activation
416 of PTN neurons has been observed or hypothesized, resulting then in the direct excitation of the STN through
417 the cortical PTN neurons when stimulating the striatum (Bauswein et al., 1989, Turner and DeLong, 2000).
418 When we model this possibility, we consider that the elicitation of action potentials in cortical neurons is
419 near-instantaneous (Turner and DeLong, 2000) and thus we do not add extra time for its generation. For
420 example, the antidromic pathway that explains the late excitation of GPe after striatal stimulation, noted
421 (*GPe* \leftarrow *Str antidromic*); *Ctx* \rightarrow *STN* \rightarrow *GPe* in Table 2, has a delay computed as if the stimulation was
422 directly originated from the cortical PTN neurons. Its formula then follows the general shape described by
423 Eq. 1, i.e. $t = \Phi + (\delta_{Ctx \rightarrow STN} + \xi) + (\delta_{STN \rightarrow GPe} + \xi)$.

424 As a general rule, each candidate pathway is computed for each response type, and the quickest pathway
425 is assumed to be the one that we observe. The exceptions are the cortical stimulations as they cause an
426 early and a late excitation, in these cases the quickest excitatory response is assumed to correspond to the
427 early excitation and the quickest excitatory response *after the inhibition* is assumed to correspond to the late
428 excitation. Overall, 39 candidate pathways corresponding to 21 couples of (stimulation / recorded response)

429 are checked against 45 experimental data. These experimental data are noted as $T_{i,j} \pm \sigma_{i,j}$ with i the number
430 of the (stimulation/response) pair and j the indice of the reference for each pair, as given in Tables 2 and 3.
431 The global score χ of the fit between the timing of selected pathways and the reference data is then computed
432 as:

$$\chi = \sum_{i=1}^{18} \left(\sum_j \exp\left(\frac{-(t_i - T_{i,j})^2}{2\sigma_{i,j}^2}\right) \right) \quad (2)$$

433 4.2 Computational Model of the Basal Ganglia

434 In this study we focus on the oscillatory activity of the BG circuitry at rest. With the exception of the
435 changes described below (transmission delays optimized to fit to experimental studies and simulation of DA
436 depletion on extra-striate receptors), the model that we present here adopts the mathematical formalism and
437 parameters we previously developed (Liénard and Girard, 2014). Briefly, each nucleus of the basal ganglia is
438 simulated with a mean-field model incorporating the temporal dynamics of neurotransmitters. Inputs from
439 cortical (cortico-striatal neurons, CSN, and pyramidal tract neurons, PTN) as well as thalamic afferents
440 (from the centromedian and the parafascicular nuclei, CM/Pf) are modeled as independent random processes
441 with different average firing rates (Bauswein et al., 1989, Turner and DeLong, 2000, Pasquereau and Turner,
442 2011, Pasquereau et al., 2015). As in Liénard and Girard (2014), the CSN input was simulated as a Gaussian
443 process centered around 2 Hz, PTN around 15 Hz and CM/Pf around 4Hz. The simulations presented here
444 were obtained using a standard deviation of 2 Hz, corresponding to a high noise in the neuronal activities.
445 The oscillatory patterns obtained with this noise level were similar to those obtained with a lower standard
446 deviation of 0.5 Hz.

447 The parameter search in Liénard and Girard (2014) extended over more than one thousand optimal model
448 parametrizations that were equally maximizing the plausibility scores defined in that study. An additional
449 assessment showed that the most of variability in these solutions is small jitter ($< 10^{-6}$ in a search space
450 normalized within $[0, 1]$) around 15 different base solutions. Thus we restricted our study to these 15 base
451 solutions, as they globally represent the optimal parametrizations of the basal ganglia obtained in Liénard
452 and Girard (2014), as we did in (Girard et al., 2021).

453 The structure of the model is very close to the one presented in Liénard and Girard (2014), with the
454 exception of the addition of plausible axonal delays and the simulation of dopamine depletion on extrastriate

455 receptors. We use a population model with mean-field formulation. Although we provide here the basic
 456 equations of our model, more details about mean-field models can be found elsewhere (e.g. Deco et al., 2008).

457 One assumption of mean-field models, commonly referred as the *diffusion approximation*, is that every
 458 neuron receive the same inputs from another population. We can hence express the mean number of incoming
 459 spikes with neurotransmitter n per neuron of the population x from population y :

$$\Psi_x^n(t) = \nu_{x \leftarrow y} \phi_k(t - \tau_{y \rightarrow x}) \quad (3)$$

460 with $\nu_{x \leftarrow y}$ the mean number of synapse in one neuron of population x from axons of population y , $\tau_{y \rightarrow x}$
 461 the axonal delay between population y and x , and $\phi_y(t - \tau_{y \rightarrow x})$ the firing rate of population y at time
 462 $t - \tau_{y \rightarrow x}$.

463 The axonal varicosity counts $\nu_{x \leftarrow y}$ is the mean count of synapses in population x that are targeted by
 464 axons from population y :

$$\nu_{x \leftarrow y} = \frac{\mathcal{P}_{y \rightarrow x} N_y}{N_x} \cdot \alpha_{y \rightarrow x} \quad (4)$$

465 with N_x and N_y the neuron counts of populations x and y , $\alpha_{y \rightarrow x}$ the mean axonal varicosity count of
 466 neurons of y with an axon targeting neurons of x , and $\mathcal{P}_{y \rightarrow x}$ the proportion of such neurons in population y .

467 Mean-field models assume that neurons' firing thresholds follow a Gaussian distribution. The mean firing
 468 rate of a population x at time t can then be approximated by:

$$\phi_x(t) = \frac{S_x^{\max}}{1 + \exp\left(\frac{\theta_x - V_x(t)}{\sigma'}\right)} \quad (5)$$

469 with $V_x(t)$ the mean potential at the soma at time t , S_x^{\max} the maximal possible firing rate, θ_x the mean
 470 difference between resting and firing thresholds, and, as per Van Albada and Robinson (2009), $\sigma' = \sigma \frac{\sqrt{3}}{\pi}$ (σ
 471 being the standard deviation of the firing thresholds).

472 The post-synaptic potential (PSP) change to the membrane potential at the location of the synapse

473 contributed by a single spike is modeled by the alpha function (Rall, 1967):

$$\Delta V_0^n(t) = ADte^{-Dt} \quad (6)$$

474 where A and D relate to the amplitude and duration of PSP and depend on the neurotransmitter n
 475 mediating the spike. They are computed as follows: $A = A_n \exp(1)$ and $D = \frac{\exp(1)}{D_n}$ (Tsirogiannis et al.,
 476 2010), using the constants reported in Liénard and Girard (2014).

477 We also model in a simple way the attenuation of distal dendrites as a function of the soma distance. By
 478 modeling the dendritic field as a single compartment finite cable with sealed-end boundaries condition (Koch,
 479 2005), we can express for population x :

$$\Delta V_{\text{soma}}^n(t) = \Delta V_0^n(t) \frac{\cosh(L_x - Z_x)}{\cosh(L_x)} \quad (7)$$

480 with $\Delta V_0^n(t)$ the potential change at the synapse, L_x the electrotonic constant of the neurons and Z_x
 481 the mean distance of the synaptic receptors along the dendrites. We further express this mean distance as a
 482 percentage of L_x : $Z_x = p_x L_x$. The electrotonic constant is then calculated according to (Koch, 2005):

$$L_x = l_x \sqrt{\frac{4}{d_x} \frac{R_i}{R_m}} \quad (8)$$

483 with R_i the intracellular resistivity, R_m the membrane resistance, l_x the mean maximal dendritic length
 484 and d_x the mean diameters of the dendrites along their whole extent for population x .

485 The mean potential of the neural population, V_x , is finally obtained by integrating the changes of potential
 486 caused by incoming spikes over time:

$$V_x(t) = \int_{-\infty}^t \sum_{(y,n)} \Psi_x^n(t') \Delta V_{\text{soma}}^n(t') dt' \quad (9)$$

487 where each couple (y, n) represents one afferent population y with spikes mediated by the neurotransmitter
 488 n .

489 The BG dynamics were simulated with a time-step of 10^{-4} ms, as in Liénard and Girard (2014), using a

490 4th order Runge-Kutta integration method.

491 The code of the model is available on github at <https://github.com/SN1885A/BCBG-model>.

492 4.2.1 Extra-striate DA depletion

493 We hypothesized that an abnormal activation of extra-striatal DA receptors, combined with lagged activity
494 due to inter-nuclei transmission delays, is the primary cause of β -band oscillations. To test this hypothesis,
495 we focused on modeling the distribution of DA receptors within the GPe and STN only, as these are the only
496 two nuclei which participate of multiple loops within the BG and could possibly cause oscillations. The GPi
497 was disregarded, as it does not form any closed loop within the BG and thus cannot cause oscillations within
498 the BG.

499 Since D2 receptors in GPe and STN are located at the pre-synaptic level only (Rommelfanger and
500 Wichmann, 2010), we simulated their deactivation by a dopamine depletion with an increase of post-synaptic
501 potentials following an incoming spike, as follows:

$$\begin{aligned}A_{\text{AMPA}}^{PD} &= \alpha A_{\text{AMPA}}^{\text{normal}} \\A_{\text{NMDA}}^{PD} &= \alpha A_{\text{NMDA}}^{\text{normal}} \\A_{\text{GABA}_A}^{PD} &= \alpha A_{\text{GABA}_A}^{\text{normal}}\end{aligned}\tag{10}$$

502 where A_{AMPA} , A_{NMDA} and A_{GABA_A} are respectively the peak post-synaptic amplitude of a spike mediated
503 by AMPA, NMDA and GABA_A. *normal* denotes their reference value defined in Liénard and Girard (2014),
504 and ^{PD} the increased level following DA depletion computed with the factor α ($\alpha \geq 1$).

505 The STN D1-like receptors are of D5 sub-type, expressed at post-synaptic sites, and with constitutive
506 activity (Chetrit et al., 2013). They have thus been modeled as modulators of the transfer function of the
507 STN neuron population (see equation next), rather than as modulators of incoming activity:

$$\theta_{\text{STN}}^{PD} = \Delta_{\text{STN}} + \theta_{\text{STN}}^{\text{normal}}\tag{11}$$

508 where θ_{STN} is the average firing threshold of STN neurons, and Δ_{STN} is the offset created by DA depletion
509 on D5 receptors ($\Delta_{\text{STN}} \geq 0$).

510 Finally, based on the lack of projective selectivity of D1 and D2 MSN in macaque monkeys, we assumed
511 that, on average, they compensate each other and that, consequently, their influence for the emergence of
512 β -band oscillations is non-essential. This simplification constitutes a relatively radical modeling choice, that

513 aims at studying the extent to which PD oscillatory phenomenon can be explained without segregated striatal
514 pathways.

515 **Code accessibility**

516 The code used to simulate the neural network is available at <https://github.com/SN1885A/BCBG-model>.

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524 References

- 525 Albin, R., Young, A., and Penney, J. (1989). The functional anatomy of basal ganglia disorders. *Trends in*
526 *Neurosciences*, 12(10):366–375.
- 527 Bauswein, E., Fromm, C., and Preuss, A. (1989). Corticostriatal cells in comparison with pyramidal tract
528 neurons: contrasting properties in the behaving monkey. *Brain Research*, 493(1):198–203.
- 529 Bellinger, S., Miyazawa, G., and Steinmetz, P. (2008). Submyelin potassium accumulation may functionally
530 block subsets of local axons during deep brain stimulation: a modeling study. *Journal of neural engineering*,
531 5(3):263.
- 532 Benazzouz, A., Mamad, O., Abedi, P., Bouali-Benazzouz, R., and Chetrit, J. (2014). Involvement of dopamine
533 loss in extrastriatal basal ganglia nuclei in the pathophysiology of parkinson’s disease. *Frontiers in aging*
534 *neuroscience*, 6.
- 535 Berardelli, A., Hallett, M., Rothwell, J. C., Agostino, R., Manfredi, M., Thompson, P. D., and Marsden, C. D.
536 (1996). Single-joint rapid arm movements in normal subjects and in patients with motor disorders. *Brain*,
537 119(2):661–674.
- 538 Berardelli, A., Rothwell, J. C., Thompson, P. D., and Hallett, M. (2001). Pathophysiology of bradykinesia in
539 Parkinson’s disease. *Brain*, 124(11):2131–2146.
- 540 Brown, P. and Marsden, C. D. (1999). Bradykinesia and impairment of eeg desynchronization in parkinson’s
541 disease. *Movement disorders*, 14(3):423–429.
- 542 Brown, P., Oliviero, A., Mazzone, P., Insola, A., Tonali, P., and Di Lazzaro, V. (2001). Dopamine dependency of
543 oscillations between subthalamic nucleus and pallidum in parkinson’s disease. *The Journal of Neuroscience*,
544 21(3):1033–1038.
- 545 Cazorla, M., de Carvalho, F. D., Chohan, M. O., Shegda, M., Chuhma, N., Rayport, S., Ahmari, S. E.,
546 Moore, H., and Kellendonk, C. (2014). Dopamine d2 receptors regulate the anatomical and functional
547 balance of basal ganglia circuitry. *Neuron*, 81(1):153–164.
- 548 Chetrit, J., Taupignon, A., Froux, L., Morin, S., Bouali-Benazzouz, R., Naudet, F., Kadiri, N., Gross, C. E.,
549 Bioulac, B., and Benazzouz, A. (2013). Inhibiting subthalamic d5 receptor constitutive activity alleviates

- 550 abnormal electrical activity and reverses motor impairment in a rat model of parkinson's disease. *The*
551 *Journal of Neuroscience*, 33(37):14840–14849.
- 552 Corbit, V. L., Whalen, T. C., Zitelli, K. T., Crilly, S. Y., Rubin, J. E., and Gittis, A. H. (2016). Pallidos-
553 triatal projections promote β oscillations in a dopamine-depleted biophysical network model. *Journal of*
554 *Neuroscience*, 36(20):5556–5571.
- 555 de la Crompe, B., Aristieta, A., Leblois, A., Elsherbiny, S., Boraud, T., and Mallet, N. P. (2020). The globus
556 pallidus orchestrates abnormal network dynamics in a model of parkinsonism. *Nature communications*,
557 11(1):1–14.
- 558 Deco, G., Jirsa, V., Robinson, P., Breakspear, M., and Friston, K. (2008). The dynamic brain: from spiking
559 neurons to neural masses and cortical fields. *PLoS Computational Biology*, 4(8):e1000092.
- 560 Destexhe, A., Mainen, Z., and Sejnowski, T. (1998). Kinetic models of synaptic transmission. *Methods in*
561 *Neuronal Modeling*, 2:1–25.
- 562 Doyle, L., Kühn, A., Hariz, M., Kupsch, A., Schneider, G.-H., and Brown, P. (2005). Levodopa-induced
563 modulation of subthalamic beta oscillations during self-paced movements in patients with parkinson's
564 disease. *European Journal of Neuroscience*, 21(5):1403–1412.
- 565 Filion, M. and Tremblay, L. (1991). Effects of dopamine agonists on the spontaneous activity of globus
566 pallidus neurons in monkeys with mptp-induced parkinsonism. *Brain Research*, 547(1):145–149.
- 567 Frank, M. (2005). Dynamic dopamine modulation in the basal ganglia: a neurocomputational account
568 of cognitive deficits in medicated and nonmedicated parkinsonism. *Journal of Cognitive Neuroscience*,
569 17(1):51–72.
- 570 Frank, M. J., Seeberger, L. C., and O'reilly, R. C. (2004). By carrot or by stick: cognitive reinforcement
571 learning in parkinsonism. *Science*, 306(5703):1940–1943.
- 572 Fujiyama, F., Sohn, J., Nakano, T., Furuta, T., Nakamura, K., Matsuda, W., and Kaneko, T. (2011). Exclusive
573 and common targets of neostriatofugal projections of rat striosome neurons: a single neuron-tracing study
574 using a viral vector. *European Journal of Neuroscience*, 33(4):668–677.
- 575 Gillies, A., Willshaw, D., and Li, Z. (2002). Subthalamic-pallidal interactions are critical in determining
576 normal and abnormal functioning of the basal ganglia. *Proceedings: Biological Sciences*, pages 545–551.

- 577 Girard, B., Lienard, J., Gutierrez, C. E., Delord, B., and Doya, K. (2021). A biologically constrained spiking
578 neural network model of the primate basal ganglia with overlapping pathways exhibits action selection.
579 *European Journal of Neuroscience*, 53(7):2254–2277.
- 580 Goldberg, J., Boraud, T., Maraton, S., Haber, S., Vaadia, E., and Bergman, H. (2002). Enhanced synchrony
581 among primary motor cortex neurons in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine primate model
582 of parkinson’s disease. *The Journal of Neuroscience*, 22(11):4639–4653.
- 583 Gurney, K., Prescott, T., and Redgrave, P. (2001). A computational model of action selection in the basal
584 ganglia. ii. analysis and simulation of behaviour. *Biological Cybernetics*, 84(6):411–423.
- 585 Holgado, A., Terry, J., and Bogacz, R. (2010). Conditions for the generation of beta oscillations in the
586 subthalamic nucleus–globus pallidus network. *The Journal of Neuroscience*, 30(37):12340–12352.
- 587 Humphries, M., Stewart, R., and Gurney, K. (2006). A physiologically plausible model of action selection
588 and oscillatory activity in the basal ganglia. *The Journal of Neuroscience*, 26(50):12921.
- 589 Iwamuro, H., Tachibana, Y., Saito, N., and Nambu, A. (2009). Organization of motor cortical inputs to the
590 subthalamic nucleus in the monkey. *The Basal Ganglia IX*, pages 109–117.
- 591 Iwamuro, H., Tachibana, Y., Ugawa, Y., Saito, N., and Nambu, A. (2017). Information processing from the
592 motor cortices to the subthalamic nucleus and globus pallidus and their somatotopic organizations revealed
593 electrophysiologically in monkeys. *European Journal of Neuroscience*, 46(11):2684–2701.
- 594 Jaeger, D. and Kita, H. (2011). Functional connectivity and integrative properties of globus pallidus neurons.
595 *Neuroscience*, 198:44–53.
- 596 Kawaguchi, Y., Wilson, C., and Emson, P. (1990). Projection subtypes of rat neostriatal matrix cells revealed
597 by intracellular injection of biocytin. *The Journal of Neuroscience*, 10(10):3421–3438.
- 598 Kita, H., Chiken, S., Tachibana, Y., and Nambu, A. (2006). Origins of gaba_A and gabab receptor-mediated
599 responses of globus pallidus induced after stimulation of the putamen in the monkey. *The Journal of*
600 *Neuroscience*, 26(24):6554–6562.
- 601 Kita, H., Nambu, A., Kaneda, K., Tachibana, Y., and Takada, M. (2004). Role of ionotropic glutamatergic
602 and gabaergic inputs on the firing activity of neurons in the external pallidum in awake monkeys. *Journal*
603 *of Neurophysiology*, 92(5):3069–3084.

- 604 Kita, H., Tachibana, Y., Nambu, A., and Chiken, S. (2005). Balance of monosynaptic excitatory and
605 disynaptic inhibitory responses of the globus pallidus induced after stimulation of the subthalamic nucleus
606 in the monkey. *The Journal of Neuroscience*, 25(38):8611–8619.
- 607 Koch, C. (2005). *Biophysics of computation: information processing in single neurons*. Oxford University
608 Press, USA.
- 609 Koshimizu, Y., Fujiyama, F., Nakamura, K. C., Furuta, T., and Kaneko, T. (2013). Quantitative analysis of
610 axon bouton distribution of subthalamic nucleus neurons in the rat by single neuron visualization with a
611 viral vector. *Journal of Comparative Neurology*, 521(9):2125–2146.
- 612 Kühn, A. A., Kupsch, A., Schneider, G.-H., and Brown, P. (2006). Reduction in subthalamic 8–35 hz
613 oscillatory activity correlates with clinical improvement in parkinson’s disease. *European Journal of*
614 *Neuroscience*, 23(7):1956–1960.
- 615 Kumar, A., Cardanobile, S., Rotter, S., and Aertsen, A. (2011). The role of inhibition in generating and
616 controlling parkinson’s disease oscillations in the basal ganglia. *Frontiers in Systems Neuroscience*, 5.
- 617 Leblois, A., Boraud, T., Meissner, W., Bergman, H., and Hansel, D. (2006a). Competition between feedback
618 loops underlies normal and pathological dynamics in the basal ganglia. *The Journal of Neuroscience*,
619 26(13):3567–3583.
- 620 Leblois, A., Boraud, T., Meissner, W., Bergman, H., and Hansel, D. (2006b). Competition between feedback
621 loops underlies normal and pathological dynamics in the basal ganglia. *The Journal of neuroscience*,
622 26(13):3567–3583.
- 623 Lévesque, M. and Parent, A. (2005). The striatofugal fiber system in primates: a reevaluation of its
624 organization based on single-axon tracing studies. *Proceedings of the National Academy of Sciences*,
625 102(33):11888–11893.
- 626 Levy, R., Hutchison, W. D., Lozano, A. M., and Dostrovsky, J. O. (2000). High-frequency synchronization of
627 neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. *The Journal of*
628 *neuroscience*, 20(20):7766–7775.
- 629 Liénard, J. and Girard, B. (2014). A biologically constrained model of the whole basal ganglia addressing the
630 paradoxes of connections and selection. *Journal of Computational Neuroscience*, 36(3):445–468.

- 631 Lindahl, M. and Hellgren Kotaleski, J. (2016). Untangling basal ganglia network dynamics and function: Role
632 of dopamine depletion and inhibition investigated in a spiking network model. *eNeuro*, 3(6):e0156–16.2016.
- 633 Marsden, C. D. (1984). Which motor disorder in Parkinson’s disease indicates the true motor function of the
634 basal ganglia? *Ciba Foundation symposium*, 107.
- 635 Marsden, C. D. (1989). Slowness of movement in Parkinson’s disease. *Movement Disorders: Official Journal
636 of the Movement Disorder Society*, 4 Suppl 1:S26–37.
- 637 Mazzoni, P., Shabbott, B., and Cortés, J. C. (2012). Motor abnormalities in parkinson’s disease. *Cold Spring
638 Harbor Perspectives in Medicine*, 2.
- 639 McCarthy, M., Moore-Kochlacs, C., Gu, X., Boyden, E., Han, X., and Kopell, N. (2011). Striatal origin of
640 the pathologic beta oscillations in parkinson’s disease. *Proceedings of the National Academy of Sciences*,
641 108(28):11620–11625.
- 642 Nadjar, A., Brotchie, J., Guigoni, C., Li, Q., Zhou, S., Wang, G., Ravenscroft, P., Georges, F., Crossman, A.,
643 and Bezard, E. (2006). Phenotype of striatofugal medium spiny neurons in parkinsonian and dyskinetic
644 nonhuman primates: a call for a reappraisal of the functional organization of the basal ganglia. *The Journal
645 of Neuroscience*, 26(34):8653–8661.
- 646 Nambu, A. (2008). Seven problems on the basal ganglia. *Current opinion in neurobiology*, 18(6):595–604.
- 647 Nambu, A., Kaneda, K., Tokuno, H., and Takada, M. (2002). Organization of corticostriatal motor inputs in
648 monkey putamen. *Journal of Neurophysiology*, 88(4):1830–1842.
- 649 Nambu, A., Tokuno, H., Hamada, I., Kita, H., Imanishi, M., Akazawa, T., Ikeuchi, Y., and Hasegawa, N.
650 (2000). Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey. *Journal
651 of Neurophysiology*, 84(1):289–300.
- 652 Nevado Holgado, A., Terry, J., and Bogacz, R. (2010). Conditions for the generation of beta oscillations in
653 the subthalamic nucleus–globus pallidus network. *The Journal of Neuroscience*, 30(37):12340–12352.
- 654 Nini, A., Feingold, A., Slovín, H., and Bergman, H. (1995). Neurons in the globus pallidus do not show
655 correlated activity in the normal monkey, but phase-locked oscillations appear in the mptp model of
656 parkinsonism. *Journal of Neurophysiology*, 74(4):1800–1805.

- 657 Oswal, A., Brown, P., and Litvak, V. (2013). Synchronized neural oscillations and the pathophysiology of
658 parkinson's disease. *Current opinion in neurology*, 26(6):662–670.
- 659 Parent, A., Charara, A., and Pinault, D. (1995). Single striatofugal axons arborizing in both pallidal segments
660 and in the substantia nigra in primates. *Brain research*, 698(1):280–284.
- 661 Pasquereau, B., DeLong, M. R., and Turner, R. S. (2015). Primary motor cortex of the parkinsonian monkey:
662 altered encoding of active movement. *Brain*, page awv312.
- 663 Pasquereau, B. and Turner, R. (2011). Primary motor cortex of the parkinsonian monkey: Differential effects
664 on the spontaneous activity of pyramidal tract-type neurons. *Cerebral Cortex*, 21(6):1362–1378.
- 665 Pavlides, A., Hogan, S. J., and Bogacz, R. (2015). Computational models describing possible mechanisms for
666 generation of excessive beta oscillations in parkinson's disease. *PLoS Comput Biol*, 11(12):e1004609.
- 667 Polyakova, Z., Chiken, S., Hatanaka, N., and Nambu, A. (2020). Cortical control of subthalamic neuronal
668 activity through the hyperdirect and indirect pathways in monkeys. *Journal of Neuroscience*, 40(39):7451–
669 7463.
- 670 Rall, W. (1967). Distinguishing theoretical synaptic potentials computed for different soma-dendritic
671 distributions of synaptic input. *Journal of neurophysiology*, 30(5):1138–1168.
- 672 Rommelfanger, K. S. and Wichmann, T. (2010). Extrastriatal dopaminergic circuits of the basal ganglia.
673 *Frontiers in neuroanatomy*, 4.
- 674 Samii, A., Nutt, J. G., and Ransom, B. R. (2004). Parkinson's disease. *The Lancet*, 363(9423):1783–1793.
- 675 Shouno, O., Tachibana, Y., Nambu, A., and Doya, K. (2017). Computational model of recurrent subthalamo-
676 pallidal circuit for generation of parkinsonian oscillations. *Frontiers in Neuroanatomy*, 11(21).
- 677 Tachibana, Y., Iwamuro, H., Kita, H., Takada, M., and Nambu, A. (2011). Subthalamo-pallidal interactions
678 underlying parkinsonian neuronal oscillations in the primate basal ganglia. *European Journal of Neuroscience*,
679 34(9):1470–1484.
- 680 Tachibana, Y., Kita, H., Chiken, S., Takada, M., and Nambu, A. (2008). Motor cortical control of internal
681 pallidal activity through glutamatergic and gabaergic inputs in awake monkeys. *European Journal of*
682 *Neuroscience*, 27(1):238–253.

- 683 Terman, D., Rubin, J., Yew, A., and Wilson, C. (2002). Activity patterns in a model for the subthalamopallidal
684 network of the basal ganglia. *The Journal of Neuroscience*, 22(7):2963–2976.
- 685 Tsirogiannis, G., Tagaris, G., Sakas, D., and Nikita, K. (2010). A population level computational model
686 of the basal ganglia that generates parkinsonian local field potential activity. *Biological Cybernetics*,
687 102(2):155–176.
- 688 Turner, R. and DeLong, M. (2000). Corticostriatal activity in primary motor cortex of the macaque. *The*
689 *Journal of Neuroscience*, 20(18):7096–7108.
- 690 Valjent, E., Bertran-Gonzalez, J., Hervé, D., Fisone, G., and Girault, J.-A. (2009). Looking BAC at striatal
691 signaling: cell-specific analysis in new transgenic mice. *Trends in neurosciences*, 32(10):538–547.
- 692 Van Albada, S., Gray, R., Drysdale, P., Robinson, P., et al. (2009). Mean-field modeling of the basal
693 ganglia-thalamocortical system. II Dynamics of parkinsonian oscillations. *Journal of Theoretical Biology*,
694 257(4):664–688.
- 695 Van Albada, S. and Robinson, P. (2009). Mean-field modeling of the basal ganglia-thalamocortical system. I
696 Firing rates in healthy and parkinsonian states. *Journal of Theoretical Biology*, 257(4):642–663.
- 697 Weinberger, M., Hutchison, W. D., and Dostrovsky, J. O. (2009). Pathological subthalamic nucleus oscillations
698 in pd: can they be the cause of bradykinesia and akinesia? *Experimental neurology*, 219(1):58–61.
- 699 Wu, Y., Richard, S., and Parent, A. (2000). The organization of the striatal output system: a single-cell
700 juxtacellular labeling study in the rat. *Neuroscience Research*, 38(1):49–62.
- 701 Yelnik, J. and Percheron, G. (1979). Subthalamic neurons in primates: a quantitative and comparative
702 analysis. *Neuroscience*, 4(11):1717–1743.
- 703 Yoshida, S., Nambu, A., and Jinnai, K. (1993). The distribution of the globus pallidus neurons with input
704 from various cortical areas in the monkeys. *Brain Research*, 611(1):170–174.

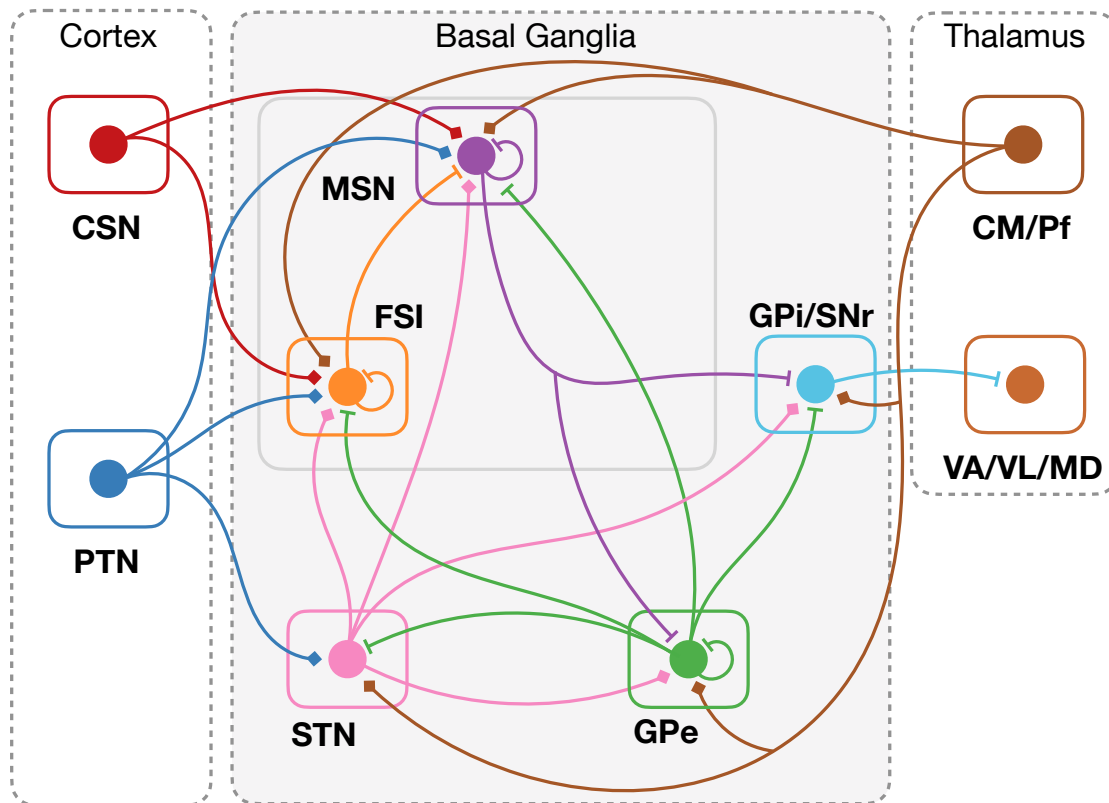


Figure 1: The simulated populations of the Liénard and Girard (2014) basal ganglia model (gray background) and their interconnections. The cortical and thalamic populations (white background) are not explicitly simulated: the cortico-striatal neurons (CSN), the pyramidal tract neurons (PTN) and the centro-median/parafascicular neurons (CM/Pf) are external inputs; the ventero-anterior, ventero-lateral and medio-dorsal neurons of the thalamus (VA/VL/MD) are the targets of the GPi/SNr output of the model. Diamond projections are excitatory, flat projections are inhibitory. All figures by Aubin, Liénard & Girard (2022); available under a CC-BY4.0 licence (<https://doi.org/10.6084/m9.figshare.21131911>).

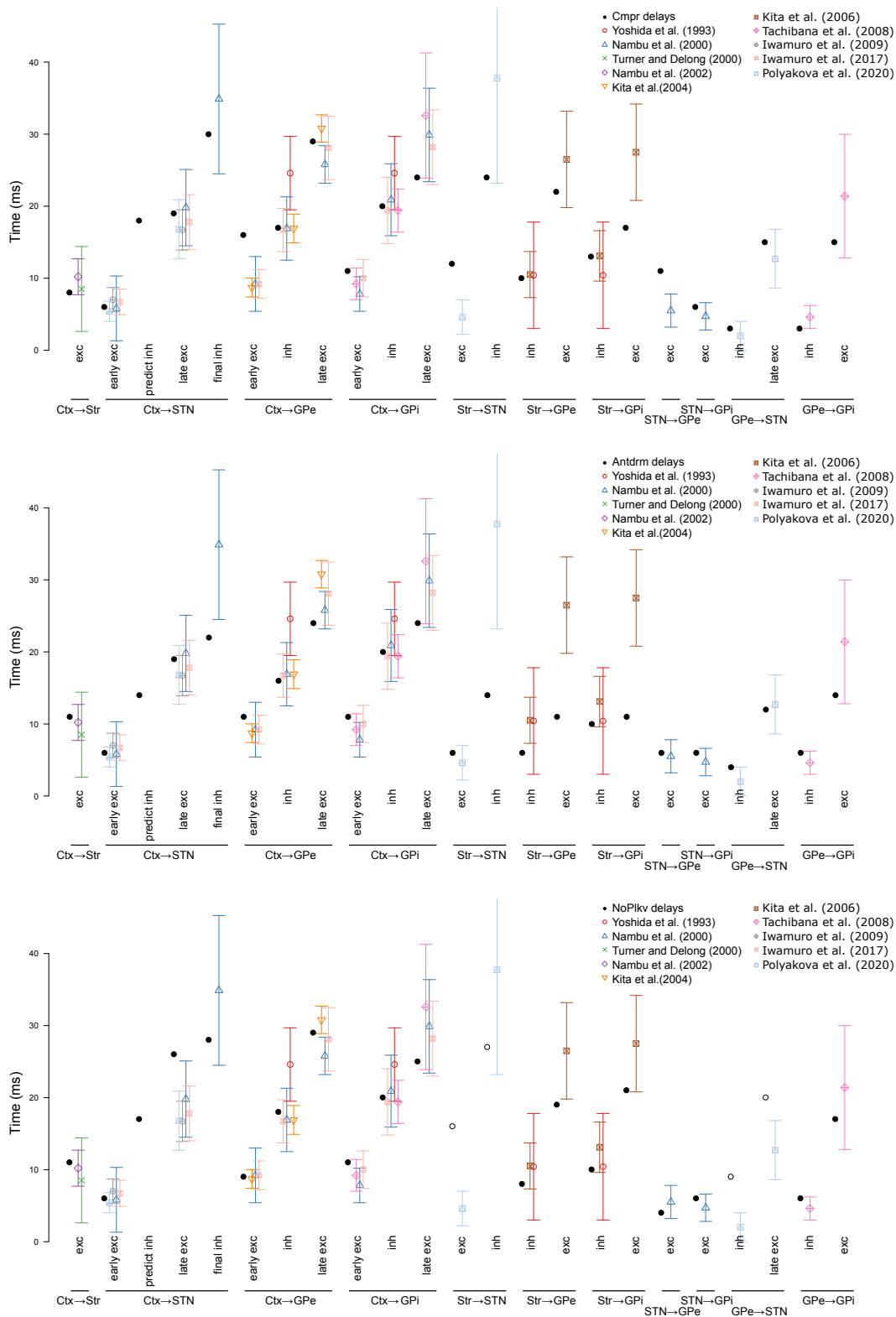


Figure 2: Comparison of the latencies of the excitatory and inhibitory effects measured after the stimulations (averages and standard deviations) from our set of reference studies, with those predicted by the three considered sets of delays. Top: compromise solution based on all the studies (Cmpr set); middle: solution obtained when allowing for antidromic activations of the cortex after striatum stimulation (Antdrm); bottom: solution obtained after exclusion of the (Polyakova et al., 2020) data (NoPlkv), the white circles are the latencies that were excluded from the optimization.

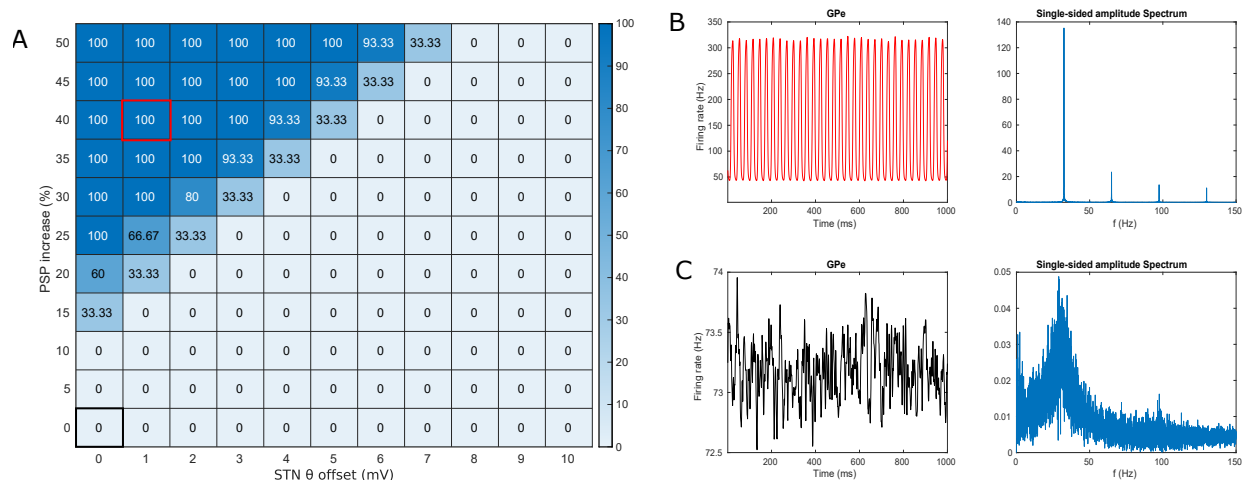


Figure 3: Emergence of oscillations under dopamine depletion with the *Cmpr* set of delays. A: proportion of the basal ganglia models that oscillate depending on the increase in the PSPs in the GPe and STN (D2 receptors) and on the increase in the firing threshold of the STN (D5 receptors). B: Oscillatory GPe activity (left) and the corresponding power spectrum (right) corresponding to a PSP increase of 40% and a STN threshold increase of 1 mV (shown with a red square in A). C: Irregular GPe activity (left) and the corresponding power spectrum (right) corresponding to the model without dopamine depletion (shown with a black square in A).

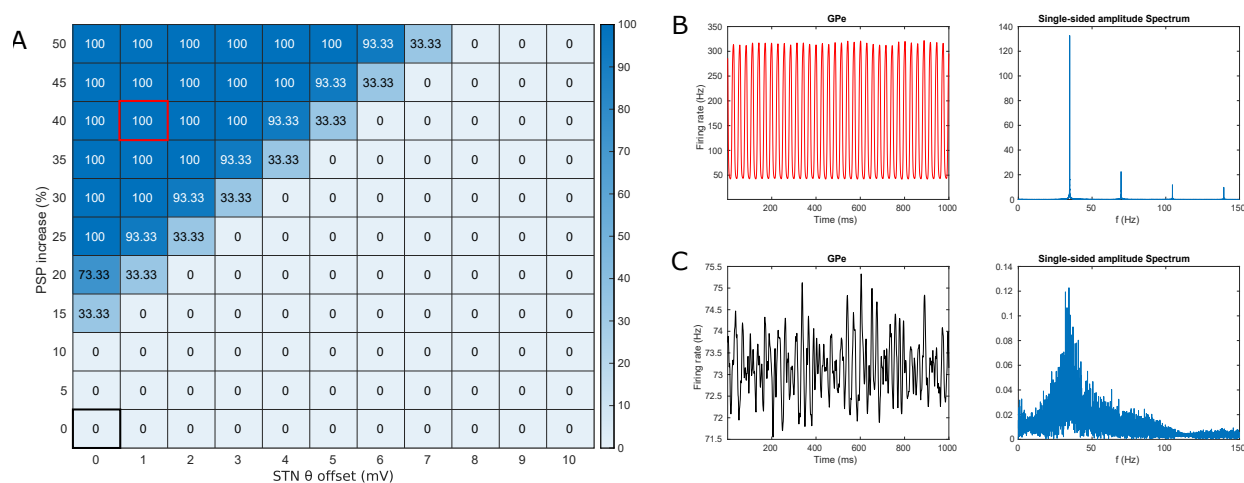


Figure 4: Emergence of oscillations under dopamine depletion with the *NoPlkv* set of delays. A: proportion of the basal ganglia models that oscillate depending on the increase in the PSPs in the GPe and STN (D2 receptors) and on the increase in the firing threshold of the STN (D5 receptors). B: Oscillatory GPe activity (left) and the corresponding power spectrum (right) corresponding to a PSP increase of 40% and a STN threshold increase of 1 mV (shown with a red square in A). C: Irregular GPe activity (left) and the corresponding power spectrum (right) corresponding to the model without dopamine depletion (shown with a black square in A).

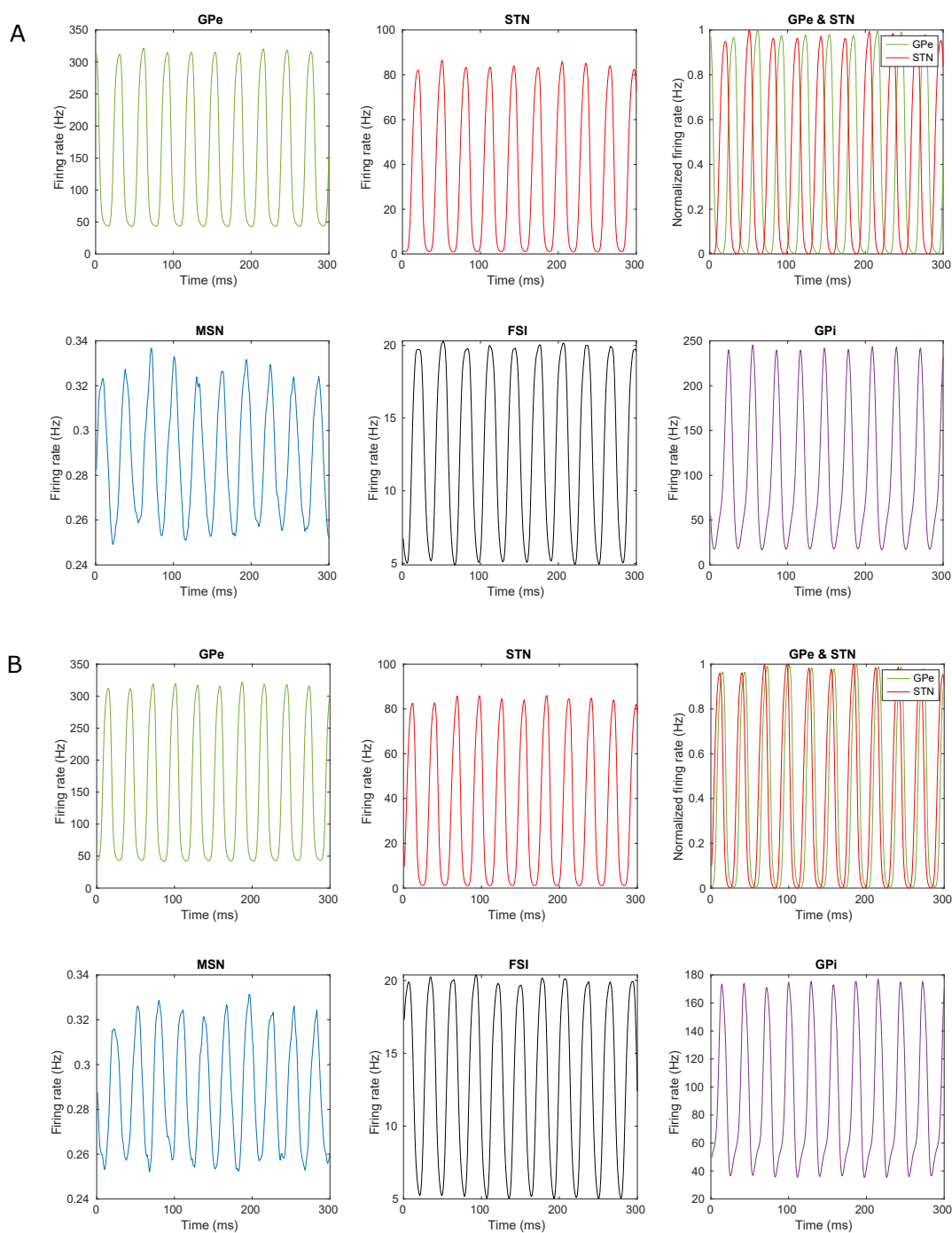


Figure 5: Oscillatory activity in the whole basal ganglia circuit, caused by DA depletion. These illustrative simulations use the parameterization #2 of the BCBG, a GPe and STN PSP increase of 40% and a STN firing threshold increase of 1mV. A: with the *Cmpr* set of delays; B: with the *NoPlkv* set of delays

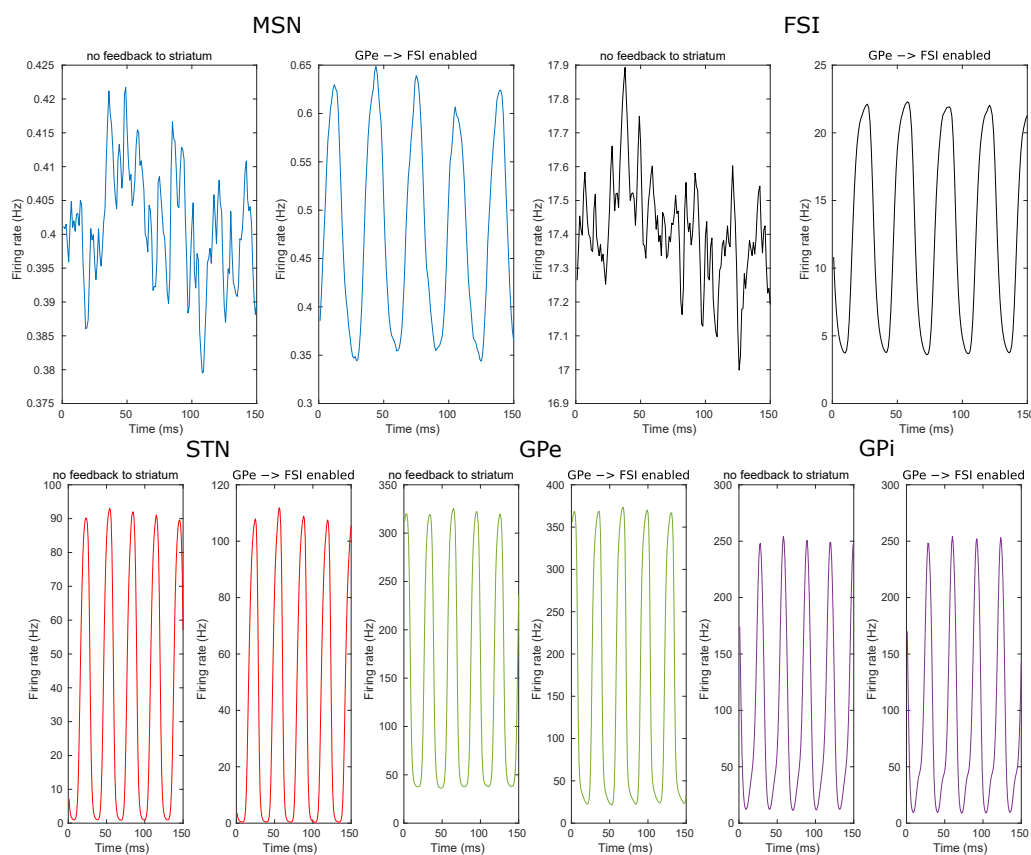


Figure 6: Transmission of the oscillations in the circuit (*Cmpr* set of delays, BCBG model parameterization #2, 40% GPe and STN input PSP increase, 1mV STN threshold increase). In the first set of simulations (left part of each panel), the feedback from the GPe and the STN to the striatum was overridden: STN and GPE input were replaced by synthetic inputs mimicking the normal GPe and STN activities. In the second set of simulations (right part of each panel), the GPe \rightarrow FSI feedback was selectively re-activated. Oscillations in the MSNs and the FSIs appears only in the second set of simulations, showing that striatal oscillations are byproduct of GPe-STN oscillations mediated selectively through the GPe \rightarrow FSI connection.

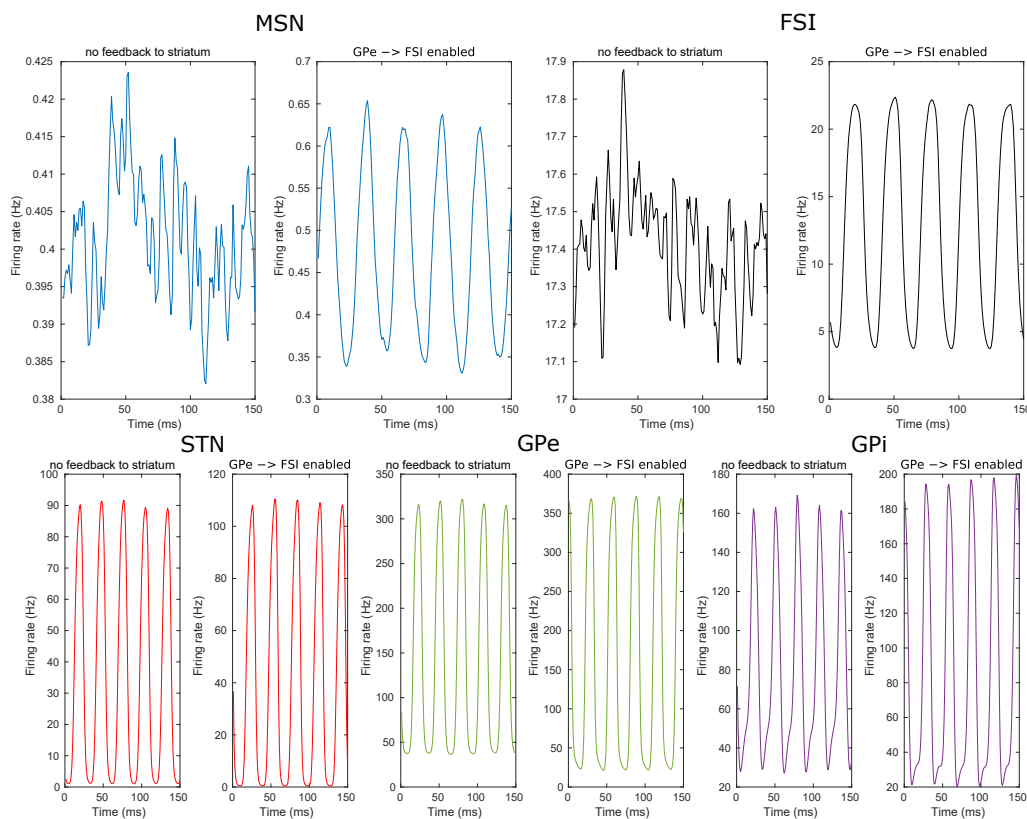


Figure 7: Transmission of the oscillations in the circuit (*NoPlkv* set of delays, BCBG model parameterization #2, 40% GPe and STN input PSP increase, 1mV STN threshold increase). In the first set of simulations (left part of each panel), the feedback from the GPe and the STN to the striatum was overridden: STN and GPe input were replaced by synthetic inputs mimicking the normal GPe and STN activities. In the second set of simulations (right part of each panel), the GPe \rightarrow FSI feedback was selectively re-activated. Oscillations in the MSNs and the FSIs appears only in the second set of simulations, showing that striatal oscillations are byproduct of GPe-STN oscillations mediated selectively through the GPe \rightarrow FSI connection.



Figure 8: Frequency of oscillation (in Hz) as a function of the axonal delays between STN and GPe. Delays from STN to GPe are listed as columns and from GPe to STN as rows. The other delays are set according to the *Cmpr* set of delays (left) and the *NoPlkv* set of delays (right). The optimized axonal delays are shown in the cells marked with a black rectangle. Colors indicate different oscillation regimes, with the β -band (15-35 Hz) shown in blue and the γ -band (35-80 Hz) shown in green.

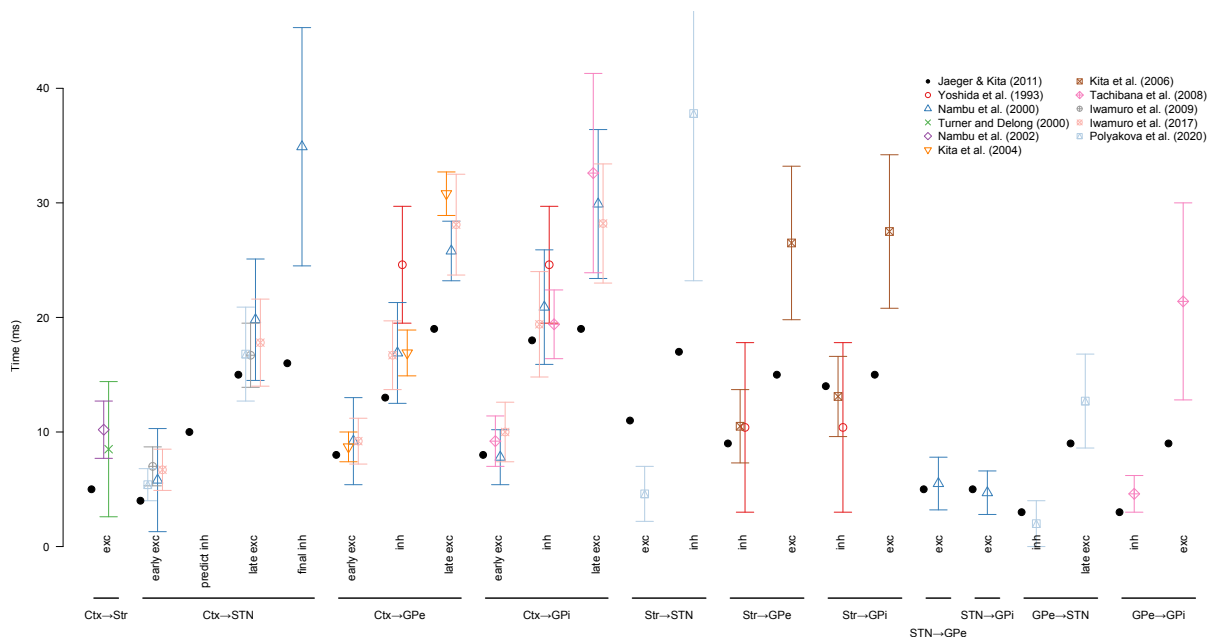


Figure 9: Comparison of the latencies of the excitatory and inhibitory effects measured after the stimulations (averages and standard deviations) from our set of reference studies, with those predicted by the set of delays of (Jaeger and Kita, 2011)

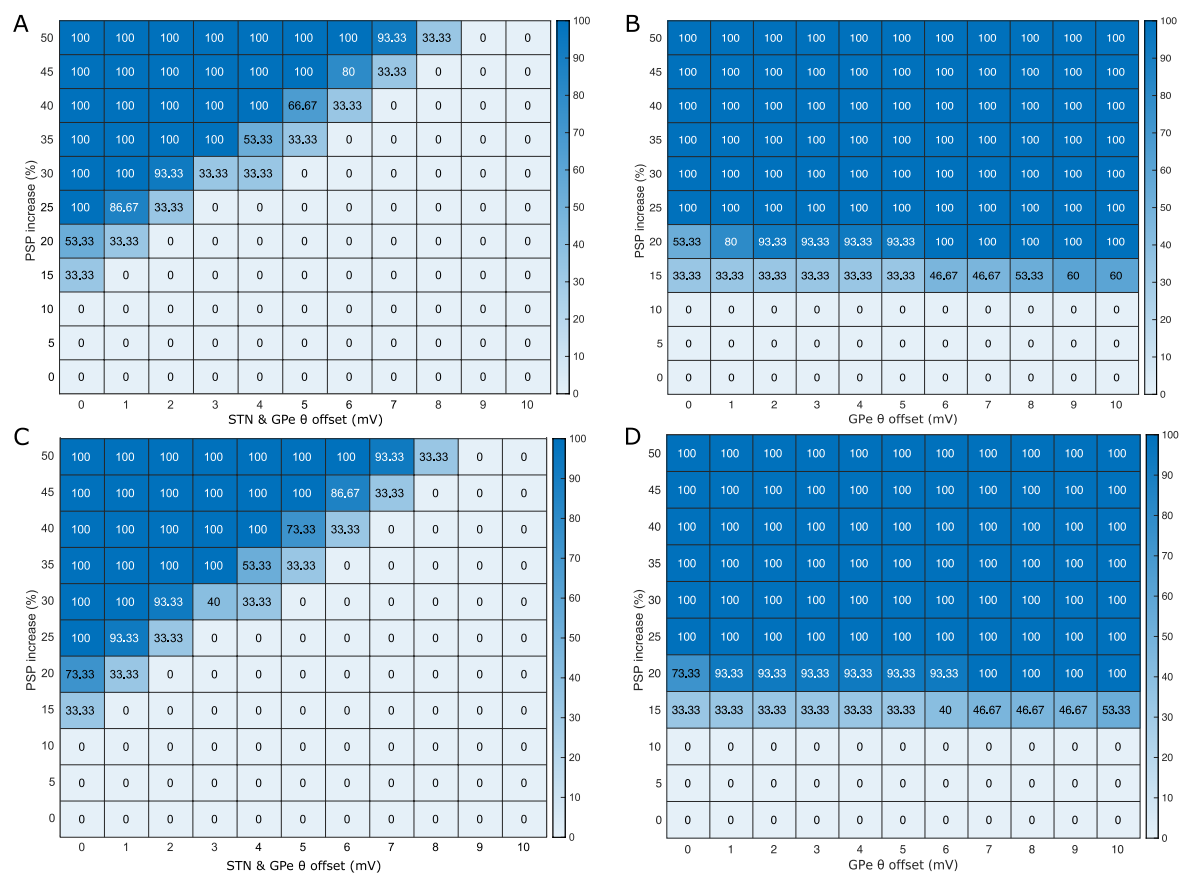


Figure 10: Effect of the simulation of D5 receptors in the GPe with regards to the emergence of oscillations under dopamine depletion. A, B: using the *Cmpr* set of delays; C, D: using the *NoPlkv* set of delays. Same as figure 3A, except that in A and C, θ is increased in both STN and GPe, and, in B and D, only in the GPe.

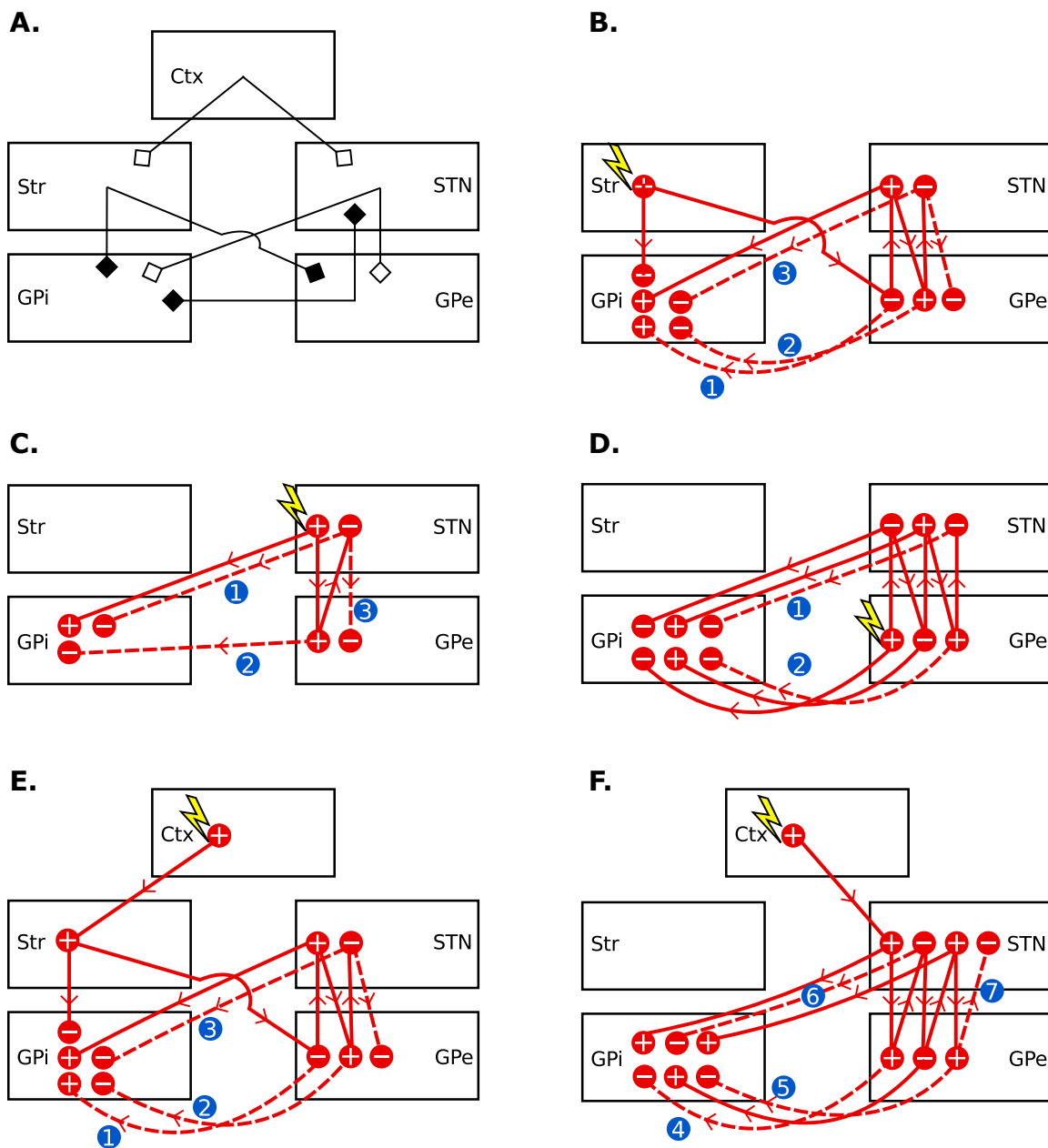


Figure 11: A. Connections considered in the transmission delay estimation. Black endings denote inhibitory connections and white endings denote excitatory connections. B-F. Possible timecourses of a stimulation originating in the striatum (B), STN (C), GPe (D) and cortex (E-F). For clarity, the cortical stimulation is subdivided into one representation of the striatal excitation consequences (E) and of the subthalamic excitation consequences (F). In all panels, circled "+" indicate that overactive nuclei and "-" indicate underactive nuclei. Successive states of overactivity or underactivity are placed from left to right if they can be ordered (e.g. after an excitation in the Str, the STN will always be overactive before being underactive). Successive states that can not be ordered are placed on different lines (e.g. after an excitation in the Str, the first state of GPI could *a priori* be either an underactivity or an overactivity). Dashed numbered links correspond to pathways that are not recruited, see text for their individual justifications.