

1 **Sensorimotor processing in the basal ganglia leads** 2 **to transient beta oscillations during behavior**

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Abstract

Brief epochs of beta oscillations have been implicated in sensorimotor control in the basal ganglia of task-performing healthy animals. However, which neural processes underlie their generation and how they are affected by sensorimotor processing remains unclear. To determine the mechanisms underlying transient beta oscillations in the local field potential (LFP), we combined computational modeling of the subthalamo-pallidal network for the generation of beta oscillations with realistic stimulation patterns derived from single unit data. The single unit data were recorded from different basal ganglia subregions in rats performing a cued choice task. In the recordings we found distinct firing patterns in the striatum, globus pallidus and subthalamic nucleus related to sensory and motor events during the behavioral task. Using these firing patterns to generate realistic inputs to our network model lead to transient beta oscillations with the same time course as the rat LFP data. In addition, our model can account for further non-intuitive aspects of beta modulation, including beta phase resets following sensory cues and correlations with reaction time. Overall, our model can explain how the combination of temporally regulated sensory responses of the subthalamic nucleus, ramping activity of the subthalamic nucleus, and movement-related activity of the globus pallidus, leads to transient beta oscillations during behavior.

Significance Statement

Transient beta oscillations emerge in the normal functioning cortico-basal ganglia loop during behavior. In this work we employ a unique approach connecting a computational model closely with experimental data. In this way we achieve a simulation environment for our model that mimics natural input patterns in awake behaving animals. Using this approach we demonstrate that a computational model for beta oscillations in Parkinson's disease can also account for complex patterns of transient beta oscillations in healthy animals. Therefore, we propose that transient beta oscillations in healthy animals share the same mechanism with pathological beta oscillations in Parkinson's disease. This important result connects functional and pathological roles of beta oscillations in the basal ganglia.

Introduction

Exaggerated cortico-basal ganglia oscillations in the beta band (15 to 30 Hz) are a common feature of Parkinson's disease (PD; Brown et al., 2001; Hammond et al., 2007; Levy et al., 2002). However, beta oscillations are not always pathological. Brief epochs of beta oscillations have been implicated in sensorimotor control in the healthy basal ganglia (Berke et al., 2004; Leventhal et al., 2012; Courtemanche et al., 2003; Feingold et al., 2015). These studies indicate that temporally regulated transient beta oscillations are important for normal functioning of the motor system.

The origin of beta oscillations in the cortico-basal ganglia system remains unknown. However, interactions between subthalamic nucleus (STN) and globus pallidus externa (GPe) can generate beta oscillations as has been shown in experimental (Bevan et al., 2002; Tachibana et al., 2011) and computational (Terman et al., 2002; Kumar et al., 2011, Pavlides et al., 2015; Wei et al., 2015) studies. Anatomically, STN and GPe are densely and reciprocally inter-connected (Shink et al., 1996). STN cells excite neurons in GPe (Kitai and Kita, 1987), which in turn receive inhibitory

68 input from GPe (Smith et al., 1990; Parent and Hazrati, 1995). Such recurrent excitation-inhibition
69 can generate oscillations (Plenz and Kitai, 1999; Brunel, 2000), which may then propagate to other
70 regions in the cortico-basal ganglia loop.

71 Beta oscillations have been proposed to play a functional role in maintaining the status quo in
72 the motor system (Engel and Fries, 2010; Gillbertson et al., 2005). This idea has been supported
73 by increased cortical beta-band activity during maintenance of a static position (Baker et al.,
74 1997), active suppression of movement initiation (Swann et al., 2009), and post-movement hold
75 periods (Pfurtscheller et al., 1996). Accordingly, beta power decreases in the cortico-basal ganglia
76 loop during movement preparation and execution (Sochurkova and Rektor, 2003; Pfurtscheller et
77 al., 2003; Alegre et al., 2005; Kuhn et al., 2004). However, recent studies have indicated a more
78 complex picture in which beta oscillations affect behavior through motor adaptation (Tan et al.,
79 2014) and modulation of task performance (Feingold et al., 2015).

80 Supporting a more complex picture of beta oscillations, we provided evidence that basal ganglia
81 beta oscillations are involved in sensorimotor processing and the utilization of cues for behavior
82 (Leventhal et al., 2012). In particular, we found that beta power increases following the sensory
83 cues and movement initiation depended on how fast the animals reacted to a sensory cue. For
84 short reaction times, LFP beta emerged after movement initiation, whereas for long reaction times,
85 two separate beta epochs occurred, one before and one after movement initiation. In addition
86 to modulation of beta power, we also observed that beta phases were affected by task events
87 differently. Sensory cues, but not movement initiation, lead to a short-latency phase reset in the
88 beta band (Leventhal et al., 2012).

89 Understanding these complex dynamics of beta oscillations is important to identify the underlying
90 mechanisms that generate beta oscillations in the cortico-basal ganglia system. Currently, it is
91 unknown whether pathological beta oscillations in Parkinson’s disease share the same mechanisms
92 with transient beta oscillations in healthy animals. If this is the case, computational models for
93 beta oscillations should be able to account for the complex beta dynamics in both healthy and
94 Parkinsonian animals. Recent network models of beta oscillations in Parkinson’s disease have em-
95 phasized that besides structural changes (e.g. connection strengths), also changes in spiking activity
96 of external inputs can promote beta oscillations (Kumar et al., 2011), which might drive transient
97 beta oscillations. Here we exploit this property by directly using activity patterns recorded in
98 healthy rats during task performance (Schmidt et al., 2013; Mallet et al., 2016) as input to our
99 computational model to study the resulting impact on the beta dynamics. Employing this novel
100 approach we find that our model can account for the complex beta dynamics in the healthy rat
101 LFP. Our results support overlapping mechanisms for pathological and healthy beta oscillations
102 and provide the basis for studying the functional role of beta oscillations in network models.

103 Results

104 To determine whether a computational model for pathological beta oscillations in the STN-
105 GPe network (Kumar et al., 2011) can account for complex beta dynamics during behavior in
106 healthy animals, we devised realistic stimulation patterns for the network model based on single
107 unit recordings in rats performing a cued choice task (Schmidt et al., 2013; Mallet et al., 2016). At
108 the beginning of each trial, the rat entered one of three center nose ports in an operant chamber
109 (“Nose-in” event; Figures 1A, B). The rat was trained to then hold its position for a variable time

110 interval (“Holding time”; 500-1200 ms) until a Go cue instructed the rat to quickly move its head
111 to the adjacent left or right side port (“Nose-out” event; Figures 1A, B). Correct performance of
112 the task was rewarded with a sugar pellet. While the animals performed the task we recorded
113 in the striatum, GPe and STN to determine activity patterns of single units during the time of
114 the Go cue and during movement initiation. Then we used these activity patterns to construct
115 realistic input patterns for our network model. The network model we use here is a large-scale
116 spiking network model consisting STN and GPe populations with conductance based synapses
117 (Kumar et al., 2011; see Methods). Stimulating the network model via the realistic stimulation
118 patterns allowed us to compare the resulting oscillatory dynamics in the model with properties of
119 oscillations in the rat LFPs.

120 *Brief, short-latency sensory responses in STN.* 27% (75/276) of STN units responded to the
121 Go cue with an increase in firing rate (Figure 1C; shuffle test, $p < 0.01$; see Methods). In line
122 with our previous reports on a subset of the same data (Schmidt et al., 2013), this included units
123 with a very short latency (around 10-30 ms), and responses of individual units were typically very
124 brief (see Figure 1C, top panel). In addition, some units responded with a longer latency (around
125 40-100 ms), so that the overall distribution of peak response latencies had a bimodal shape (Figure
126 1D). To mimic this STN response pattern to salient sensory stimuli, we simulated the Go cue in
127 our model simulations below by using brief excitatory pulses with the same latency distribution.
128 These pulses were then used as input to 27% randomly chosen STN model neurons (“sensory”
129 STN neurons) to match the fraction of responding STN units in our single unit data.

130 *Movement-related activity in striatum and GPe.* 30% (100/320) of putative medium spiny
131 neurons (MSNs) in the striatum increased their activity during contralateral movements (Figure
132 1E; see Methods; also see Schmidt et al., 2013). We focused here on contralateral movements
133 as most neurons typically responded more during contralateral than ipsilateral movements (Gage
134 et al., 2010; Schmidt et al., 2013). In GPe, 40% (61/149) of the units decreased their activity
135 during contralateral movements (Figure 1F; shuffle test, $p < 0.05$; see Methods), possibly reflecting
136 input from indirect pathway MSNs. Therefore, we assumed in the network model that striato-
137 pallidal inhibition drives the GPe firing rate decreases during movement. We implemented this by
138 generating inhomogeneous Poisson spike trains with a rate modulation following the MSN firing
139 pattern during movement (Figure 1E). These spike trains were then used as inhibitory inputs to
140 40% of the network model GPe neurons (“motor” GPe neurons) to match the fraction of GPe units
141 with movement-related firing rate decreases in the single unit data. Note that we restricted our
142 analysis of GPe units to putative prototypical neurons (Mallet et al., 2016) because they receive
143 input from MSNs and project to STN, while arkypallidal GPe neurons probably receive different
144 inputs and do not project to STN (Mallet et al., 2012; Dodson et al., 2015).

145 *Ramping activity in STN and GPe while rats wait for the Go cue.* In addition to single unit
146 responses that could be classified as sensory or motor, in STN and GPe we found many units
147 which exhibited a firing pattern that resembled a “ramp”, a continuous change in firing rate.
148 A ramping pattern was present in the activity of 80% (216/276) of the STN units with either
149 significantly increasing (positive ramp) or decreasing (negative ramp) firing rate while the animal
150 was waiting for the Go cue (Figures 2A, B). Among the 216 ramping STN units, 44% (96/216)
151 showed positive ramps (Figure 2A), whereas 56% (120/216) showed negative ramps (Figure 2B).
152 However, the mean firing rate increase for the positive ramp units was four times as high as the
153 mean firing rate decrease for the negative ramp units (4 Hz increase vs. 1 Hz decrease; inset in
154 Figure 2B, bottom). The positive ramp was also observed in the average firing rate of the whole

155 STN population starting 500 ms before the Go cue (data not shown). Functionally, these ramps
156 may correspond to a brake signal, preventing premature movement initiation (Frank, 2006).

157 We found a similar pattern in the GPe with 71% (106/149) of the units exhibiting a significant
158 ramping activity before the Go cue (Figures 2C, D). Among these, 47% (50/106) showed positive
159 ramps (Figure 2C) and 52% showed negative ramps (Figure 2D). As for the STN units, on average,
160 the amplitude of the positive ramp in GPe was four times as high as the amplitude of the negative
161 ramp, resulting in a net positive ramp in the population activity (data not shown). One property of
162 the positive ramp STN and GPe units was that in long reaction time trials their activity remained
163 elevated after the Go cue (Figures 2A, C, bottom panels). This property played a key role for the
164 beta dynamics in the model below.

165 Based on these ramping patterns in STN and GPe, we designed inputs to the model STN
166 neurons that lead to similar activity ramps (see Methods). Due to the excitatory drive from STN
167 to GPe, in the model the ramps in STN activity resulted in corresponding ramps in GPe.

168 *Sensorimotor model inputs modulate time course of beta oscillations.* As a previous modeling
169 study demonstrated that excitatory input to STN or inhibitory input to GPe can induce transient
170 beta oscillations (Kumar et al., 2011), we hypothesized that the sequence of ramp, Go cue and
171 movement-related activity patterns (Figures 3A, B) accounts for the complex beta dynamics in
172 the LFP (Leventhal et al., 2012). First, we reproduced the time course of beta power modulation
173 during movement initiation (Leventhal et al., 2012) using an extended data set of GPe recordings
174 (Schmidt et al., 2013; Mallet et al., 2016). In the rat LFPs beta power started to increase before
175 the time of movement initiation and then showed a pronounced peak just after movement onset
176 (Figure 3C, top). The time course of beta power in the network model exposed to our single-unit
177 stimulation patterns (Figure 3B) matched the experimentally observed results (Figure 3C, bottom),
178 including the pre-movement beta power increase, the pronounced beta peak during movement, and
179 the second beta peak related to the movement out of the side port (see Methods). The network
180 model beta time course was in this case determined by the STN ramping activity, combined
181 with the sensory responses of the STN neurons and the striato-pallidal motor inputs (Figure 3B).
182 This is an important result because it connects single unit activity during task performance with
183 oscillatory network dynamics.

184 Here, we compared the experimental LFP data with the model population firing rate (Figure
185 3C). However, the origin of the LFP and its relation to spiking activity are not well understood in
186 the basal ganglia. It seems that the LFP mostly reflects synchronized postsynaptic currents (Nie-
187 dermeyer and Lopez da Silva, 1998; Nunez and Srinivasan, 2005; Jensen et al., 2005; McCarthy et
188 al., 2011). However, we found that the time course of beta oscillations was very similar, irrespec-
189 tive of whether we used the population firing rate or the summation of inhibitory or excitatory
190 postsynaptic currents to represent the experimental LFP data (data not shown). Therefore, to stay
191 consistent with previous models (e.g. Kumar et al., 2011; Pavlides et al., 2015; Nevado-Holgado
192 et al., 2014), we continue to use the population firing rate in the model to determine the presence
193 of beta oscillations.

194 *Sensory responses in STN lead to a beta phase reset.* In addition to the described changes in
195 beta power, the phases of beta oscillations can be modulated by specific events in the behavioral
196 task. Sensory cues (like the auditory Go cue) that did not lead to a distinctive increase in beta
197 power were nevertheless followed by a short-latency phase reset in the LFP (Leventhal et al.,

2012). By contrast, beta power increases during movement were not accompanied by a phase
reset in the beta band (Leventhal et al., 2012). Here, we confirm this result for GPe recording
sites using an extended data set (Figures 4A, E; Schmidt et al., 2013; Mallet et al., 2016). To
determine which properties of the neural signal lead to a phase reset or to a power increase in the
beta band, we calculated grand averages of raw LFP traces (Figure 4C). We found that briefly
after the Go cue a single beta cycle was visible. This short oscillation was rather weak and could
only be visible when looking at the mean of the LFP data over many trials (Figure 4C). This
brief beta epoch was associated with beta phase reset in the LFP data, following the Go cue
(Figure 4A). Interestingly, providing brief stimulation to the “sensory” STN neurons in the model
leads to a brief low-amplitude beta oscillation, which also only became visible when inspecting
the mean population firing rate over many stimulations (Figure 4D). Similar to the experimental
data, “sensory” stimulation of the model STN leads to beta phase reset in the ongoing activity
of the network model (Figure 4B). Therefore, we conclude that brief excitatory inputs to STN
can induce weak and brief, phase-locked beta oscillations in the STN-GPe network, mimicking the
experimentally observed results.

Beta elevation around the time of movement onset was not accompanied by a phase reset in
both the rat LFP data and in the model (Figures 4E, F). It might seem counterintuitive that
a strong stimulation leading to a clear increase in beta power, did not reset the phase, whereas
a weaker stimulation did. However, STN neuronal responses to the Go cue are brief, compared
to the longer movement-related increases in the activity of MSNs (Figures 1C-E). Therefore, we
hypothesized that the duration of neural responses to sensory and motor events might be the key
difference. To test this, we systematically varied the duration of the inputs to the model “sensory”
STN neurons and “motor” GPe neurons (note that the inputs are inhomogeneous Poisson spike
trains with firing rate patterns of a half cosine wave; see Methods). We found that for brief inputs
(leading to brief changes in the neuronal activity) there was a phase reset in the ongoing activity
of the network model (Figure 5). Longer stimulations of “motor” GPe neurons elevated the beta
power without phase reset (Figures 5C, D). For stimulation durations longer than a single beta
period in the model (i.e. about 50 ms), we only observed beta power elevation without phase
reset (Figures 5C, D). In fact, the maximal phase reset in the network model occurred when
the stimulation duration was 25 ms, equaling half the beta cycle (Figures 5B, D). For the short
stimulation duration the time to get to the maximum of the half cosine firing rate pattern in short
(i.e. the slope is larger). This effectively leads to no trial-to-trial variability because all realizations
of the Poisson process with such a brief firing rate pattern are very similar (with respect to the
spike times). This similarity in the input then leads to a similar response in the network model
and therefore a phase reset across trials. In contrast, for longer stimulation the time to get to the
maximum of the half cosine firing rate pattern is longer (with smaller slope). This leads to more
trial-to-trial variability with respect to the spike times in the realization of the Poisson process.
Correspondingly, this translates into trial-to-trial variability in the response of the network model
to the long stimulation and therefore a random phase across trials.

Longer stimulations of the “sensory” STN neurons did not elevate the beta power in the network
model (Figure 5A). This is because “sensory” STN units made up a smaller fraction (27%) of
the STN population in our model compared to 40% “motor” GPe units (see above). The long
stimulation of a small fraction of the STN neurons was not sufficient to bring the network model
into the oscillatory state. In general, for a certain stimulation strength, the fraction of stimulated
neurons in the network model is an effective parameter to determine the amount of evoked beta
power (Kumar et al., 2011).

244 *Disentangling the complex relationship between reaction time and beta dynamics.* The time
245 course of beta oscillations depends on how fast the animal initiates movement in response to the
246 Go cue (Leventhal et al., 2012). For short reaction times, the mean LFP beta power shows a single
247 peak after movement initiation. For long reaction times, the mean LFP beta power shows two
248 peaks, with the first peak before and the second peak after movement initiation (see highlighted
249 300 ms epochs preceding and following Nose Out in Figure 6A, right; see also Leventhal et al.,
250 2012). The bimodal shape of the mean beta power for long reaction time trials is also visible when
251 aligned to the Go cue (Figure 6A, left). A straightforward idea would be that the first peak of the
252 mean beta power for long reaction time trials is mostly driven by the Go cue or, alternatively, by
253 the upcoming movement. However, if the beta peak was driven by the Go cue, we would expect
254 a higher peak for the data aligned to the Go cue than for the data aligned to movement onset.
255 Accordingly, if the beta peak was related to the movement, we would instead expect a higher
256 peak for the data aligned to the movement onset. In contrast, despite variability in reaction time,
257 this peak had a similar shape and amplitude for both alignment to the Go cue and to movement
258 onset. Therefore, this beta peak does not seem to be simply driven by a sensory or motor event.
259 With the help of our network model, we disentangle the mechanisms underlying these reaction
260 time-dependent complex features of beta.

261 Using our stimulation patterns based on single unit recordings, we studied how different reaction
262 times affect the time course of beta power. We found a strikingly similar effect of reaction time
263 on the time course of beta power in the network model (Figure 6B). For long reaction time trials
264 the model exhibited two separate peaks in the mean beta power with the same time course as the
265 experimental LFP data (Figure 6B). Furthermore, the peak of the mean beta power in the model
266 after movement onset for short reaction time trials had a higher amplitude than in long reaction
267 time trials, similar to the experimental LFP data (see right panels in Figures 6A and 6B). The
268 ability of the model to capture the fine details of the complex beta power modulation became
269 visible even at the single-trial level (Figures 6C, D). As in the experimental data, changes in mean
270 power modulation were reflected as a change in the probability of a transient beta oscillation,
271 rather than as only a gradual increase in the oscillation amplitude.

272 To understand the mechanisms underlying the complex relationship between beta and reaction
273 times, we can now use our network model to determine the contribution of each stimulation
274 component. Before the Go cue, ramping activity of the STN neurons in the model causes a
275 gradual increase in beta power (mostly because of an increase in probability of beta), starting
276 almost 600 ms before the Go cue (Figures 6B, D and Figure 7). At the time of the Go cue the
277 sensory responses of the STN neurons generate a weak and brief beta oscillation in the model
278 (green traces in Figure 7). In short reaction time trials this brief beta oscillation overlaps with
279 beta oscillations driven by “ramp” and “motor” inputs (as sensory and motor events are temporally
280 close). This overlap results in an interaction of ongoing beta (driven by “ramp” input) with beta
281 driven by “motor” input, leading to high beta power around the time of movement onset (Figures
282 6B and 7, top). For long reaction time trials, after the Go cue, but before movement initiation, the
283 “sensory” and “ramp” inputs determine the beta dynamics in the model. The interaction between
284 the “sensory” and “ramp” inputs leads to the first, high-amplitude beta peak for long reaction
285 time trials (Figures 6B and 7, bottom). As Go cue and Nose Out events are temporally distant
286 for long trials, this high-amplitude beta power starts to decay before the time of movement onset.
287 This is followed by another beta epoch due to “motor” input which leads to the second peak of
288 beta power, after the time of movement onset, for long reaction time trials (Figures 6B, D and

289 7). The amplitude of this second peak is smaller, compared to the peak after movement onset for
290 short reaction time trials (Figure 6B, right), because it lacks the interaction with STN excitation
291 due to the Go cue (Figure 7). Functionally, the first beta peak in long reaction time trials may be
292 linked to the prolongation of movement initiation in high beta states (Levy et al., 2002; Brown et
293 al., 2001; Chen et al., 2007; Pogosyan et al., 2009). Thereby our model connects “ramp” activity
294 in STN with the generation of beta oscillations and potential functional roles as a “brake” (Frank,
295 2006).

296 *Our results are robust to the STN-STN recurrent connectivity in the network model.* In the
297 network model we used, the STN neurons received excitatory synaptic inputs from other STN
298 neurons with a connection probability of 2% (Kumar et al., 2011). However, several experimental
299 studies indicate that the STN-STN recurrent connectivity is very rare or do not exist (Hamond
300 and Yelnik, 1983; Sato et al., 2000; Parent and Parent 2007; Koshimizu et al., 2013). Therefore,
301 we modified the network model parameters to test if the model without STN-STN connections
302 is also able to capture the behaviorally relevant dynamics of the LFP beta oscillations. Indeed,
303 with slight modifications of parameters (see Methods), all key results, including the time course of
304 beta around the time of movement preparation and execution (Figure 8A), the beta phase reset
305 (Figures 8B, C), and the complex relationship between beta and reaction time (Figures 8D, E),
306 were reproduced. This demonstrates that our model account of transient beta oscillations does
307 not depend on STN-STN recurrent connectivity.

308 In summary, our results show that the combination of 1) sensory responses of STN neurons,
309 2) movement-related inhibition of GPe neurons, and 3) ramping activity in STN, account for the
310 complex properties of beta power modulation over time, beta phase reset and correlations with
311 reaction time of rat electrophysiological recordings in the basal ganglia. Thereby, the model allows
312 us to make clear predictions about the underlying mechanisms and provides the basis for studying
313 functional consequences on neural processing and behavior.

314 Discussion

315 Oscillations in the LFP often reflect sensory, cognitive and motor aspects of neural processing,
316 but can be difficult to interpret due to a lack of understanding how and why network oscillations
317 emerge. Furthermore, we currently face a gap between firing patterns of single neurons and larger
318 scale network dynamics. Here we addressed this by a combination of experimental data with
319 computational modeling to study how firing patterns in single unit recordings of task-performing
320 healthy rats affect basal ganglia network dynamics. Although our computational model was origi-
321 nally used to describe beta oscillations in Parkinson’s disease, we found that this model can also
322 account for many properties of beta oscillations in healthy animals. Thereby, we are able to char-
323 acterize potential neuronal mechanisms underlying oscillations, relate healthy to pathological beta
324 oscillations, and provide avenues for studying functional roles of beta oscillations in behavior.

325 Neuronal mechanisms of beta oscillations

326 Both computational and experimental studies have implicated the STN-GPe network in beta
327 oscillations in Parkinson’s disease (Brown et al., 2001; Magill et al., 2001; Terman et al., 2002;
328 Bevan et al., 2002; Rubin and Terman, 2004; Brown and Williams, 2005; Mallet et al., 2008a;

329 Tachibana et al., 2011; Stein and Bar-Gad, 2013; Nevado-Holgado et al., 2014; Pavlides et al.,
330 2015; Wei et al., 2015). Moreover, it has been proposed that cortico-subthalamic excitation as well
331 as striato-pallidal inhibition can generate beta oscillations in a network model of the subthalamo-
332 pallidal loop (Gillis et al., 2002; Kumar et al., 2011; Nevado-Holgado et al., 2014; Pavlides et al.,
333 2015; Wei et al., 2015; Ahn et al., 2016). In line with this we show that a combination of temporally
334 regulated subthalamic excitation and pallidal inhibition reproduces the dynamics of transient beta
335 oscillations observed in the healthy basal ganglia during behavior. Therefore, our findings support
336 the idea that the same network that is responsible for beta oscillations in Parkinson's disease may
337 also be involved in the generation of healthy beta oscillations in the basal ganglia.

338 Alternative to the STN-GPe network, also other mechanisms for the generation of beta oscillations
339 have been proposed, including networks of striatal MSNs (McCarthy et al., 2011), feedback
340 projections from GPe back to striatum (Corbit et al., 2016), or spread of cortical beta to STN.
341 However, our model supports the role of the STN-GPe network in the generation of beta oscillations
342 due to the close correspondence between single unit activity patterns and the resulting
343 complex time course of beta oscillations. To what degree other models for the generation of beta
344 would be able to account for the complex time course and behavioral correlates of beta remains
345 to be shown. While increased striatal spiking increases beta oscillations in several models (Mc-
346 Carthy et al., 2011; Kumar et al., 2011; Corbit et al., 2016), our model emphasizes in addition
347 the role of excitatory inputs to STN for the transient dynamics of beta oscillations. Overall, as
348 beta oscillations are a heterogeneous phenomenon with different frequency and behavioral corre-
349 lates (Szurhaj et al., 2003; Kilavik et al., 2012; Feingold et al., 2015), it is likely that cortical and
350 subcortical circuit contain several circuits and mechanisms for the generation of beta oscillations,
351 e.g. to permit long range communication (Fries, 2005). Therefore, these different models are not
352 necessarily exclusive and a key future challenge will be to disentangle the different circuits and
353 their interaction. Nonetheless we have shown that the STN-GPe network is sufficient to explain
354 many features of beta oscillations in awake behaving animals.

355 **Concurrent activation of direct and indirect MSNs during movement**

356 Activity of direct pathway MSNs (striato-nigral) promote actions while indirect pathway MSNs
357 (striato-pallidal) suppress actions (Albin et al., 1989; Alexander and Crutcher, 1990; Kravitz et al.,
358 2010; Freeze et al., 2013; Schmidt et al., 2013; Roseberry et al., 2016). However, here we considered
359 movement-related increases in MSN activity (Figure 1E) as inhibitory input to the model GPe
360 (Figures 3A, B), without knowing whether the recorded MSNs are part of the direct or indirect
361 pathway. This model assumption is supported by evidence that direct and indirect pathway MSNs
362 are concomitantly active during movement preparation and execution (Cui et al., 2013; Isomura et
363 al., 2013). Nevertheless, there might be important activity differences between direct and indirect
364 pathway neurons coordinating behavior. Whether co-activation of indirect pathway MSNs during
365 movement reflects the suppression of alternative actions (Hikosaka et al., 2006; Redgrave et al.,
366 2010) or is also important to activate specific neural assemblies in motor cortex (Oldenburg and
367 Sabatini, 2015) remains unclear. Furthermore, almost 60% of direct pathway MSNs, possess
368 collateral terminal fields in GPe (Cazorla et al., 2014). Therefore, it seems likely that during
369 movements GPe receives increased inhibitory input from striatal MSNs as incorporated in the
370 model.

STN as a brake in the motor system

We found that many STN neurons exhibited a ramp in their firing rate while the animal was waiting for the Go cue. During this time it is essential for the animal not to initiate premature movements in order to receive the food reward (error trials were not rewarded). Building on previous models of STN providing a “hold-your-horses” signal (Frank, 2006), these ramps might prevent or delay the execution of movements. Correspondingly, in our experimental data the ramps reached a plateau after the Go cue, which was linked to the reaction time (i.e. the plateau persisted longer in trials with a long reaction time; Figure 2A, bottom). Therefore, these ramps might modulate the readiness for movement initiation exerted on downstream structures. However, we also observed (data not shown) that the population activity of the STN ramps did typically last until the time of movement initiation or even briefly longer, indicating that the offset of this STN ramp does not provide a motor command itself. Instead, high STN activity might ensure that only coordinated movement commands (potentially signaled by striatal output), but not premature movement impulses, lead to motor output.

Conceptually, our model provides an important link between putative “hold-your-horses” ramping activity in STN, beta oscillations and reaction times. The ramping activity (Figures 3A and 3B) increased spiking activity of the STN neurons and, consequently, lead to also more beta oscillations in the model (Kumar et al., 2011). This was key in accounting for the experimentally observed bimodal shape of the mean beta power for long reaction time trials in the model (more specifically, to generate the first peak of the mean beta power for long reaction time trials; Figure 6B).

The STN ramps might be due to cortical drive. For example, in the motor cortex of monkeys similar ramping activity has been observed while the animals anticipated sensory cues and needed to prevent premature movements (Confais et al., 2012). Furthermore, other cortical areas including right inferior frontal cortex and the pre-supplemental motor area project to STN and have been implicated in motor suppression (Wessel and Aron, 2017). In general, cortico-subthalamic excitation has previously been proposed to be important for the generation of beta oscillations (Tachibana et al., 2011; Pavlides et al., 2015). Importantly, the STN ramps during the hold period increased the probability of transient beta oscillations in our model. This fits well with anti-kinetic aspects of beta oscillations (Brown and Williams, 2005), and with STN activity correlating with slowness of movement observed during the progression of Parkinson’s disease (Bergman et al., 1994; Remple et al., 2011).

Behavioral relevance and model predictions

Beta oscillations seem to comprise a heterogeneous phenomenon with potentially different functions and mechanisms depending on the brain region (Szurhaj et al., 2003; Kilavik et al., 2011; Feingold et al., 2015). Here we extend this view by proposing that transient, non-pathological basal ganglia beta oscillations can be driven by two distinct inputs. Firstly, beta oscillations can be driven by excitatory inputs to STN, including the ramping firing rate increases that might be linked to preventing premature movements (see above). Secondly, in the model, beta oscillations were also driven by increased striato-pallidal inhibition during movement. Therefore, our model provides an explanation for why beta oscillations in some cases can be “antikinetic” (Brown and Williams, 2005), but in other cases can also appear during movement (Leventhal et al., 2012).

413 Whether and how these two different modes of beta oscillations make functional contributions,
414 e.g. by differential communication and signaling with other brain regions (Fries, 2005), is an open
415 question.

416 Based on our model we make several experimentally testable predictions. Firstly, the two modes
417 of beta generation, via inhibition of GPe and excitation of STN, might have different signatures
418 in LFP recordings. If the beta oscillation is generated by striatal inhibition of GPe, the beta
419 oscillation begins with a decrease in GPe activity. If the beta oscillation is generated by STN
420 excitation (e.g. by cortical input), then the beta oscillation begins with an increase in STN and a
421 subsequent increase in GPe activity. Although we do not know yet how spiking in the STN and
422 GPe relates to patterns in the LFP, these two modes could e.g. translate into different onset phases
423 of beta oscillations. Therefore, we presume that transient beta oscillations could be classified based
424 on their onset phase, and that this is indicative of whether the oscillation was driven by input to
425 GPe or STN. Despite practical challenges, such as detecting the exact onset phases of beta in noisy
426 LFPs, this might provide valuable insights into whether the two modes of beta generation have
427 distinct behavioral correlates.

428 Secondly, our model makes specific predictions about the relation between activity of MSNs
429 projecting to GPe and the timing of beta oscillations (McCarthy et al., 2011). In recordings of
430 identified direct and indirect pathway MSNs, our model predicts that the activity of the D2 MSNs
431 predicts the timing of beta oscillations more accurately than the activity of the D1 MSNs. One
432 complicating factor is that this distinction does not apply to beta oscillations driven by cortical
433 excitation of STN.

434 Another model prediction arises from our observation that the duration of excitatory inputs to
435 STN determines whether a phase reset occurs in the LFP or not. Sensory neuronal responses (like
436 the auditory responses in STN; Figures 1C, D) are typically brief. We propose that sensory cues
437 from other modalities have the same effect, so that e.g. visual cues that lead to brief excitations
438 of STN also lead to a phase reset in the LFP signal. Furthermore, in addition to sensory cues,
439 brief optogenetic stimulation of STN might yield the same effect. Whether these cue-induced beta
440 phase resets play also a functional role, e.g. in the temporal coordination with inputs from other
441 regions, remains to be shown.

442 Finally, we predict that changes in the structure of the STN ramping activity affects the prob-
443 ability of beta oscillations. If the STN ramps indeed reflect a “hold your horses” signal (Frank,
444 2006), changes in the behavioral paradigm that manipulate the readiness for movement initiation
445 should directly affect the ramping activity. For example, if the cost for the animal of a premature
446 response is increased, the corresponding ramping activity might change its time course and ampli-
447 tude. In the model this would directly translate into changes in the time course and probability
448 of transient beta oscillations.

449 In conclusion, the direct combination of our computational model with experimental data pro-
450 vides a connection between single unit activity and network oscillations. This helps us to study the
451 functional contributions of transient beta oscillation during sensorimotor processing in a behavioral
452 context.

Materials and methods

Network model. The basic model structure and the parameter settings are the same as in Kumar et al. (2011). Briefly, the model includes 1000 excitatory STN neurons, and 2000 inhibitory GPe neurons. Neurons were implemented as leaky-integrate-and-fire neurons. Synaptic input was modeled as transient exponential conductance changes. All model neurons receive uncorrelated Poisson spike trains as inputs so as to achieve previously reported baseline activities for STN (15 Hz) and for GPe (45 Hz; Bergman et al., 1994; Raz et al., 2000). All network simulations were written in python using pyNN as an interface to the simulation environment NEST (Gewaltig and Diesmann, 2007).

For the model variant without recurrent connections in STN (Figure 8), we used slightly different parameters for the connection probabilities, synaptic weights and transmission delays (Table 1). Furthermore, the background Poisson input to the model neurons was adjusted so that the neurons had a broader distribution of baseline firing rates that closer matched the firing rate distribution in the rat data (Schmidt et al., 2013; Mallet et al., 2016).

Table 1: Comparison of model parameters in Kumar et al. (2011) and the modified model without recurrent STN connections.

Kumar et al., 2011	Modified model
$CP_{STN-STN} = 0.02$	$CP_{STN-STN} = 0$
$CP_{STN-GPe} = 0.02$	$CP_{STN-GPe} = 0.022$
$CP_{GPe-STN} = 0.02$	$CP_{GPe-STN} = 0.035$
$CP_{GPe-GPe} = 0.02$	$CP_{GPe-GPe} = 0.02$
$J_{STN-STN} = 1.2$	$J_{STN-STN} = -$
$J_{STN-GPe} = 1.2$	$J_{STN-GPe} = 1.2$
$J_{GPe-STN} = -1.135$	$J_{GPe-STN} = -0.8$
$J_{GPe-GPe} = -0.725$	$J_{GPe-GPe} = -0.725$
$d_{STN-STN} = 2$	$d_{STN-STN} = -$
$d_{STN-GPe} = 5$	$d_{STN-GPe} = 6$
$d_{GPe-STN} = 5$	$d_{GPe-STN} = 6$
$d_{GPe-GPe} = 2$	$d_{GPe-GPe} = 3$

CP: Connection Probability, J: Synaptic weight, d: Delay (in ms)

Electrophysiological data. We combined previously recorded data sets of tetrode recordings in different basal ganglia subregions of rats performing a stop-signal task (for details see Leventhal et al., 2012; Schmidt et al., 2013; Mallet et al., 2016). In total we recorded 276 STN units from overall 44 recording sessions in 5 different rats, 149 putative prototypical GPe units from 41 recording sessions in 4 different rats, and 326 putative MSNs from 97 recording sessions in 9 different rats. Between two recording sessions tetrodes were typically moved by at least $80\mu\text{m}$, and we therefore considered units recorded in different sessions as different units. Animals performed

474 a stop-signal task, but here we only analyzed the subset of correct Go trials in which the animal
475 moved contralateral to the recording site.

476 *Analysis and modeling of sensory and motor responses.* To identify STN neurons responding to
477 the Go cue instructing contralateral movement (Figures 1C, D), we used a shuffle test to determine
478 whether neural activity significantly increased within 150 ms after the Go cue. The time of each
479 spike within -500 ms to +200 ms relative to the Go cue was changed to a random spike time
480 within the same time window. Then we compared the number of actual spikes with the number of
481 shuffled spikes in small time windows after the Go cue (15 non-overlapping 10 ms windows from
482 0 to 150 ms after the Go cue). We repeated this procedure 10000 times and used the fraction of
483 shuffles in which the number of shuffled spikes exceeded the number of actual spikes as the p-value
484 to estimate statistical significance. STN neurons showing a p-value less than 0.01 for at least one
485 bin after the time of the Go cue were considered as sensory responsive. We performed the same
486 shuffling method on GPe neurons to select movement responsive GPe neurons (Figure 1F), using
487 all spikes within -1s to +1s relative to movement onset to detect firing rate changes for 50 ms
488 time windows from 0 to 250 ms after movement onset (i.e. 5 non-overlapping time bins). GPe
489 neurons showing a p-value less than 0.05 for at least one bin after movement onset were considered
490 as movement responsive.

491 To simulate sensory responses of STN neurons to the Go cue (Figures 1C, D), we used inho-
492 mogeneous Poisson generators, each of which targeted one STN neuron in the model. The firing
493 rate modulation of each inhomogeneous Poisson generator was a half sine wave with a duration of
494 20 ms and maximum amplitude of 200 Hz. The latency of the sensory stimulation for each STN
495 neuron in the model was considered as the time interval between the peak of the half sine wave
496 and the time of the Go cue, which was taken randomly from the latency distribution of the sensory
497 STN neurons in our experimental data (Figure 1D). Since in our single unit data 27% of the STN
498 neurons responded to the Go cue, for each simulation we targeted 27% of randomly chosen STN
499 neurons (as “sensory” STN neurons) in the network model.

500 Average firing rates of MSNs in our data were sorted based on their peak time within the interval
501 from one second before to one second after movement initiation. MSNs with a peak firing rate
502 between 150 ms before to 150 ms after movement onset were considered as movement-responsive
503 MSNs ($n = 100$; see Figure 1E). Firing rates of the movement-responsive MSNs were summed up
504 and used as the firing rate pattern of an inhomogeneous Poisson generator representing striato-
505 pallidal movement-related inhibition in the network model. Since 40% of the GPe neurons in our
506 experimental data showed movement-related inhibition, for each simulation we targeted randomly
507 chosen 40% of the GPe neurons (as “motor” GPe neurons) in the network model.

508 *Analysis and modeling of firing rate ramps.* To determine whether a recorded unit showed a
509 ramping firing pattern, we computed the average firing rates of each unit from one subregion over
510 trials with a 50 ms sliding time window moving in steps of 10 ms from 1 s before the time of Go cue
511 to the time of Go cue. Each resulting average firing rate was then normalized to values between 0
512 and 1 and then mean-subtracted before applying principal component analysis. First, we computed
513 the corresponding covariance matrix of all normalized zero-mean firing rates. and then performed
514 eigendecomposition on the covariance matrix using the *eig* function of MATLAB. The projection
515 p of each normalized zero-mean average firing rate r to the first eigenvector (corresponding to the
516 maximum eigenvalue) was then computed as the normalized dot product: $p_i = \langle r_i, v_1 \rangle / \lambda_1$, where i
517 is the unit index and v_1 the eigenvector with the largest eigenvalue λ_1 . This yielded one projection

518 value p_i for each recorded unit. As the first eigenvector had a positive ramp over time, positive
519 and negative projection values corresponded to positive and negative activity ramps of a recorded
520 unit over time, respectively. The standard deviation of the projection distribution from a random
521 covariance matrix is $1/\sqrt{n}$ (Anderson, 2003), with n being the number of units. We considered
522 neurons with a projection larger than $2/\sqrt{n}$ or smaller than $-2/\sqrt{n}$ as positive and negative ramp
523 neurons, respectively (Figures 2A, B). This analysis method was applied to determine positive and
524 negative ramps in GPe and STN.

525 To simulate the positive and negative ramps in the activity of the STN neurons observed before
526 the Go cue (Figures 2A, B), for each simulation, we divided STN neurons in the network model
527 into two non-overlapping subpopulations. The fraction of STN neurons in each subpopulation in
528 the network model was similar to the fraction we obtained from our experimental data (i.e. 34%
529 of neurons exhibited a positive ramp, 43% a negative ramp). We used an inhomogeneous Poisson
530 generator with a positive ramp firing rate pattern as excitatory input to the positive ramp STN
531 subpopulation in the model. The positive ramp in the firing rate of the inhomogeneous Poisson
532 generator started 500 ms before the Go cue at 0 Hz and reached 250 Hz at the time of the Go
533 cue and stayed constant until the movement onset (Figure 3B). Such a stimulation lead to a 4 Hz
534 increase in the activity of the positive ramp STN subpopulation in the network model during the
535 500 ms time interval preceding the Go cue, similar to what we observed in our experimental data
536 (Figure 2A).

537 Similarly, to simulate the negative ramp in the activity of STN neurons, we used another
538 inhomogeneous Poisson generator with a positive ramp firing rate pattern as inhibitory input to
539 the negative ramp STN model neuron subpopulation. The positive ramp in the firing rate of the
540 inhibitory inhomogeneous Poisson generator started 500 ms before the time of Go cue at 0 Hz and
541 reached 350 Hz at the time of the Go cue and stayed constant until the movement onset. Such a
542 stimulation pattern lead to a 1 Hz decrease in the activity of the negative ramp STN neurons in
543 the network model during 500 ms time interval preceding the Go cue, similar to what we observed
544 in our experimental data (Figure 2B).

545 *Time-frequency analysis.* The power spectrogram was computed by convolving the GPe popu-
546 lation firing rate in the model with a standard Morlet wavelet ($\sigma = 0.849/f$) of integer frequencies
547 ($f = 1$ to 500 Hz), and taking the logarithm of the squared magnitude of the resulting time
548 series. To generate Figure 3C, bottom, we computed the mean spectrogram across 400 simulations
549 of the model. The same method was used for GPe LFP data to generate Figure 3C, top. For each
550 time point in the spectrogram, we summed the power in the beta range (15 to 30 Hz) and divided
551 it by the summed power across all frequencies (1 to 500 Hz) to obtain continuous relative beta
552 power, shown in Figures 4A, 4B, 4E, 4F, and 6B.

553 *Mean resultant length.* The GPe population firing rate in the network model was convolved with
554 the standard Morlet wavelet of each integer frequency in the beta band (15 to 30 Hz). For each
555 frequency, the Hilbert transform of the filtered signal was computed to obtain a phase over time.
556 The phase spread for each time point was then calculated by computing the length of the mean
557 resultant vector over all trials using $MRL(t) = \frac{1}{n} \sum_n e^{i\theta(n,t)}$, where $\theta(n,t)$ is the phase of the n th
558 trial at time t ($n = 400$ for the model). This results in a continuous measure of phase spread for
559 each frequency in the beta range. The mean resultant lengths shown in Figure 4 were computed
560 by taking the average across all beta frequencies.

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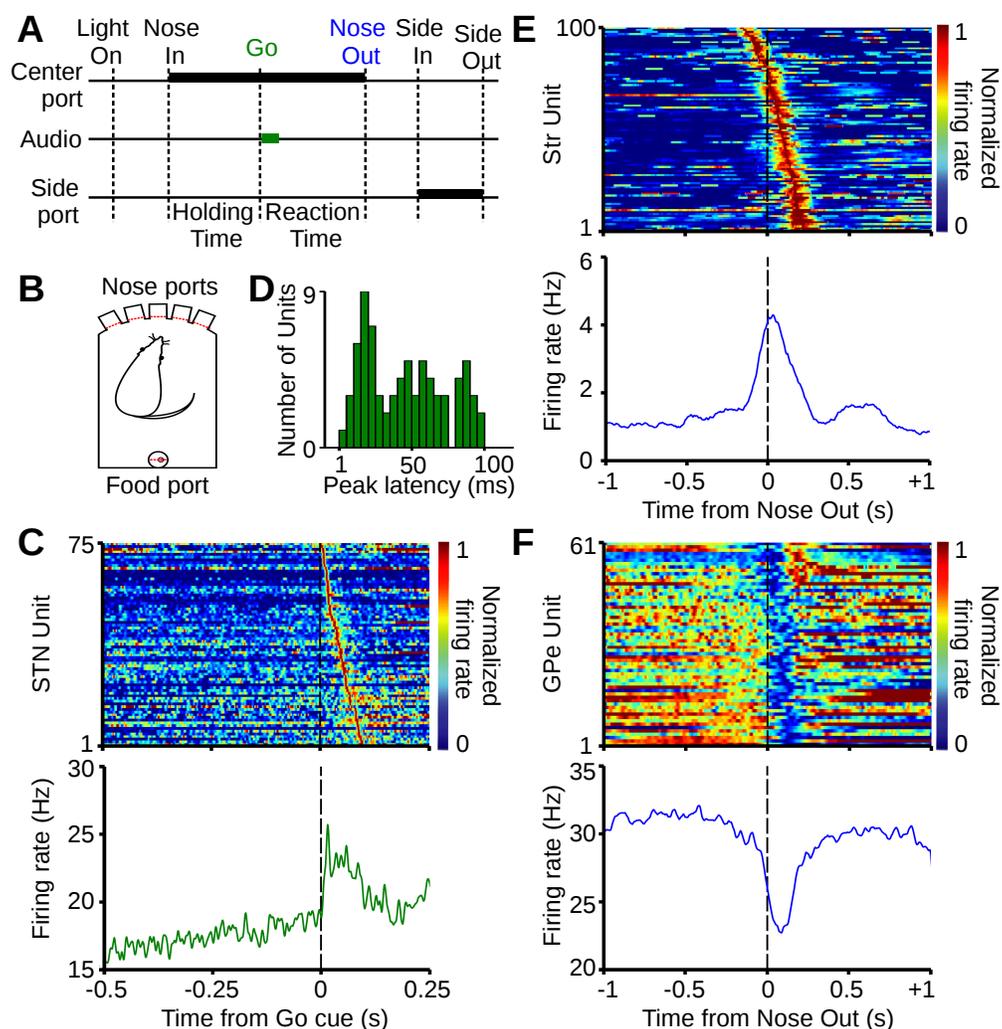


Figure 1: Single unit responses to sensory and motor events during performance of the behavioral task. **A**, Sequence of behavioral events during the experiment. Thick black bars show the position of the animal and thick green bar shows the occurrence of the sensory cue. Holding time refers to a random time delay (500 to 1200 ms) in which the animal waits in one of the three central ports for the sensory cue. Reaction time is measured as the time between the onset of the Go cue and movement initiation (Nose Out). **B**, Scheme of the operant chamber with five nose ports in front and a food port in the back. **C** (top) Normalized mean firing rates of single STN units responding to the Go cue with an increase in firing rate (sorted by peak latency; each row shows activity of one unit). Bottom, corresponding mean firing rate of the STN subpopulation. **D**, Distribution of peak latencies relative to the time of Go cue for STN neurons shown in C. **E** (top) Normalized firing rates of single units in the striatum (putative MSNs) increasing their activity around movement onset (sorted by time of peak activity). Bottom, corresponding mean firing rate of the subpopulation. **F**, Same as E, for GPe subpopulation decreasing activity around movement onset.

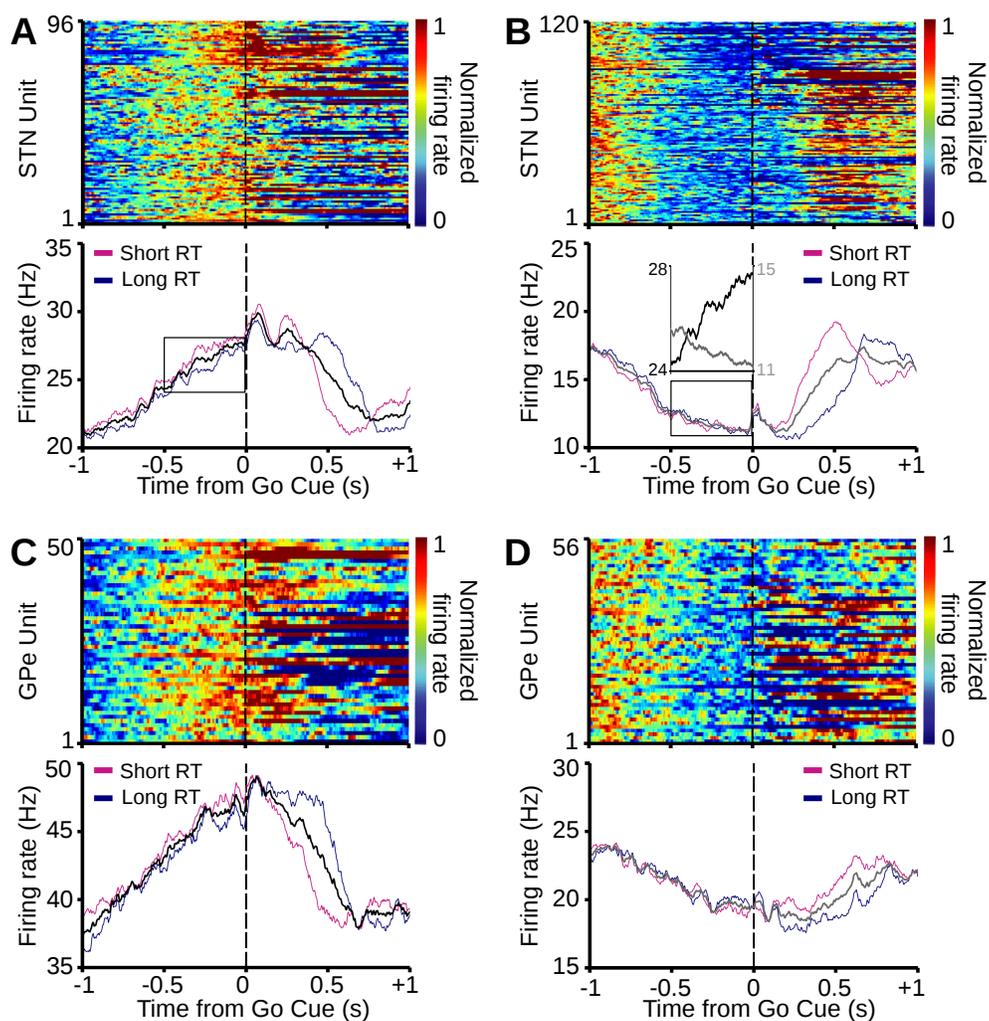


Figure 2: Ramping activity in STN and GPe while the animal is waiting for the Go cue. **A** (top) Normalized mean firing rate of single STN units with a positive ramp in firing rate before the Go cue. Bottom, corresponding mean firing rate of the STN subpopulation in all trials (black) and subsets of long (cyan) and short (magenta) reaction time trials. **B**, Same as A, for single STN units with a negative ramp in their firing rate before the Go cue. Inset, direct comparison between average firing rates of neurons in A, and B, corresponding to the areas inside the black rectangles. **C**, **D**, Similar to A and B, respectively, for GPe units.

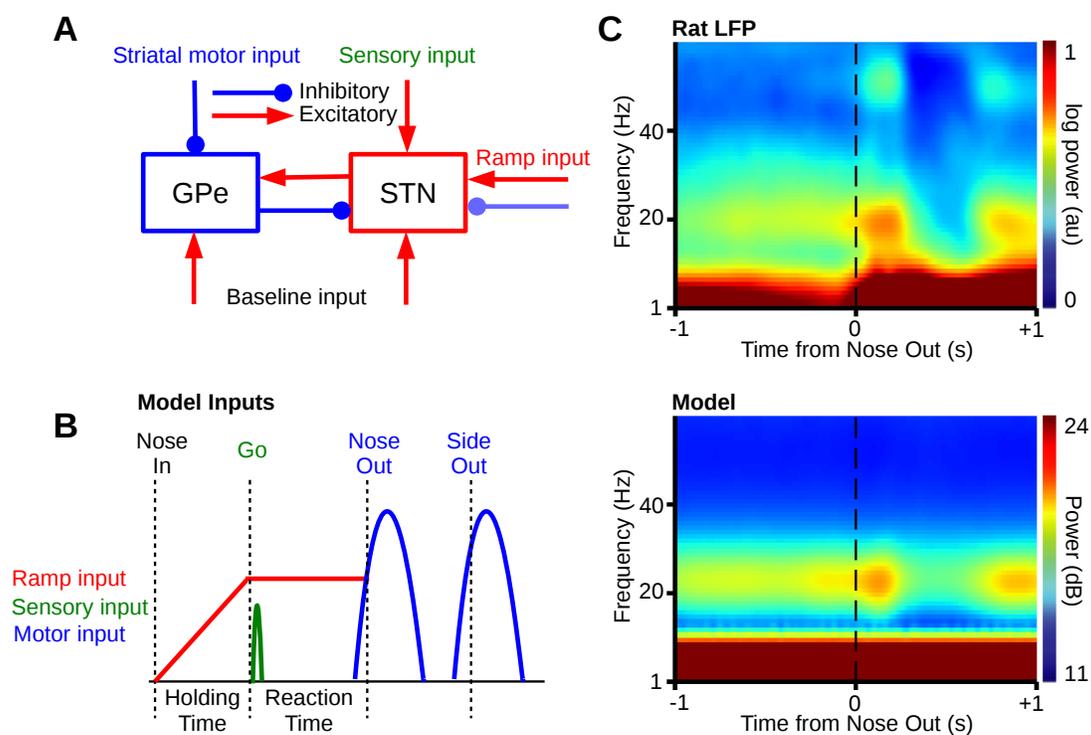


Figure 3: Computational model of beta oscillations stimulated with biologically realistic input patterns. **A**, Scheme of the STN-GPe spiking neuronal network model. Motor input is provided as striatal inhibitory input to the GPe whereas sensory input is provided as excitatory input to the STN. Brake input comprises separate excitatory and inhibitory inputs to separate STN subpopulations (see Methods). **B**, Schematized temporal sequence of inputs to the network model during simulation of the behavioral task. **C** (top) Mean spectrogram of GPe LFP data showing modulation of LFP beta power during movement initiation. Bottom, Mean spectrogram (over 400 simulations) of GPe average firing rates for simulation of correct Go trials in the network model matching the time course of beta power in the experimental data.

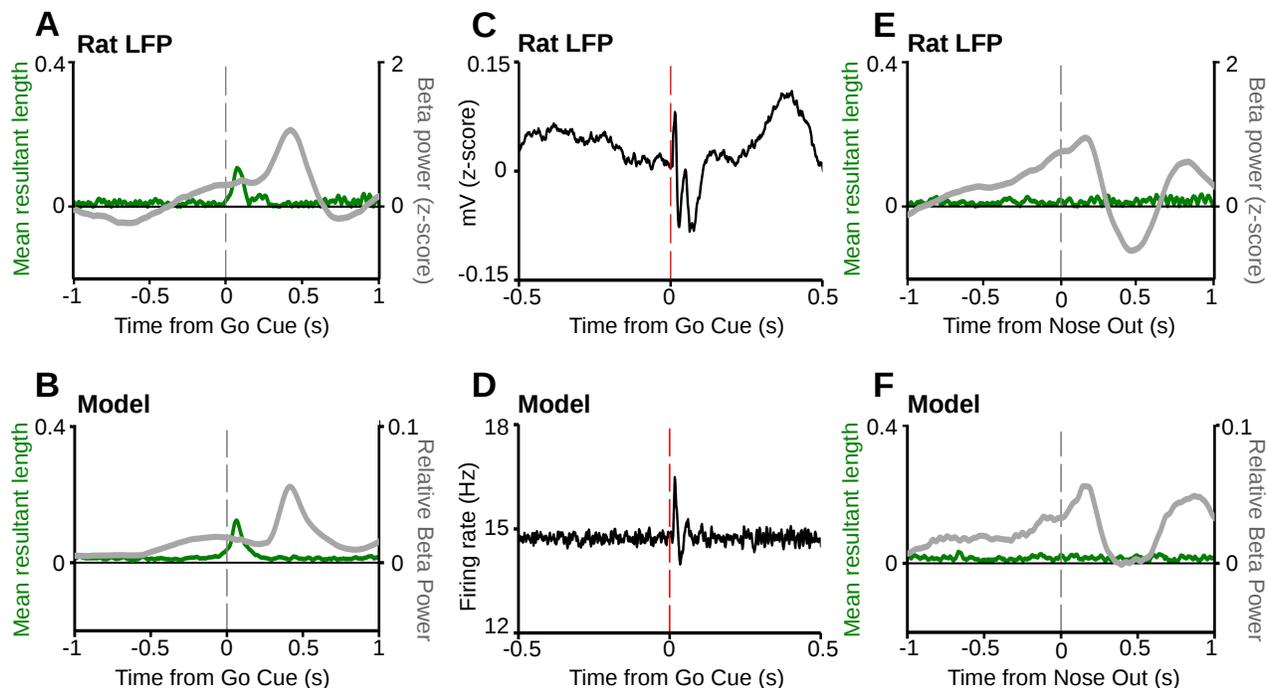


Figure 4: Sensory cues lead to a beta phase reset in both experimental data and in the network model. **A, B**, Time resolved beta mean resultant length (left axes, green) and beta power (right axes, gray) of GPe LFP data during correctly performed contralateral go trials averaged across all rats (**A**) and of the network model GPe population firing rate (**B**; average of 400 simulations). Note that sensory input is associated with a phase reset in both experimental data and in the model, shown as a brief increase in the value of the mean resultant length after the Go cue. **C**, Mean of the raw experimental STN LFP data, over all correctly performed contralateral go trials, aligned to the Go cue. **D**, Mean of the STN population firing rates in response to the Go cue in the network model (average of 400 simulations). **E, F**, The same analysis and simulations as in **A** and **B**, respectively, but aligned to movement onset. Note that the phase distribution is random during initiation and execution of movement in both the rat and the network model (no increase in the mean resultant length around movement onset).

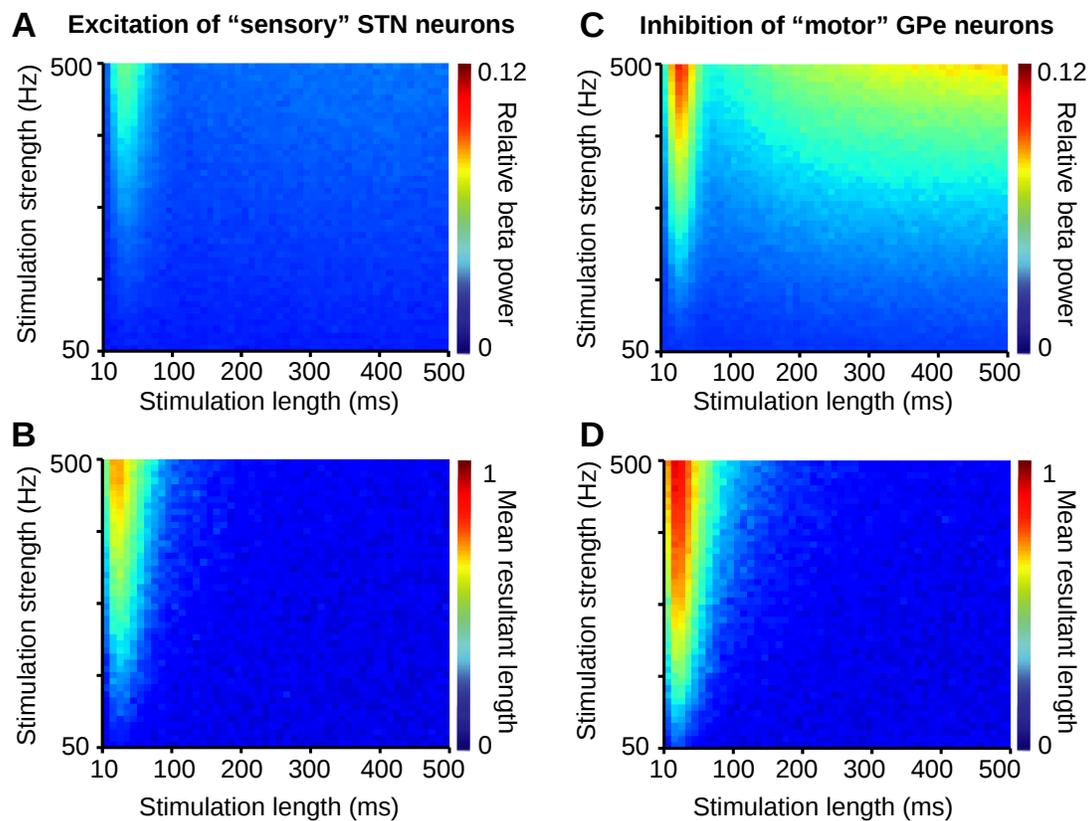


Figure 5: Effect of stimulation duration on beta power and phase reset in the network model. **A, B**, Relative beta power (A) and beta phase reset (B; measured by the mean resultant length) in the model GPe caused by excitatory input to the 27% "sensory" STN neurons of varying duration (x-axis) and strength (y-axis). **C, D**, Relative beta power (C) and phase reset (D) in the model GPe caused by inhibitory input to the 40% "motor" GPe neurons (see Methods) of varying duration (x-axis) and strength (y-axis). Note that in all panels we measure beta oscillations based on the GPe population firing rate.

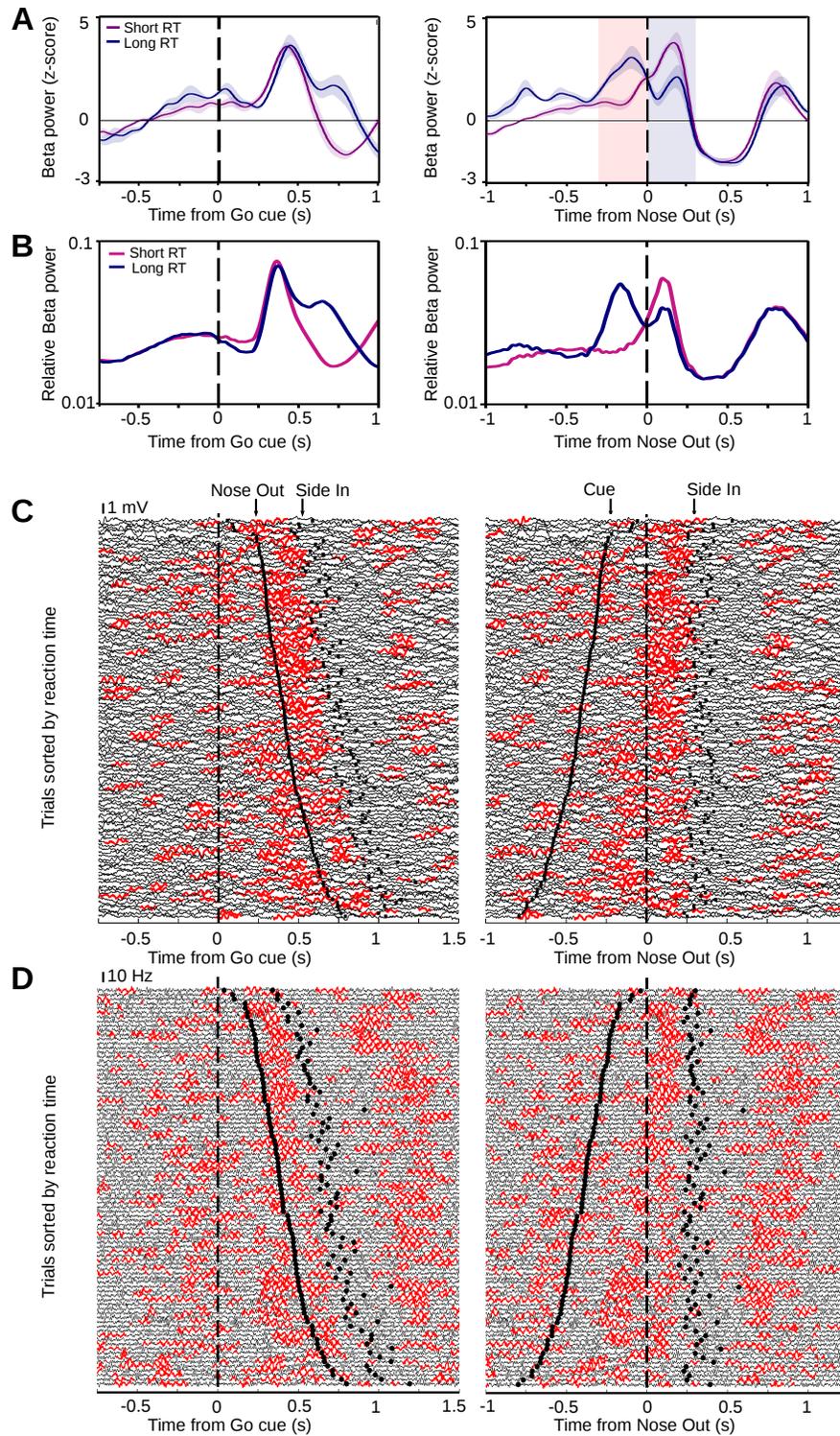


Figure 6: Relationship between beta oscillations and reaction time. **A**, Mean beta power of striatal LFP data for short (<500 ms) and long (>500 ms) reaction time trials aligned to the Go cue (left) and movement onset (right), averaged across rats (adapted from Leventhal et al., 2012, with permission from Elsevier). **B**, Mean relative beta power of GPe population firing rates in the network model aligned to the Go cue (left), and movement onset (right), averaged across 400 simulations. **C**, Single-trial striatal LFP traces from a single recording session, sorted by reaction time, aligned to the Go cue (left) and movement onset (right) with beta epochs marked in red (adapted from Leventhal et al., 2012, with permission from Elsevier). **D**, Same visualization for single-trial model simulations with each trace showing the population firing rate of GPe neurons in the network model. For simulation of each trial, the model reaction time was randomly selected from the experimental data.

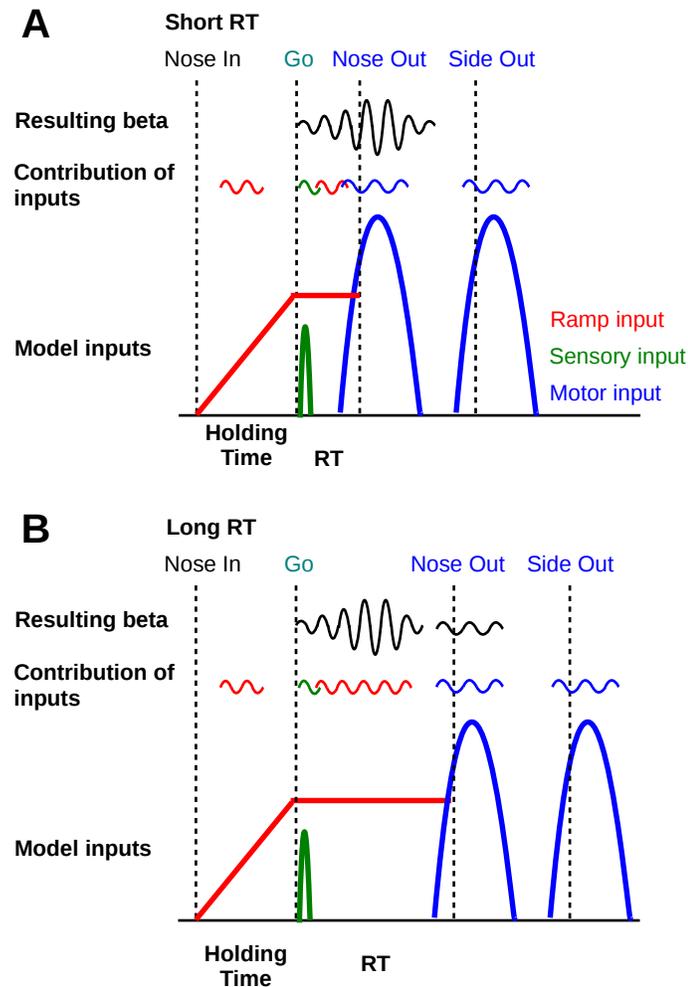


Figure 7: Scheme of contribution of each stimulation component to the generation of beta oscillations in short (A), and long (B) reaction time trials. Red, green, and blue schematized beta oscillations show the contribution of each individual input (ramp, sensory, and motor inputs, respectively) without the other one. Note that for short reaction time trials, interaction between beta oscillations due to ramp, sensory, and motor inputs leads to transient increase in beta power around the time of movement onset (black trace shows the net effect of the interaction). For long reaction time trials, interaction between beta oscillations due to sensory and ramp inputs leads to transient increase in beta power before the time of movement onset which is followed by another beta epoch due to motor input (black traces show the net effect of the interaction).

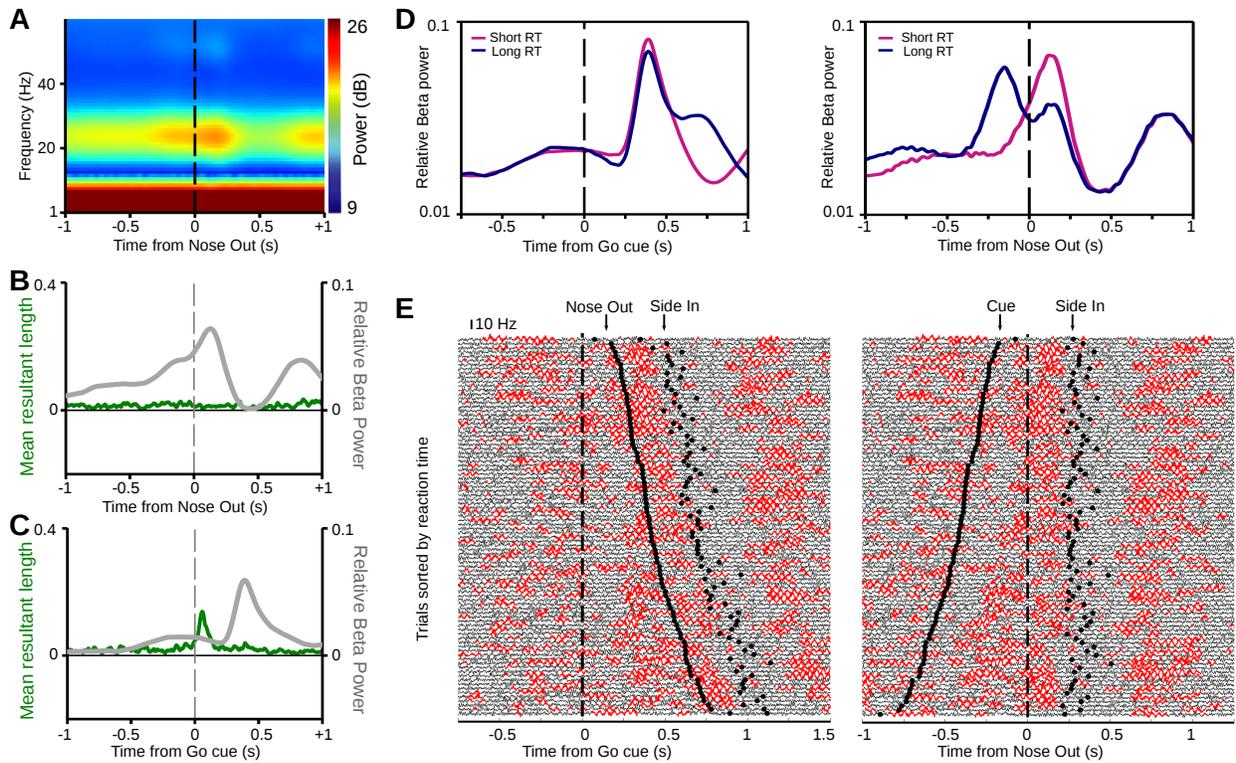


Figure 8: The network model without recurrent connections in STN reproduces all key results. **A**, Mean spectrogram (over 400 simulations) of GPe average firing rates for simulation of correct Go trials in the modified network model matching the time course of beta power in the experimental data. **B**, **C**, Time resolved beta mean resultant length (left axes, green) and beta power (right axes, gray) of the GPe population firing rate in the modified network model, aligned to the movement onset (**B**) and to the Go cue (**C**; average of 400 simulations). **D**, Mean relative beta power of GPe population firing rates in the modified network model aligned to the Go cue (left), and movement onset (right), averaged across 400 simulations. **E**, Single-trial simulations of the modified network model, sorted by reaction time, with each trace showing the population firing rate of GPe neurons, aligned to the Go cue (left) and movement onset (right; beta epochs are marked in red).