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Neurons in the monkey's subthalamic nucleus differentially encode motivation and effort

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Neurons in the monkey's subthalamic nucleus differentially encode motivation and effort

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1 TITLE

2 Neurons in the monkey's subthalamic nucleus differentially encode motivation and effort

3

4 ABBREVIATED TITLE

5 Motivation and effort in monkey's STN

6

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20 CONFLICT OF INTEREST

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22

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34

35 ABSTRACT

36

37 The understanding of the electrophysiological properties of the subthalamic nucleus (STN)
38 neurons is crucial since it represents the main target of deep brain stimulation for the
39 treatment of Parkinson's Disease and obsessive compulsive disorders. The study of its non-
40 motor properties could shed light on the cognitive and motivational alterations possibly
41 encountered after stimulation. In this study, we recorded the activity of STN neurons in two
42 male behaving monkeys (*Macaca mulatta*) while they performed a visuomotor motivational
43 task in which visual cues indicated which amount of force was required to obtain which
44 amount of reward. Our results evidenced force- and reward-modulated neurons. After the
45 occurrence of the visual stimuli, the force-modulated neurons mainly fired when a high effort
46 was required. Differently, the activity of the population of reward-modulated neurons
47 encoded the motivational value of the stimuli. This population consisted of neurons
48 increasing or decreasing their activity according to the motivational ranking of the task
49 conditions. Both populations could play complementary roles, one in the implementation of
50 the difficulty of the action and the other in enhancing or slowing its execution based on the
51 subjective value of each conditions.

52

53 SIGNIFICANT STATEMENT

54

55 An increasing number of studies confers a role to the subthalamic nucleus (STN) in
56 motivational and reward-related processes. However, the electrophysiological bases of such
57 properties at the neuronal level remains unclear. The present study investigated the
58 modulation of STN neuronal activity in monkeys performing a motivational task in which the
59 force to produce and the reward obtained were manipulated. We found two main populations
60 of neurons, one modulated by the effort required and the other integrating the motivational
61 subjective value of the stimuli. This last population could help at improving decision-making
62 to act or not, depending on the subjective value set by the motivational context. This
63 highlights the pivotal role of STN in valuation of cost/benefit for decision-making processes.

64

65 KEYWORDS

66 Subthalamic nucleus – Monkey – Reward – Effort – Motivation – Electrophysiology

67

68 INTRODUCTION

69

70 Clinical and experimental data have shown that the basal ganglia (BG) are involved in goal-
71 directed behaviors and play a role in several processes including selection and execution of
72 actions, but also reward-related learning and integration of reward value. The subthalamic
73 nucleus (STN) is considered as one of the two main input structures of the BG with the
74 striatum, since it receives direct inputs from the cortex via the hyper-direct pathway (Nambu
75 et al. 2002; Haynes and Haber 2013). The involvement of the STN in motivational processes
76 is supported first anatomically by the presence of direct projections from the ventromedial
77 prefrontal cortex, the orbitofrontal cortex and the anterior cingulate cortex (Takada et al.
78 2001, Nambu et al. 2002, Haynes and Haber, 2013, Nougaret et al. 2013), known for their
79 pivotal role in the integration of reward information. Second, STN lesion and deep brain
80 stimulation (DBS) studies in rodents have shown its involvement in impulsivity and
81 perseverative behaviors towards sweet food reward (Baunez and Robbins 1997, Baunez et al.
82 2002), opposite motivation for natural reward and drug of abuse (Baunez et al. 2005; Rouaud
83 et al 2010) and that it could affect the amount of salience allocated to stimuli conveying
84 reward-related information (Baunez et al 2002; Uslaner et al. 2008). Accordingly, numbers of
85 clinical studies using DBS to treat motor symptoms of Parkinson's disease (PD) reported
86 cognitive and motivational side effects such as impulsive choices and alteration of decision-
87 making (Frank et al. 2007, Cavanagh et al. 2011, Coulthard et al. 2012). Third,
88 electrophysiological recordings acquired in PD patients while performing cognitive tasks
89 revealed strong relationships between the oscillatory activity of the local field potential
90 (LFPs) of the STN and the mechanisms of response inhibition and regulation of decision
91 processes (Cavanagh et al. 2011, Brittain et al. 2012, Zavala et al. 2014). Studying the STN
92 LFP oscillations also revealed that the subjective cost of an action, the subjective value of a
93 reward (Zenon et al. 2016) and the specific motor effort to assign to a motor response are
94 represented at STN level (Tan et al. 2015) and that this structure is involved in monetary
95 reward processing (Fumagelli et al. 2015) and economic decisions (Rosa et al. 2013).
96 Moreover, electrophysiological data from behaving rodents and non-human primates indicate
97 that STN neurons are modulated by cues predicting reward and reward occurrence
98 (Matsumura et al., 1992 ; Darbaky et al., 2005; Teagarden and Rebec, 2007; Lardeux et al.,
99 2009, 2013; Espinosa-Parrilla et al 2013, 2015 ; Breyse et al 2015), that they could link
100 reward information to the motor output (Espinosa-Parrilla et al., 2013) and differentiate
101 reward types and relative values of reward (Lardeux et al., 2009 ; 2013 ; Breyse et al 2015 ;

102 Espinosa-Parrilla et al 2015). The STN activity correlates with the discharge balance and
103 produce a matching change of the BG downstream structure (Deffains et al. 2016). By acting
104 on the output structures of the BG, STN could suppress undesired movements by stimulating
105 their inhibitory influence (Isoda and Hikosaka, 2008 ; Mink, 1996), but conversely, it could
106 thus also enhance some actions by alleviating this influence, impairing decision-making
107 (Frank 2006). Taken together, these studies suggest a critical role of the STN in decision-
108 making and motivated behaviors and a strategic position in the cortico-BG-cortical loops
109 involving the prefrontal cortices.

110 It remains unknown however how these functions are exerted at single-cell level by STN
111 neurons and particularly how two major components of a motivated behavior, the effort it
112 requires and the benefit it brings, are integrated. To this aim, the activities of STN neurons
113 were recorded while monkeys had to exert one of two possible levels of force on a lever to
114 gain one reward of two possible magnitudes. Visual stimuli, displayed simultaneously, were
115 used to indicate to the animals the level of force required and reward magnitude on board.
116 They set a motivational value for each condition and triggered the movement. Activities were
117 analysed after stimuli occurrence, to examine whether these two variables were encoded by
118 the same or by different populations of neurons. Our data suggest that a population of STN
119 neurons encode mainly the effort to be produced when a high effort is required, whereas
120 another population of STN neurons not only encode the expected reward, but the subjective
121 motivational value of the action requiring integration of reward and force values.

122

123 MATERIAL AND METHODS

124

125 **Animal and Apparatus**

126 We trained two male rhesus monkeys (*Macaca mulatta*), weighing 8 and 7 kg at the beginning
127 of the experiments (Monkeys M and Y, respectively), to apply and maintain a pressing force
128 on a lever in response to visual cues to receive a liquid reward. All experimental procedures
129 were in compliance with the National Institutes of Health's Guide for the Care and Use of
130 Laboratory Animals, the French laws on animal experimentation, and the European Directive
131 on the protection of animals used for scientific purposes.

132

133 **Behavioral Procedures**

134 The monkeys were seated in a Plexiglas primate chair and in front of a panel supporting a 17-
135 in. screen on which visual cues could be presented. It was positioned 18 cm from the monkey.

136 A lever outfitted with strain gauges in the lower part of the panel was positioned at waist
137 level. At the front panel of the primate chair, a sliding door was opened to allow the animal to
138 position its hand on the lever. The liquid reward (apple sauce diluted with water) was
139 delivered through a distributor equipped with a peristaltic pump installed outside the
140 recording room and released via a metal spout positioned directly in front of the monkey's
141 mouth. Figure 1A illustrates the trial schedule. At the beginning of a trial, the monkeys had to
142 develop a basal pressing force on the lever during a 1-sec preparatory period. This force was
143 determined as between 0% and 20% of the maximal force, experimentally defined at 900 g
144 based on the capabilities of the animals. After this preparatory period, two visual cues, a green
145 one and a red one, each being either a filled circle or a filled square, were displayed vertically
146 in the center of the screen. Their shapes indicated, for the green stimulus, the level of force
147 the animals had to produce on the lever, and for the red stimulus the size of the upcoming
148 reward. A green circle indicated that the animals had to produce a force between 20% and
149 55% of the maximal force (180–495 g; low force: f) and a green square, a force between 55%
150 and 90% of the maximal force (495–810 g; high force: F). Similarly, a red circle indicated to
151 the animals that they could receive a small amount of reward (0.3 mL; small reward: r),
152 whereas a red square indicated that a large amount of reward could be delivered (1.2 mL;
153 large reward: R). Consequently, there were four possible combinations of cues (fR , FR , fr ,
154 and Fr) that set the four different conditions of the task. In response to a pair of stimuli,
155 monkeys had to increase their pressing force on the lever to reach the required force in a
156 period shorter than 1 sec and hold this force for 1 sec (holding time) to get the reward.
157 According to the shape of the red stimulus, monkeys were rewarded with a small or large
158 reward for each correct trial. The pair of stimuli was extinguished as soon as the reward was
159 delivered. A vertical rectangle representing the range of the required force, located below the
160 pair of stimuli, helped the monkeys to reach the required force. Indeed, a white cursor
161 displayed in the rectangle indicated the force developed on the lever in real time when they
162 were in the required force range. To keep cues constant across trial conditions, the animals
163 saw the same rectangle for both the low and high force ranges. Once the reward was
164 delivered, the monkeys returned to a basal pressing force in preparation for the next trial. The
165 next trial did not begin until the total duration of the current trial had elapsed, i. e. 4.5 sec
166 regardless of the animal behavior. Monkeys could fail to perform a trial in three different
167 cases. First, they did not reach the required force within the 1-sec force development period.
168 These trials were considered as “omission errors”. Second, they did not hold the required
169 force for at least 1 sec (holding time). These trials were considered as “holding errors”. Last,

170 they developed a force which was greater than the upper limit of the required force (495 and
171 810 g for the low and high forces, respectively). These trials were considered as “threshold
172 errors”. After an error, the same condition was presented again to the monkeys until they
173 performed the trial correctly in order to prevent the monkey avoiding the trials of a particular
174 condition. Moreover, trials in which the monkeys began to increase their pressing force within
175 100 msec after the occurrence of the cues were considered as anticipations and were excluded
176 from the database. Both monkeys were extensively trained (4–6 months) until they achieved a
177 performance of 80% of correct trials. In each recording session, the four different conditions
178 were displayed pseudorandomly from trial to trial. The same condition was not displayed
179 more than three times sequentially if trials were performed correctly.

180

181 **Surgery**

182 The surgery protocol was the same than previously described in Nougaret and Ravel (2015,
183 2018). Under anesthesia (first intramuscular injection of ketamine (10 mg/ kg) and xylazine
184 (0.5 mg/ kg), followed by deep anesthesia induced by isoflurane), two monkeys were
185 implanted over the left hemisphere with a polyether-ether-ketone (PEEK) recording chamber
186 (19-mm inner diameter). These recording chambers were positioned with a 20° angle laterally
187 in the coronal plane. For Monkey M, the targeted stereotaxic coordinates, relative to the ear
188 bars, were +18 mm on the antero-posterior axis and +16 mm in laterality. For Monkey Y, they
189 were + 14 mm in the antero-posterior axis and + 16 mm in laterality. These landmarks were
190 based on the atlas of Saleem and Logothetis (2007). Moreover, a device for head restraint for
191 the future neuronal recordings composed of two titanium cylinders embedded in orthopedic
192 cement (Palacos with gentamycin) was fixed to the skull with titanium orthopedic bone
193 screws. Antibiotics (Marbocyl, 2 mg/ kg) and analgesics (Tolfedine, 4 mg/ kg) were
194 administrated to the monkeys on the day of the surgery and for the 4 following days. The
195 antibiotics (Marbocyl, 2 mg/mL) were also used to fill the recording chamber before sealing it
196 with a removable cap.

197

198 **Electrophysiological Recordings**

199 The extracellular activity of single neurons was recorded with microelectrodes while the
200 monkeys performed the task with head immobilization. These microelectrodes were custom-
201 made with glass-insulated tungsten following the technique of Merrill and Ainsworth (1972).
202 To reach the BG structures, the microelectrode was inserted inside a stainless-steel guide tube
203 (diameter = 0.6 mm) lowered below the surface of the dura, and was advanced using a manual

204 hydraulic microdrive (M096; Narishige). The microelectrode was connected to a preamplifier
205 situated close to the microdrive. The electric signal was then amplified 5,000 times and
206 filtered at 0.3– 1.5 kHz and was converted to digital pulses through a window discriminator
207 (Neurolog; Digitimer). A computer using a custom-designed software written in LabVIEW
208 (LabVIEW; National Instrument) was used to present the visual stimuli on a screen in front of
209 the monkey, to deliver the reward and to store in real-time the force developed by the animal
210 on the lever and the digital pulses from neuronal activity.

211 The microelectrode was lowered to isolate neurons while the monkey was performing the
212 task. Single neurons were isolated from the background noise and from other neurons by
213 continuously monitoring on an oscilloscope the waveform of the recorded neuronal impulses.
214 Before recording in the STN, anterior limit of the external pallidal segment (GPe) was
215 identified for another study (Nougaret and Ravel 2018) and neurons from both caudate
216 nucleus and putamen were recorded (Nougaret and Ravel 2015). Additionally, the preliminary
217 mapping we performed, based on the atlas of Saleem and Logothetis (2007), allowed us to
218 map electrophysiologically the surrounding structure of the STN and was very helpful to
219 define its boundaries. STN neurons were identified based on their firing characteristics
220 described in previous studies (Wichmann et al., 1994; Darbaky et al., 2005; Isoda &
221 Hikosaka, 2008; Espinosa-Parrilla et al., 2013, 2015) and on the characteristic firing patterns
222 associated with neurons in regions dorsal and ventral to the structure that daily helped us to
223 insure the localization of our recordings. Indeed, along the electrode trajectory, were
224 encountered the thalamus, zona incerta, the STN and finally the substantia nigra pars
225 reticulata (SNr) or pars compacta (SNc). The differences in the baseline activity of these
226 structures and their background noises made clear the transitions between them. The very
227 specific and high frequency activity of the SNr was particularly useful to confirm the
228 localization of neurons previously recorded along the electrode track. The activity of the first
229 well-isolated and stable STN unit in a trajectory was recorded for at least 10 trials per
230 condition. After recording from a STN neuron, the electrode was moved forward until another
231 STN neuron was encountered. Data from all STN neurons recorded were included in
232 analyses.

233

234 **Localization of Recordings**

235 To assess the localization of our recordings, we used a high-resolution MRI scan for each
236 monkey with electrodes positioned in trajectories from which we recorded neurons from the
237 STN, the GPe and the striatum. MR images were collected using a T1-weighted sequence

238 (recovery time = 1700 msec, echo time = 4.414 msec, flip angle = 30°, in-plane resolution =
239 0.6×0.6 mm, thickness = 0.6 mm). On the basis of the localization of these electrode tips, we
240 extrapolated the inferior/superior, anterior/posterior, and medial/lateral positions of each
241 recorded neuron to generate a 3-D reconstruction of the whole neuronal population using
242 Brainsight software (Brainsight; Rogue Research). The coordinates of each neurons were
243 calculated based on their relative distance with the midpoint of the interaural line for each
244 monkey. Because of the difficulties to clearly evidence the STN boundaries based on MR
245 images, each neuron was then projected on a reconstruction of the STN based on the
246 coordinates of its boundaries on the Atlas of Saleem and Logothetis (2007).

247

248 **Data Analyses**

249 All data analyses were performed using conventional statistical procedures with the R
250 statistical computing environment (R Development Core Team, 2011), excepted the
251 population decoding analysis that was performed using the neural decoding toolbox (Meyers
252 2013) on Matlab (The MathWorks, Inc., Natick, MA, USA). Data were analyzed from 8,469
253 trials performed (correct and incorrect) by the animals while a total of 78 STN neurons were
254 recorded.

255

256 **Behavioral Analyses**

257 Two different measures were analyzed to evaluate the animal's behavior, the reaction times
258 (RTs) and the acceptance levels. The RTs were defined as the duration between the onset of
259 the cues and the time at which the monkey started to increase its pressing force on the lever
260 and were only calculated for correct trials. After changed into z-scores for normalization
261 purpose, a two-way ANOVA was performed with required force and expected reward as the
262 two factors. Acceptance levels were computed by dividing the total number of trials accepted
263 by the animal in a given condition (correct trials + holding and threshold errors) by the total
264 number of trials proposed to the animal in this condition (trials accepted + omission errors)
265 and compared with a Pearson's chi-squared test. This acceptance level reflects whether the
266 animal chose to perform the task or not, depending on the level of force and the reward size.
267 The force developed by the animals in each trial at each time of the task was collected and
268 averaged by condition to highlight possible differences within a same range of force between
269 two different reward conditions.

270

271 **Electrophysiological Analysis**

272 *Response of STN neurons to the force and reward factors*

273 We focused our analysis on the “cue-threshold period” (Figure 1A) that started with the
 274 occurrence of the cues and ended when the force developed on the lever exceeded the lower
 275 threshold of the force range. It corresponded to the period in which the animal saw the cues,
 276 integrated their significance and reacted to them accordingly to reach the required force range.
 277 The duration of this period varied across trials depending on the animal’s behavior. In our
 278 task, the force required to correctly perform the trial, based on the shape of the stimuli and the
 279 force applied by the animals on the lever highly covariate and could not be inserted as factors
 280 of the same model for electrophysiological analysis. To disentangle the “motor” modulation,
 281 that is, modulation by the force applied by the animals on the lever, from the “factors”
 282 modulation, that is, the force required, the expected reward, and the interaction between both,
 283 we have performed a two-step iterative generalized linear model (GLM). First, we considered
 284 a model in which the force applied (*ForceApplied*) could be explained by the amount of
 285 required force (*Force*), the amount of expected reward (*Reward*), the interaction between both
 286 factors (*Force:Reward*) and a residual part not explained by these factors
 287 (*ResidualsForceApplied*) as follow:

$$ForceApplied = Force + Reward + Force:Reward + ResidualsForceApplied$$

288 The goal of this first iteration was to extract the residual part *ResidualsForceApplied*, that was
 289 the part of the force applied not explained by the factors. This part was then used in the
 290 second iteration together with the force and reward factors. It allowed to evaluate the
 291 modulation of the firing rate by the force applied, after the modulation by the factors had been
 292 extracted from it. We defined the second iteration as follow:

$$FiringRate = ResidualsForceApplied + Force + Reward + Force:Reward \\ + ResidualsFiringRate$$

293 *ResidualsForceApplied* represented the modulation by the force applied on the lever not
 294 explained by the force and reward factors. *Force* represented the modulation by the amount of
 295 force required, *Reward* the modulation by the size of expected reward and *Force:Reward* the
 296 modulation by the interaction between both. *ResidualsFiringRate* represented the part of
 297 variance not explained by these variables. To minimize the probability of making Type I
 298 errors under the null hypothesis and to compensate the high risk of Family Wise Error rate
 299 due to multiple comparisons (78 neurons), we performed bootstrap analyses for the second
 300 iteration (Lindquist & Mejia, 2015; Maris & Oostenveld, 2007). This allowed us to compute *p*
 301 *values* without making assumptions on the distribution of the data. It consisted of randomly
 302 resampling the neuronal data to obtain replications of the same size as the original data set.

303 This procedure was performed 9999 times the analysis for each neuron, each time with a
304 different resampling. The likelihood ratio was extracted for each resampled data set and
305 compared with the one obtained from the original data set. Then, if the original likelihood
306 ratio fell in the highest ventile (equivalent *p value* of .05), the neuron was considered to be
307 significantly modulated by the factor of interest. The number of neurons modulated by the
308 force applied and by the force and reward factors and their interaction were collected. For
309 each neuron, a force selectivity index (FSI) and a reward selectivity index (RSI) were
310 estimated. These selectivity indices (SI) were defined as follows:

$$SI = \frac{(\mu_1 - \mu_2)}{\sqrt{((SS_1 + SS_2)/(df_1 + df_2))}}$$

311 In this formula, μ_x was the mean of the *FiringRate* during the cue-threshold period. SS_x was
312 the sum of the squares of the difference between the mean firing rate and the firing rate in
313 individual trial for each pair of condition described below. df_x was the degree of freedom
314 (number of trials - 1) for each pair of conditions described below (Peck, Lau, & Salzman,
315 2013). For each neuron, the FSI was computed by comparing the neuronal activity during
316 trials in the high force conditions (Fr and FR, represented by the subscript number 1) with the
317 neuronal activity during trials in the low force conditions (fr and fR, represented by the
318 subscript number 2). A positive FSI indicated a stronger modulation in the high force
319 conditions, whereas a negative index indicated a stronger modulation in the low force
320 conditions. In the same way, for each neuron, the RSI was computed comparing, the neuronal
321 activity during trials in the large reward conditions (fR and FR, represented by the subscript
322 number 1) with the neuronal activity during trials in the small reward conditions (fr and Fr,
323 represented by the subscript number 2). A positive RSI indicated a stronger modulation in the
324 large reward conditions, whereas a negative index indicated a stronger modulation in the
325 small reward conditions.

326 *Alignment on the Reaction time*

327 The previous analysis was also performed in a 150-ms period following the RT to assess the
328 influence of movement initiation on STN neuronal activity. As for the Cue-Threshold period,
329 the number of significantly modulated neurons were computed and the selectivity indices
330 were estimated during this period. The average spike-density was also calculated aligned on
331 the reaction time to determine if the neural response was triggered by the cue onset or the
332 movement initiation (Figure 3D). Because, it was clearly triggered by the cue onset, the
333 analysis described later were only applied on the Cue-Threshold period and with the neuronal
334 activity aligned on the cue onset.

335 *Relation between the anatomical localization and the selectivity indices.*

336 Each recorded neuron was reported on tridimensional representation of the brain and potential
337 correlations between their localization inside the STN and their capacity to encode the factors
338 of the task (FSI and RSI) were investigated. Pearson correlations were performed contrasting
339 the FSI or the RSI of each neuron with its position in millimeters in antero-posteriority,
340 laterality and depth.

341 *Independence of subpopulations of neurons*

342 The level of dependence between neurons belonging to subpopulations responding to the
343 factors of the task was assessed using resampling methods. From the whole population of
344 neurons (N), we defined the neurons selective for the amount of force N_{force} , the neurons
345 selective for the amount of reward N_{reward} and the neurons selective for both, N_{FR} . Then, we
346 reassigned randomly the previously computed p values for force and reward to have a
347 simulated population of neurons. This resampling was performed 20,000 times and allowed us
348 to have the distribution of the number of neurons N_{FR} found by chance. The position of our
349 measured N_{FR} on this distribution allowed us to determine the dependency between both
350 populations, i. e. if the encoding of a factor was predictive or preclusive to the encoding of the
351 other factor.

352 *Neural decoding analysis*

353 We performed a neural decoding analysis using the neural decoding toolbox developed by
354 Meyers (2013). This analysis used a maximum correlation coefficient classifier method
355 trained to discriminate, in our case, among the 4 conditions of the task or between the two
356 levels of a task factor, and to compute the decoding accuracy. Each recorded cell activity was
357 formatted as a sequence of average activity by bins of 150 ms sampled at 20 ms intervals
358 (overlap 130 ms) for each trial. For this population analysis, we first considered the whole
359 population of 78 neurons and defined the optimal split factor (k = highest number of trials in
360 each condition for each site). We decided to eliminate the 11 neurons with an insufficient
361 number of trials in each condition for such analysis and to perform it on 67 neurons (sites)
362 sharing at least 17 trials (k) per condition ($4 \times 17 = 68$ data points). The following step was to
363 randomly select from all the available data points of each site a population of 68 data points to
364 shape a pseudopopulation of neurons (i. e. neurons recorded separately but treated as recorded
365 simultaneously) with an equal number of data points. Then the data were normalized into z-
366 score to allocate the same weight to each neuron and avoid the influence of a higher firing
367 rate on the decoding method. The classifier was trained using $k - 1$ number of splits and next
368 tested on the remaining split. This procedure was repeated 50 times to increase the strength of

369 the results, generating new splits and consequently new pseudopopulations. The results were
370 then averaged over these 50 runs. To estimate the significance of the classifier accuracy, a
371 permutation test was performed by shuffling the labels and randomly assigned them to the
372 conditions before re-running it. This procedure was repeated 10 times to obtain a null
373 distribution of the decoding accuracies. The times when the decoding accuracies were above
374 what was considered chance level were considered as statistically significant. The
375 significance level was considered reached if the real decoding accuracies were greater than all
376 the ones of the shuffle data in the null distribution for at least 5 consecutive significant bins.
377 Always considering the whole population of neurons, when the decoding analysis of the force
378 and reward factors was performed separately, we chose a k of 25 and 26 respectively,
379 allowing us to consider 77/78 neuron and to remove only 1 cell. For the decoding analysis of
380 the subpopulations of neurons modulated by the force or reward factors, we used different k ,
381 adapted for each situations. For the force modulated neurons ($n = 19$) we used, $k = 13, 18$ and
382 17 respectively to test the decoding of the condition, the reward factor and the force factor,
383 allowing us to consider the whole population -1 ($n=18$) to test the condition, and the whole
384 population ($n = 19$) to test the factors. For the reward modulated neurons ($n = 15$) we used, k
385 =12, 26 and 25 to test the decoding for the condition, the reward factor and the force factor
386 respectively. It allowed us to consider the whole population ($n = 15$) in all cases.

387

388 RESULTS

389

390 Behavioral results

391 Behavioral analyses were performed on trials completed while STN neurons were recorded
392 (78 neurons, 30 from Monkey M, 16 days of recording and 48 from Monkey Y, 24 days of
393 recordings).

394 *Reaction Times*

395 Average RTs (i.e. time to reach the lower threshold of the required force after the occurrence
396 of cues) were computed from the correct trials only (2,337 from Monkey M and 3,942 from
397 Monkey Y; Figure 2A). RTs were significantly shorter for the large reward trials than for the
398 small reward ones in Monkey M (two-way ANOVA on RT z score, $p_{\text{reward}} < 0.001$, $F(1,$
399 $2333) = 95.9$) and in Monkey Y (two-way ANOVA on RT z score, $p_{\text{reward}} < 0.01$, $F(1,$
400 $3938) = 7.34$). Although there was a slight decrease in the high force condition for both
401 monkeys, the two-way ANOVA revealed that there was no significant difference on the RTs
402 between the high force trials and the low force trials (Monkey M, $p_{\text{force}} > 0.05$, $F(1,2333) =$

403 2.85; Monkey Y, p .force >0.05 , $F(1,3938) = 0.07$). In both monkeys, there was no interaction
404 effect between the required force level and the size of the expected reward on the RTs.

405 *Acceptance level*

406 Both monkeys shared an acceptance level, ordered from the highest to the lowest, for the
407 conditions low force/high reward (fR), then high force/high reward (FR), then low force/small
408 reward (fr), and finally high force/small reward (Fr) (Figure 2B). For both monkeys, the 4
409 conditions were thus ranked in the same preference order. The size of expected reward
410 seemed to be more relevant than the level of effort required for them to decide whether to
411 perform the task or not. In the most accepted fR conditions, monkeys decided to perform the
412 action in 98.7% (Monkey M) and 98.9% (Monkey Y) of the trials. In contrast, in the least
413 accepted Fr conditions, they only performed the action in 81.2% (Monkey M) and 87.7%
414 (Monkey Y) of the trials. FR trials were accepted more frequently (96.9% for Monkey M and
415 96.3% for Monkey Y) than fr trials (86.0% for Monkey M and 94.2% for Monkey Y). The
416 overall difference between the accepted trials and the rejected ones was highly significant for
417 both monkeys (Monkey M: $\chi^2 = 191.05$, $p < 0.001$, Monkey Y: $\chi^2 = 157.03$, $p < 0.001$).
418 Moreover, a 2-by-2 comparison revealed that each level of acceptance was different from the
419 others (Monkey M: $\chi^2 > 4.93$, $p < 0.05$, Monkey Y: $\chi^2 = 5.67$, $p < 0.05$). These results show
420 that the monkeys understood the task and have valued each condition before deciding to
421 perform the trial or not. Indeed, the effort to be made and the size of the expected reward
422 contributed to compute the subjective value of each condition for both monkeys. As depicted
423 in Figure 2C, for the same amount of force required, the average force applied by the animals
424 was slightly different depending on the expected/received reward in some periods. This result
425 led us to consider the force applied as a variable in our analyses of the neuronal activity to
426 isolate a reward or a force effect from motor response due to a mechanical modulation.

427

428 **Electrophysiological Results**

429 *STN neurons activity during the cue-threshold period*

430 Our visuomotor task allowed us to explore how STN neurons integrated visual cues carrying
431 effort and reward-related information comparing to motor-related ones. During the cue-
432 threshold period, corresponding to the period in which the visual stimuli significance was
433 integrated and the response developed, 10.3% of neurons (8/78) modulated their activity
434 depending on the force applied by the animal on the lever, while 36/78 (46.2%) modulated
435 their activity depending on the task factors. Among these neurons, 19/36 (52.8%) showed a
436 ‘force effect’, a difference in their activity between the high and low force trials, 15/36

437 (41.6%) showed a ‘reward effect’, a difference in their activity between large and small
438 reward trials. It is important to note that only one cell belonged to both populations and that
439 the group of neurons showing a force effect was independent of the one showing a reward
440 effect (resampling method, equivalent p value = 0.065). The encoding of force was neither
441 predictive nor preclusive to the encoding of reward and vice versa. On these 36 neurons, 4
442 showed an interaction effect (11,1%). The distribution of the force and reward selectivity
443 indices for each of the 78 neurons and the average spike-density of the whole recorded
444 population are shown in Figure 3. The overall distribution of the FSI during this period
445 (Figure 3A, green histogram) was significantly positive and not centered on 0 (Wilcoxon
446 signed rank test, $V = 2279$, $p = 0.00023$) and the RSI distribution showed the same tendency
447 (Wilcoxon signed rank test, $V = 1921$, p -value = 0.0584, Figure 3A, red histogram). The
448 window chosen for the analysis, between cue onset and threshold included the initiation of the
449 movement by the animal. To control for the influence of movement initiation on the STN
450 neuronal activity, the same analysis was performed but now aligned on the RT and the results
451 compared with the one obtained for the Cue-Threshold period. During a period of 150 ms
452 from the RT, 15.4% of neurons (12/78) modulated their activity depending on the force
453 applied by the animal on the lever, while 26/78 (33.3%) modulated their activity depending
454 on the task factors, 6 of them were present in both categories. The majority of them, 20/26
455 (76.9%), showed a ‘reward effect’, only 4/26 (15.4%) showed a force effect and 3/26 (11.5%)
456 showed an interaction effect (Figure 3C). The overall distributions of FSI and RSI during this
457 period showed the same but not significant tendency to be majoritarily positive than during
458 the Cue-threshold period (Figure 3C, FSI: Wilcoxon signed rank test, $V = 1860$, $p = 0.1115$;
459 RSI: Wilcoxon signed rank test, $V = 1904$, $p = 0.07$).

460 The average spike-density, aligned on cue onset or on RT (Figure 3D), shows that even if
461 slightly higher when aligned on RT, the response of STN neurons was clearly triggered by the
462 occurrence of the visual cues. For this reason, we considered the Cue-threshold period the
463 most relevant to further analyze the activity of STN neurons, and this period will be the only
464 one considered in the following analysis.

465 *Distribution of the FSI and RSI of responding STN neurons*

466 Among the 19 neurons showing a force effect, a significantly higher number of neurons
467 (exact binomial test, $p = 0.0007$) were FSI+ (17/19; i.e. stronger response for the larger force)
468 and the remaining ones FSI- (2/19; stronger response for the lower force). Conversely, among
469 the 15 neurons showing a reward effect, a comparable number of neurons (exact binomial
470 test, $p = 0.61$) were RSI+ (9/15) and RSI- (6/15). As illustrated in Figure 4A, the spike density

471 of the 19 neurons showing a force effect reflects the dominance of the FSI+ neurons and their
472 response after the presentation of the cues. We did not observe any difference in terms of
473 average spike density or distribution of the RSI for these 19 neurons, and the spike density of
474 the conditions sharing the same force required (fr/fr and Fr/FR) was comparable. It was not
475 the case for the 15 neurons showing a reward effect. Indeed, they were equally distributed
476 between RSI+ and RSI- neurons (9 vs 6 neurons respectively). However, we observed a
477 significant negative correlation between the force and reward indices of these 15 neurons
478 (Pearson correlation, $r = -0.56$, $p = 0.028$) showing that the higher the RSI, the lower the FSI
479 will be and the lower the RSI, the higher the FSI will be. This reveals that, even if not
480 showing a force effect, most of the neurons showing a reward effect also integrate force
481 value. Both subpopulations of reward modulated neurons (RSI+ and RSI-) were observed
482 separately and revealed interesting features. The boxplot (Figure 4B, bottom left) and the
483 average spike-density along time (Figure 4B, middle) show that the RSI+ and the RSI-
484 neurons encoded the task conditions following the motivational ranking of the 4 task
485 conditions (fR/FR/fr/Fr). Indeed, RSI + neurons increased their activity with the most
486 favorable conditions of the task. At the single cell level, the raster shown on Figure 4B upper
487 right evidenced this pattern of activity. As a population, we observed a tendency of positive
488 correlation between their average activity in the cue-threshold period and the task conditions
489 (Pearson correlation, $r = 0.23$, $p = 0.18$, Figure 4B, bottom left, “Positive RSI”). On the other
490 hand, RSI- neurons decreased their activity in the most favorable conditions of the task. As a
491 population, we observed a significant negative correlation between their average activity in
492 the cue-threshold condition and the task conditions (Pearson correlation, $r = -0.44$, $p = 0.03$,
493 Figure 4B, bottom left, “Negative RSI”). At the single cell level, the raster shown on Figure
494 4B bottom right evidenced this pattern of activity. As a whole, the reward modulated neurons
495 encoded the motivational value conveyed by the visual stimuli rather than only the size of the
496 reward by increasing or decreasing their activity according to the task conditions and their
497 subjective value.

498 *Neural decoding analysis*

499 We performed a neural decoding analysis (Meyers, 2013) based on the training of a classifier
500 to discriminate among the 4 different conditions, between both reward conditions (r and R)
501 and between both force conditions (f and F). This analysis allowed us to evaluate three new
502 aspects of the STN neuronal activity. The results are depicted in Figure 5. First, by
503 performing the training of the classifier at one time point and testing its capacity to decode the
504 activity at different time points (Figure 5A,B,C, left), we figured out whether the encoding of

505 the condition, force or reward information by STN neurons was static or dynamic. The
506 dominance of the decoding accuracy confined along the main diagonal suggests that the
507 representation of the condition and its factors was mainly sustained by a dynamic rather than
508 a stationary code. The difference between these two representations is still a topic of interest
509 but dynamic codes have been described to support complex stimulus transformation, as
510 reported previously in studies interested in the representation of cognitive problems (Crowe et
511 al. 2010), observed actions (Lanzilotto et al. 2019) and the ability to solve tasks more
512 generally (Meyers 2018). The second and third aspects concern the temporal course of the
513 decoding of information and the comparison of the decoding accuracy on selective and non-
514 selective neurons. We observed, considering the whole neuronal population (Figure 5,
515 middle) that the information regarding the amount of reward was integrated before (Figure
516 5B, middle, first significant bin: 160 ms after the occurrence of the cues, red curve) the
517 information regarding the amount of force (Figure 5C, middle, first significant bin: 360 ms
518 after the occurrence of the cues, green curve). Moreover, we evaluated the decoding accuracy
519 of different neuronal populations, the neurons showing a reward effect, the neurons showing a
520 force effect and the remaining neurons. Interestingly, the 15 neurons showing a reward effect
521 (Figure 5A, right, red curve) decoded the task conditions 180 ms after the occurrence of the
522 cues while the neurons showing a force effect significantly discriminate among the four
523 conditions 700 ms after the occurrence of the cues. This main difference between both
524 populations confirms our preceding analysis, the neurons showing a force effect were only
525 involved in the encoding of the force whereas the neurons showing a reward effect also
526 integrated a force information, allowing them to significantly decode among the task
527 conditions. This result was confirmed when we looked further in the decoding of the force by
528 the reward modulated neurons and vice versa. Indeed, even if late, the reward modulated
529 neurons showed an increase in the decoding accuracy after the occurrence of the cues (Figure
530 5C, bottom, red curve) that the force modulated neurons did not show for the amount of
531 reward at this time (Figure 6C, bottom, green curve).

532 *Localization of the Recordings*

533 The reconstruction of the electrode trajectories allowed us to extrapolate the location of each
534 recorded neuron. The complete reconstruction along the 3 different planes is depicted on
535 Figure 6. From the midpoint of the interaural line, the average coordinates of our recording
536 were: laterality: $4.95\text{mm} \pm 0.71$ (min = 3.07mm, max = 6.68mm), antero-posteriority:
537 $14.08\text{mm} \pm 0.92$ (min = 12.86mm, max = 16.01mm), depth = 11.29 ± 1.09 (min = 8.55, max =
538 13.75). Based of the reconstruction made from the atlas of Saleem and Logothetis (2007), the

539 majority of the recorded neurons were located in anterior half of the nucleus. We performed
540 Pearson correlations to find potential link between the strength of STN neurons response (FSI
541 or RSI) and the coordinates of the neuron's location (Laterality, Antero-posteriority and
542 Depth). We found that, the neurons recorded more medially (Pearson correlation, $r = -0.24$, p
543 $= 0.034$) and deeper (Pearson correlation, $r = 0.24$, $p = 0.031$) exhibited higher FSI. No
544 significant correlation between the neuron's location and the RSI was found.

545

546 DISCUSSION

547

548 The present data brought new evidence about the functional properties of the STN neurons
549 and their role in the integration of force, effort and motivational information. Our task
550 allowed us to extract and differentiate information about 1) the encoding of force, i. e. the
551 force developed physically on the lever, 2) the effort, i.e. the force requested on the lever in
552 response to the green stimulus and 3) the motivation to act, i.e. an integration of the effort and
553 the reward size to compute the motivational value specific of a pair of visual stimuli. First, we
554 found that STN neurons, at single cell level, were mainly involved in independent processes
555 with cells significantly modulated by the effort, i. e. the force requested to develop on the
556 lever, or by the reward size, i. e. the amount of reward the animal can get at the end of the
557 trial. Second, these two populations exhibited different patterns of modulation, the effort-
558 modulated neurons were mainly active when a high effort was required, whereas the reward-
559 modulated neurons did not only respond to the reward amount, but they also integrated, as a
560 population, the motivational value of the stimuli. Third, the population of reward-modulated
561 neurons was composed of neurons increasing or decreasing their activity in the most
562 favorable condition of the task and exhibiting an activity according to the motivational
563 ranking of the four task conditions. Fourth, the reward-modulated neurons seem to encode
564 first the reward size and then integrate the amount of force required.

565

566 **STN neurons encode the effort to produce rather than the force developed**

567 Our results revealed an interesting feature about the STN neurons' properties. Indeed, during
568 the cue-threshold period, when the animal must extract information from the cues and react to
569 them accordingly, the proportion of neurons encoding the force required (low vs high) was
570 higher than the proportion of neurons encoding the force developed. The work of Tan and
571 colleagues (2013, 2015) showed similar evidence from recordings of the local field potentials
572 (LFP) of STN of Parkinsonian patients (PD). They first showed a decreased power in the beta

573 band and an increased power in the gamma band when the effort required increased (Tan et
574 al. 2013). In a second study (Tan et al. 2015), the authors disambiguate the effort from the
575 force, asking the patients to exert different levels of force on a lever with the index or the little
576 finger. For a same effort, a lower force was produced if the little finger was used. They
577 demonstrated that STN activity encoded the effort rather than the absolute force and
578 suggested a role of the basal ganglia in determining the effort to be attributed to a response
579 more than in the parametrization of the movement itself. This is in line with behavioral
580 studies in humans showing that individuals used the sense of effort more than the
581 proprioceptive feedbacks to evaluate the force generation (Jones and Hunter, 1983, Carson et
582 al. 2002, Proske et al. 2004). Recording the potentials evoked by transcranial magnetic
583 stimulation of the motor cortex in peripheral muscles used in their task, Carson et al. (2002)
584 showed that the sense of effort was not based on central motor command and proposed that it
585 was associated with the activity of structures upstream of the motor cortex. The notion of
586 effort to invest in an action was the center of the task performed by PD patients in the study of
587 Zenon et al. (2016) that showed a neural response to the effort cues in the 1-10 Hz band of the
588 STN LFP. Moreover, and in line with our results, the authors highlighted that the responses
589 observed were more informative of the level of effort rather than the actual quantity of force.
590 Interestingly, in our data, the deeper and the more medial the recordings, the higher the FSI. It
591 has been recently demonstrated (Stephenson-Jones et al. 2016) that a pathway between the
592 medial STN and the habenula-projecting globus pallidus (GPh) was involved in signaling
593 when an outcome was aversive or worse than expected (Stephenson-Jones et al. 2019). We
594 could hypothesize that the neurons encoding a high effort to be produced, located on the
595 medial border of the STN, projected on the GPh and transferred a negative signal, to the
596 lateral habenula. This hypothesis is supported by the fact that in rodents, a subpopulation of
597 STN neurons could encode aversive reinforcers (Breyse et al. 2015). In a task similar to ours,
598 Varazzani and colleagues (2015) reported a modulation of the noradrenergic neurons of the
599 locus coeruleus (LC) by the task difficulty at the moment of the action. To date, no direct
600 connections between the LC and the STN have been reported but we could hypothesize on an
601 influence of LC effort-related activity on STN neurons indirectly through a prefrontal
602 pathway. This last point is also supported by the fact that the force effect appeared later
603 during the trial than the reward effect. It might well be possible that the reward-modulated
604 neurons are directly sensitive to the cues information, while the force-modulated ones are
605 reflecting a more integrated process like action preparation at some point.
606

607 **STN neurons encode the motivational value of the combined visual stimuli**

608 Neural correlates between STN neurons' activity and stimuli predictive of a reward or the
609 reward itself have been previously shown in rodents (Baunez et al. 2002, 2005, Teagarden
610 and Rebec 2007, Lardeux et al. 2009, 2013, Breysse et al. 2015, Baunez 2016) and in non-
611 human primates (Matsumura et al. 1992, Darbaky et al. 2005, Espinosa-Parilla et al. 2013,
612 2015). The population of reward-modulated neurons we recorded also integrated, as a
613 population, information about the force required, as shown by the negative correlation
614 between the RSI and FSI of these neurons, and their ability to decode the condition and not
615 only the reward size. STN neurons are known to be directly interconnected with a number of
616 prefrontal areas (Takada et al. 2001, Nambu et al. 2002, Haynes and Haber, 2013) with some
617 degree of overlap between STN territories (Haynes and Haber 2013, Nougaret et al. 2013).
618 They would allow the gestion of conflict during decision-making by inhibiting the cortical
619 activity through the STN-GPi-Thalamus-Cortex (GPi: Globus Pallidus internal segment)
620 pathway. This enables a control of impulsivity by allocating a temporal window necessary for
621 the scrutiny of the different available options (Frank et al. 2007, Cavanagh et al. 2011). The
622 role of STN in the control of impulsivity and decision making has been largely documented in
623 both rats and humans (see for review Eagle and Baunez, 2010; Breysse et al. 2020; Frank et
624 al. 2007). In our study, this subpopulation of STN neurons could send a forerunner
625 information to the output structures of the BG or to the GPe regarding the estimation of the
626 subjective reward value, i.e. integrating also the effort in the valuation of the reward. This
627 information would help at improving the decision-making, promoting or slowing down or
628 stopping the execution of the action as suggested by Isoda and Hikosaka (2008). This
629 computation could be under the influence of dopamine neurons known to play a role in value-
630 based behaviors in a similar paradigm (Varazzani et al. 2015). Another target of these STN
631 neurons could be the ventral pallidum (VP) with whom it shares reciprocal connections
632 (Haber and Knuston 2010). The VP contains cells that display distinct reward modulations
633 depending on the expected outcomes, the reward-positive and reward-negative types
634 (Tachibana and Hikosaka 2012). Moreover, because the reward-positive neurons combined
635 expected reward values and expected costs, the authors argued that the VP neuronal activity is
636 used for modulating impending motor actions. Considering the reciprocal connections
637 between the STN and the VP and the populations of positive and negative RSI neurons we
638 found in the STN, we can hypothesize that these two structures would work together to update
639 the value of a behavioral context and modulate a corresponding motor output. The temporal
640 dynamic would be interesting to compare between the VP and STN. However, the present

641 study shows that the encoding of the reward size was a fast processing (180 ms) that occurs
642 before integration with the force-related information. The fact that STN neurons are able to
643 integrate both information in a sequential order is in line with the LFP recordings in PD
644 patients tested in a similar task showing modulation of activity with regard to the net
645 subjective value (Zenon et al 2016). Interestingly enough, these comparable results were
646 obtained with a simultaneous combined cue presentation here, while in the task used with the
647 patients, the cue indicating the size of the reward was presented before the cue related to the
648 effort to produce (Zenon et al 2016). In monkeys, it has been reported (Espinosa-Parilla et al.
649 2015) that STN neurons are only sensitive to the value of the outcome at its occurrence in the
650 context of a choice. Here, we extend the precedent findings, showing the encoding of the
651 motivational value of the visual stimuli by STN neurons, in the absence of choice to be made.
652 The differences in the conclusions could be partly explained by the differences between the
653 task used here and the one used by Espinosa-Parilla and colleagues, in the fact that, in our
654 task, the reward amount varied but not its identity and, second, that various levels of force
655 were needed and lead to different efforts, implying a cost-benefit integration.

656

657 **Limitations of our interpretations and future perspectives**

658 The present study demonstrates new features on STN neurons properties and completes our
659 previous findings on the activity of the GPe neurons (Nougaret and Ravel 2018) and the
660 tonically active neurons of the striatum (Nougaret and Ravel 2015) in the same paradigm.
661 Indeed, the integration of the motivational value of the visual stimuli was only found in the
662 STN as a population, placing this structure as an essential node modulating motivated
663 behaviors within the BG circuitry. In our study, there was no choice to be made between two
664 options, the choice was to perform or not the action and we recorded only few omission trials
665 in each condition making difficult to study the monkey's decision to make the action or not,
666 unlike in the study recording STN LFPs in Parkinsonian patients using a similar task (Zenon
667 et al 2016). Consequently, our results raised conclusions about the incentive motivation rather
668 than decision making about performing a motivated action. Moreover, to have a more
669 complete view on how motivational information is processed within the BG, it would be of
670 great interest to compare the properties of STN neurons with the ones of projection neurons of
671 the striatum, the other main input structure of the circuit. Also, the STN is at the center of at
672 least two main pathways within the basal ganglia, the indirect and the hyperdirect pathway,
673 and our recordings did not allow us to identify whether the recorded neurons received mainly
674 inputs directly from the cortex or indirectly through the striatum and the GPe. Complementary

675 studies involving inactivation of specific pathways could help to shed light on the
676 contribution of each cortical and subcortical inputs in goal-directed behaviors and on STN
677 neuronal responses. In addition, the understanding of how STN neurons encode motivational
678 information appears fundamental to comprehend the non-motor neuropathologies involving
679 dysfunctions of the BG such as addiction and obsessive compulsive disorders and the
680 alterations of reward-based behaviors encountered in patients with Parkinson's Disease.
681 Today, the deep brain stimulation of the STN (STN-DBS) introduced by Benabib and
682 colleagues (Limousin et al. 1995) is used worldwide to alleviate the motor symptoms in PD
683 patients but it also affects the cognitive and motivational deficits observed. Animal and
684 clinical studies reported that STN-DBS can improve these non-motor deficits but can also
685 make them worse (Chaudhuri and Shapira 2009; Castrioto et al. 2014), in some cases
686 triggering an apathy that cancels the motor improvement observed in PD patients (Martinez-
687 Fernandez et al. 2016). However STN-DBS can also reduce the oscillations between hypo
688 and hyperdopaminergic states and diminish the compulsive use of dopaminergic medication
689 and other forms of impulse control disorders observed in some PD patients (Lhommée et al.
690 2012; Eusebio et al. 2013). Interestingly, STN DBS applied in Parkinsonian patients
691 performing a similar task to that used here increased their level of acceptance for trials
692 involving a higher cost (Atkinson-Clément et al. 2019). This may be explained by either a
693 faulty encoding of the effort or an increased motivation for the reward, in line with former
694 studies showing an increased motivation for sweet food when an effort is required in a
695 progressive ratio schedule of reinforcement (Rouaud et al. 2010), unlike when no effort is
696 implied (Vachez et al. 2020). In contrast to what is reported with food reward, STN lesions or
697 DBS reduce motivation for substances of abuse (cocaine, heroin and alcohol) (Baunez et al.
698 2005; Rouaud et al. 2010; Lardeux and Baunez 2008; Pelloux and Baunez 2017, Wade et al.
699 2017), suggesting it could be an interesting target for addiction treatment (Pelloux and Baunez
700 2013). Beneficial effects of STN DBS have been indeed shown on escalated heroin or cocaine
701 intake (Wade et al. 2017; Pelloux et al. 2018). It was further shown that abnormal oscillatory
702 activity within the STN might be associated with the escalated drug intake (Pelloux et al.
703 2018). Further work will thus be needed to understand more thoroughly how STN neuronal
704 activity plays its role in motivational processes and how it could contribute to repair
705 pathological states.

706

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913

914 FIGURE LEGENDS

915

916 **Figure 1.** Task design and localization of the subthalamic nucleus recordings. A. Task design.
917 A trial started when the monkey applied a basal force on the lever and maintained it during a
918 one-second preparatory period after which a pair of visual stimuli appeared on the screen

919 (occurrence of the visual stimuli). In response to these stimuli, the monkey had to increase its
 920 pressing force until it reached the required force range materialized by a rectangle and a
 921 gauge on the screen (the time to reach the target force being the cue threshold period), and
 922 held its force for 1 second (i.e. holding period) to obtain the reward. B: Table illustrating the
 923 combinations of visual stimuli. Four possible pairs of visual stimuli indicated to the animal
 924 the force to be developed and the size of the upcoming reward. Green represented the force (F
 925 or f) and red the reward (R or r), a circle meant small (f or r) and a square meant large (F or
 926 R). The example condition shown in A was low force/large reward. C. Left. MR image from
 927 monkey Y (Left) and Monkey M (right) respectively at +13 mm and +14 mm from the
 928 midpoint of the interaural line. Both images have been reoriented to fit the electrode track
 929 (Monkey Y: angle AP -4.5/Lat 18; Monkey M: angle AP 6/Lat 17).

930

931 **Figure 2.** Behavioral performance of both monkeys. A. Reaction times (RT) of the monkeys
 932 in the 4 conditions of the task. r: small reward, R: large reward, solid black lines: high force,
 933 dashed black lines: low force. The error bars represent the standard error to the mean. The
 934 stars indicate the influence of force and reward on the animal reaction time (2-way ANOVA:
 935 $**p<0.01$, $***p<0.001$). B. Acceptance level of the animals in the 4 conditions of the task
 936 (fR: low force/large reward; FR: high force/large reward; fr: low force/small reward; Fr: high
 937 force/small reward). The stars indicate significant difference between the proportions of
 938 accepted trials on the total number of trials performed in a given condition (Pearson's Chi-
 939 squared: $*p<0.05$, $***p<0.001$). C. Mean of the force developed on the lever along the trial
 940 by the animals in the 4 conditions of the task. Black lines: high force, gray lines: low force,
 941 thick lines: large reward, thin lines: small reward. The dashed vertical line represents the
 942 occurrence of the visual stimuli.

943

944 **Figure 3.** Distribution of the FSI and RSI, average activity of STN neurons among the task
 945 conditions and comparison of cue versus RT alignment. A. Scatter plots of force- versus
 946 reward-selectivity indices for each individual neuron during the Cue-Threshold period. FSIs $>$
 947 0 indicate higher modulation in the high force conditions. RSIs $>$ 0 indicate higher
 948 modulation in the large reward conditions. The color of the dots indicates the significance of a
 949 modulation (force, reward or interaction effect) in the GLM analysis. Filled green circles
 950 represent the neurons showing a force effect. Unfilled red circles represent the neurons
 951 showing a reward effect. For scaling reason, a neuron with a RSI of 2.45 is not represented on
 952 the scatterplot. Black crosses represent neurons showing an interaction effect and small gray

953 dots represent neurons without modulation by the task factors. The superimposed histograms
954 represent the distribution of the FSI (green) and the RSI (red) of the 78 neurons. B. Average
955 spike-density ($\sigma = 30$) of the whole population ($n = 78$) of STN neurons. The horizontal
956 dashed line represents the baseline activity and the 4 solid color lines the 4 conditions of the
957 task (purple: fR, orange: FR, green: fr, blue: Fr). The vertical dashed line represents the
958 occurrence of the visual cues. C. Same representation than in (A) for a period of 150 ms from
959 the reaction time. D. Average spike-density ($\sigma = 50$) of the whole population all condition
960 combined. The vertical dashed line represents the occurrence of the visual cues for the
961 activity represented in blue and the RT for the activity represented in gray. The activity is
962 slightly higher ($<1\text{Hz}$) when aligned on the RT but clearly triggered by the Cue onset.

963

964 **Figure 4.** Distributions of the FSIs and RSIs during the Cue-Threshold period and average
965 spike-density of STN neurons showing a force or a reward effect. Same representation than in
966 Figure 3. **A.** Indices distribution and average spike-density for the neurons showing a force
967 effect. Left: Scatter plot of force- versus reward-selectivity indices for the neurons showing a
968 force effect ($n = 19$; green filled circles). The black line represents the Pearson's correlation
969 between the FSI and RSI of the 19 neurons. The gray arrow indicates the neuron taken as
970 example on the right panel of the figure. Middle: the average spike-density shows the higher
971 activity in the high force conditions after the occurrence of the cues (materialized by the
972 vertical line at time 0). Right: raster plot of a cell showing a force effect. Each line represents
973 a trial and each dot the occurrence of a spike. The trials are sorted among the 4 conditions. In
974 this example, the activity is higher in the high force conditions than in the low force ones after
975 the occurrence of the visual cues. **B.** Indices distribution and average spike-density for the
976 neurons showing a reward effect. Left, up: Scatter plot of force- versus reward-selectivity
977 indices for the neurons showing a reward effect ($n = 15$; empty red circles). The black line
978 represents the Pearson's correlation between the RSI and FSI of the 15 neurons, revealing a
979 significant correlation. The gray arrows indicate the neurons taken as example on the right
980 panel of the figure. Middle: the average spike-density of the separated populations of neurons
981 showing a reward effect. Middle, up: average spike-density of the neurons with a positive RSI
982 ($n = 9$) showing higher activity in the large reward conditions after the occurrence of the cues
983 (materialized by the vertical line at time 0), but also decreasing response with the high force.
984 Middle, bottom: average spike-density of the neurons showing a negative RSI ($n = 6$)
985 showing lower activity in the large reward conditions after the occurrence of the cues
986 (materialized by the vertical line at time 0), but also increasing slightly with the high force.

987 Left, bottom: Boxplot representing the average activity during the Cue-threshold period and
 988 among the 4 conditions of the task of both subpopulations of reward modulated neurons RSI
 989 + and RSI -. The boxplots illustrate the influence of the force on the reward modulated
 990 neurons. Only for RSI -, the effect of force is significant. Purple: fR; orange: fR; green: fr;
 991 blue: Fr. Right: Raster plots of neurons showing a positive (up) and a negative (bottom)
 992 reward effect at the occurrence of the cues. The influence of the force on the reward
 993 modulated neurons is visible at the population and at the single cell-level.

994
 995 **Figure 5.** Dynamic encoding of relevant information of the task along the trial. **A.** Results
 996 obtained following the training of a classifier at a time t_1 (y-axis) and testing this classifier at
 997 a time t_2 (x-axis) for the decoding of the task condition. Left: Bi-dimensional map of the
 998 decoding accuracy in which each pixel represents the decoding accuracy at a time t_2 with a
 999 training of the classifier performed at t_1 . The higher decoding accuracy along the main
 1000 diagonal shows the dynamic decoding of the task condition. The black lines indicate the
 1001 occurrence of the visual cues. Middle: the black curve represents the decoding accuracy along
 1002 the main diagonal, at lag 0 (when $t_1 = t_2$) for the whole population of recorded neurons.
 1003 Right : Similar representation analyzing separately the neurons showing a force effect (green),
 1004 a reward effect (red) and the remaining ones (gray). The thick lines at the bottom of the plots
 1005 represent the significance of the decoding accuracy above the chance level (at 25%, 4
 1006 conditions). The time is the beginning of the first of five significant consecutive bins based on
 1007 the same analysis performed with a shuffle of the condition labels. **B. and C.** Same
 1008 representation than in A. for the decoding of the amount of reward (**B**) and the amount of
 1009 force (**C**). The trials are pooled between the small reward (fr and Fr) conditions versus the
 1010 large reward (fR and FR) conditions for the decoding of the amount of reward. Inversely, they
 1011 are pooled between the low force (fr and fR) conditions versus the high force conditions (Fr
 1012 and FR) for the decoding of the amount of force. The chance level represented by the black
 1013 line is 50% in both cases.

1014
 1015 **Figure 6.** Topography of the neuronal recordings in the subthalamic nucleus. The three
 1016 bidimensional plots on the left represent the projections of each recorded cell from the
 1017 midpoint of the interaural line. Up left: AP vs Laterality: horizontal view. Up right: Depth vs
 1018 Laterality: coronal view. Bottom left: Depth vs AP, sagittal view. Right: three-dimensional
 1019 reconstruction of the cell distribution and theoretical boundaries of the STN based on the atlas
 1020 of Saleem and Logothetis (2007). The filled circles represent the neurons recorded in Monkey

1021 Y and the filled squares the neurons recorded in Monkey M. The ellipsoids on the
1022 bidimensional plots represent the 95% of the cell distribution for each population of cells,
1023 green: neurons showing a force effect (n = 19), red: neurons showing a reward effect (n = 15),
1024 black: remaining neurons (n= 45).
1025











