The Anterior Caudate Nucleus Supports Impulsive Choices Triggered by Pramipexole

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Abstract

BACKGROUND: Pramipexole is a dopamine agonist used as a treatment in Parkinson's disease and restless legs syndrome to reduce motor symptoms, but it often induces impulse control disorders (ICD). In particular, patients with ICDs tend to make more impulsive choices in delay discounting task, i.e. they choose small immediate rewards over larger delayed ones more often than patients without ICD and healthy subjects do. Yet the site of action of Pramipexole that produces these impulsive choices remains unknown. Based on the heterogeneity of cortico-striatal projections and the massive dopamine innervation of the striatum, we hypothesized that impulsive choices triggered by dopamine treatments may be supported by a specific striatal territory.

METHODS: In this study, we compared Pramipexole intramuscular injections to intra-cerebral microinjections within the three striatal territories in healthy monkeys trained to execute the delay discounting task, a behavioral paradigm typically used to evaluate impulsive choices.

RESULTS: We found that Pramipexole intramuscular injections induced impulsive choices in all monkeys. Local microinjections were performed inside the anterior caudate nucleus, the ventral striatum and the anterior putamen and reproduced those impulsive choices when Pramipexole was directly injected into the caudate nucleus, while injections into the ventral striatum or the putamen had no effect on the monkeys' choices.

CONCLUSIONS: These results, consistent with clinical studies, suggest that impulsive choices triggered by Pramipexole are supported by the caudate nucleus, allowing us to emphasize the importance of dopamine modulation inside this striatal territory in decision processes underlying impulsive behaviors.

Introduction

Pramipexole (PPX) is a dopamine $D_{2/3}$ receptor agonist used as treatment in Parkinson's disease, restless legs syndrome and fibromyalgia to reduce sensorimotor symptoms, but it often leads to Impulse Control Disorders (ICDs). ICDs are a complex group of impulsive behaviors, including pathological gambling, compulsive shopping, and hypersexuality that occur in 14 to 46 % of Parkinson's patients[1–3], 7% of patients with restless legs syndrome[4] and also in fibromyalgia patients[5] treated with PPX. In delay discounting task (DDT), commonly used to measure decisional impulsivity, ICD patients tend to make more impulsive choices[6], i.e. they choose small immediate rewards (SIR) over larger delayed ones (LDR) more often than healthy people do. Delay discounting paradigms are built using the concept of temporal discounting, based on the fact that humans and animals tend to devaluate future outcomes. Choosing the immediate but smaller alternative is considered impulsive and is also referred to as an aversion to delay of reinforcement.

There is strong evidence that dopamine plays a key role in impulsive behaviors, modulating decision-making and influencing motivational state[7]. The striatum, in which there is high $D_{2/3}$ receptor density, seems to be a central structure in impulsivity networks[8]. It has been hypothesized that interactions between the frontal cortex and the three striatal subterritories, the caudate nucleus (CdN), the ventral striatum (VS; which includes the nucleus accumbens) and the putamen, are involved in different types of impulsivity, with cognitive and motor impulsivity likely mediated by distinct cortico-striatal circuits[9].

Based mainly on studies in Parkinson's patients in which a striatal receptor hypersensitivity is associated with the dopamine depletion, and in rodents without dopaminergic lesions[10–12], it is well established that PPX induces impulsive choices in DDT, yet its precise site of action remains

unknown. However, it has been shown that the VS and CdN both encode temporal discounting, and may thus be involved in impulse choices[13]. PPX has a preferential affinity for D_3 receptors[14] and the high density of D_3 in the VS[15] makes it a good candidate to induce impulsive choices. This hypothesis is supported by evidence showing the VS is involved in reward expectation and subjective value[16,17]. The other and less described hypothesis regarding processes of impulsive choices is the CdN. There is evidence showing that the lateral and medial prefrontal cortex (LPFC and MPFC) and the CdN[18–21] are involved in temporal discounting and decision-making, suggesting that the cortico-striatal loop, including the CdN, is implicated in impulsive choices.

To investigate the neural basis of impulsive choices triggered by acute PPX administration in healthy animals (without dopamine receptor hypersensitivity), we trained monkeys to perform the DDT, evaluating their basic impulsive state. As macaque striatum is anatomically and functionally similar to that of humans, and as they perform well in this task[22], they are a relevant model to study impulsive behaviors. As PPX had never been tested in monkeys performing DDT, intramuscular PPX was first administered to increase impulsive choices and to reproduce effects similar to those observed in healthy rodents or at least in part in clinical studies. Then, to determine which striatal territory processes impulsive choices, intracerebral microinjections of PPX were performed directly inside the three subterritories to compare the effects on various impulsivity markers. To check that PPX action remained local and selective during a microinjection, PET scans using ^{11}C-raclopride were performed following PPX microinjection inside the CdN, which was the only effective site to induce impulsive choices.

Methods

Animals and Surgical Procedure

Three monkeys were used in the study: a female *Macaca mulatta* (Monkey T, 5 kg) and 2 males *Macaca fascicularis* (Monkeys A and K, 6 kg). Animal care and housing complied with NIH guidelines (1996) and the 2010 European Council Directive (2010/63/UE) recommendations. The procedures were approved by the French National Committee (#991-2015063017055778). During the experiment, each animal was seated in a primate chair and trained to perform the behavioral task. Monkeys A-K were trained to perform our instrumental task during a period of eight months (2 hours/day and 5 days/week), while monkey T, who already knew another decision task (Saga et al., 2017), learned the meaning of conditioned stimuli and showed stable performances in two months.

For all monkeys, after training, a plastic and head holder was fixed to the skull under general anesthesia and sterile conditions. Proper positioning of the chamber was estimated using structural MRI scans (1.5 T; CERMEP, France). The center of the MRI-compatible chamber was aligned based on the anterior commissure (AC) to allow penetrations in the right anterior striatum. Detailed descriptions can be found our previous studies[23,24].

Apparatus and delay discounting task

During experimental sessions, a color video monitor equipped with a touch-sensitive screen was placed in front of the monkey and an infrared-sensitive resting key was installed on the primate chair on which the monkey kept its left hand to run the task. Presentation© (Version 18.0, Neurobehavioral Systems, Inc., CA) and Scenario Manager softwares (ISCJM, Bron, France)

controlled the successive presentation of visual cues displayed on the screen, monitored behavioral responses (screen touches), and regulated reward delivery timing. Single drops of apple juice (0.12 or 0.28 mL) were delivered via a sipper tube attached to a computer-controlled solenoid valve for successful trials.

In each DDT trial (Fig. 1A), the animal was required to make a choice between a SIR and a LDR. When the monkey held the resting key with its left hand, a trial began with a small white dot appeared on the center of the screen. After 1.3-s, two peripheral cues were presented on the screen (1-s duration). One was a conditioned stimulus associated with an SIR (unique volume/delay combination: 0.12 mL and no delay), whereas the other indicated an LDR (six possible volume/delay combinations: 0.28 mL given after variable delays). In our paradigm, we used a total of six visual cues per animal to inform them about the upcoming delay associated with the LDR (monkeys T-K: 0, 1.5, 3, 4.5, 6 and 12-s; monkey A: 0, 1.5, 3, 4.5, 6 and 9-s). The maximum delay (12-s) was reduced a bit for the monkey A (9-s) because he was not willing to complete the task with a longer waiting time. The cue positions were randomly modified across the trials to avoid a possible directional bias. 0.5-s after cue offset, two green squares appeared in the same two positions, cueing the animal to touch one of the targets (within 1.5 s). Prior to the experimental period, the animals learned reward value (volume/delay) associated with each conditioned stimulus (visual images using fractal geometry) during a training period (>8-months) and were then free to choose any option they preferred. Depending on the chosen target, fruit juice was delivered after the selected reward delay period (short or long). The trials were separated by a 0.8-s inter-trial interval. Each choice combination (small vs. large reward) was repeated 30 times in a given block of trials, and the six possible blocks were presented in pseudo-random order across the session by ensuring there was no immediate repetition of the same block. To minimize day-to-day variations in the animals' performance due to a change in their

motivational state, each monkey performed the task with a constant number of blocks (14 blocks for monkey A vs. 22 and 28 blocks for monkey K and T, respectively).

Errors in task performance were categorized as follows: 1) Premature response occurred when the monkeys were unable to keep their hand on the resting key before target presentation, 2) Non-initiated choice (omission) occurred when the monkeys did not initiate a response during the 2-s target presentation, and 3) inaccurate action occurred when the monkeys touched the screen outside the target zone. When premature responses appeared during cue presentation, the cues were removed and the current trial was stopped, followed by an inter-trial interval.

Pramipexole administrations

Acute intramuscular PPX injections (0.1 mg/kg) were first performed five minutes before the animal started to perform the DDT. PPX was administered once a week and control days were defined as behavioral sessions collected one day before and two days after the testing day. Intra-striatal PPX microinjections were then performed on monkeys T and A (6 µL with 1 µg/µL), inside the CdN, VS and putamen by unilateral injection in the right hemisphere. From our previous studies[23,24], we know that this type of intra-striatal injections induces behavioral disorders with bilateral expression. Moreover, as the monkeys performed the task with their left hand, injections into the right hemisphere allow controlling for any potential effect on motor and attentional abilities, usually expressed in the contralateral side of the injection. Each striatal territory was tested during four sessions per monkey, and the microinjections were repeated twice weekly (with a minimum delay of 3 days between drug administrations). The anatomic locations were determined using MRI scans and electrophysiological mapping[25]. Injections into the CdN and the Put were in the two-thirds dorsal part of the anterior striatum, while the injections into the VS were performed in the ventral third (AC +4) corresponding to the core of the nucleus

accumbens in rodents [26–28]. By producing local inhibitory dysfunctions in this identical part of the VS, we previously identified this striatal region as being related to anxiety disorders. For the statistical analysis of local injections, control days were defined as the days before testing. For all types of PPX administrations, we never observed any effect beyond the day of injection.

Analysis of behavioral data

In the model used to analyze the animal's choices, the probabilities that the monkey would choose the SIR over the LDR was calculated for each block of trials. A fitting logistic function was plotted using an exponential function to estimate temporal discounting behavior. The exponential discount model was found to provide a better fit for our monkeys' behaviors than the hyperbolic discount function (the models were compared using Akaike's Information Criteria). The temporally discounted value (DV) was therefore calculated as follows:

$DV = A \exp(-kD)$,

where A is the volume of the reward, D is the length of the delay and k is the steepness of the discount function[29]. The model parameters [the discount factor k (s^{-1}) and the temperature parameter of the logistic function] were simultaneously estimated using a maximum likelihood procedure[13,22,30]. Larger k values indicated more impulsive choices, while smaller k values indicated more patience[31–33]. Based on the estimated logistic curve, the indifference point, i.e. the delay at which the animal indifferently chose the SIR or the LDR, was also calculated to characterize temporal discounting. The lower this point, the more sensitive to delay and impulsive the animal is.

Impulsivity markers (k values and indifference points) were compared between conditions (control vs. PPX days) and task periods (blocks were categorized into three equivalent temporal segments) using two-way ANOVAs. The local effects of intra-striatal PPX microinjections were

then investigated by considering only the early period in each behavioral session (i.e. to prevent drug diffusion effects). Reaction times (RT, the interval between cue appearance and key release), movement times (MT, the interval between key release and target capture) and error rates were tested across drug conditions using a Mann-Whitney U-test. As the data sets were not normally distributed (Kolmogorov–Smirnov test, $p > 0.05$), non-parametric tests were used.

PET imaging

A PET scan with [^{11}C]-raclopride, a $D_{2/3}$ receptor ligand, was performed following a PPX microinjection in the anterior CdN of monkey A. As already reported in our previous studies[24,34], the non-displaceable binding potential (BP) of [^{11}C]-raclopride with (test) and without (control) drug injection was calculated. By comparing these conditions (control – test), the intracerebral extent of PPX effects on $D_{2/3}$ receptors was then detected. Detailed descriptions can be found in Neumane et al. (2012) [24] and in *supplementary*.

Results

Delay discounting behavior in monkeys

To estimate individual temporal discounting and to detect further impulsive decisions, we trained three monkeys to perform the DDT (Fig. 1A), in which they chose freely between a fixed SIR and variable LDRs. All three animals chose the option yielding the larger reward when both rewards were offered immediately or after a short waiting time, but as the delay to obtain the larger reward increased, they alternatively preferred the SIR. This shift in preference indicates that the monkeys took into account both reward magnitude and delay to assess subjective values and make their choice. Based on each behaviorally derived preference curve, a discount function was estimated to determine how subjective value declined with delay (Fig. 1B). Consistent with

previous findings in a range of species such as rats[35], macaques[16] and humans[36], the discount curves were characterized by exponential and hyperbolic models. Although both functions well approximated the animals' task performance for the majority of the behavioral sessions, the exponential discount function was found to provide the better fit in 85% of the cases (medians ± sem: AIC_{exp} = 306 ± 25 vs. median AIC_{hyp} = 311 ± 26). Thus, only results obtained using the exponential discount function are reported in the present study (monkey K: AIC_{exp} = 368 ± 23; monkey T: AIC_{exp} = 382 ± 28; monkey A: AIC_{exp} = 301 ± 22). We calculated a median discount factor *k* value of 0.14, 0.19 and 0.24 s^{-1} for monkeys T, K and A, respectively. Based on this, monkey A was therefore the most impulsive (high *k* value) animal in normal conditions, while monkey T was the most patient (low *k* value). The animals showed relatively stable discount rates across sessions and *k* values were in the same range as those reported in earlier monkey studies using the DDT[13,22,30,37]. The estimated discount rates matched the indifference points calculated using the decision curve, in which equal preference between options occurred with a delay of 5.2, 3.7 and 3.6 seconds for monkeys K, T and A, respectively. The *k* measures were inversely correlated with the indifference points (Spearman rho = - 0.86; $P < 0.001$), reinforcing the view that both behavioral markers are informative in evaluating the degree of impulsive choices[38,39].

Notably, the monkeys' choices and temporal discounting were found to be slowly altered by the accumulation of trials through each session ($F > 3.6$, $P < 0.05$, one-way ANOVA). Figure 1B shows the decision curves and corresponding discount functions computed using one example session of monkey K in which the trials were grouped into three temporal segments (early, intermediate and late periods). Here, a rightward drift in the decision curve was observed during task performance, indicating that the animal was gradually more patient across trials. The initial discount rate was measured with a value of 0.19, before being reduced to 0.18 s^{-1} at the end of the

experimental session. As the temporal discount could vary throughout a daily session, such an effect was controlled for in our further analysis.

Impulsive choices induced by Pramipexole

While the three monkeys were performing the DDT, the overall effects of PPX administration on the animals' choices were investigated by performing intramuscular injections (Fig. 2). For each monkey, four distinct sessions with PPX administration were compared to control days (n=8). Of the three animals tested, two were found to qualify as being more impulsive with the drug injections (drug x periods, two-way ANOVA). Figure 2A illustrates the decision curves obtained for the early period of the experimental session, i.e. when the drug effect was most powerful (*post hoc* Tukey-Kramer comparison). Following PPX injections, monkeys K and T showed an increase of 21% and 27% in their *k* values, respectively ($F > 22$, $P < 0.001$). The higher this discount rate increased the more sensitive to delay and impulsive each animal became. These changes in time discounting were paired with a decrease in indifference points ($F > 8$, $P < 0.01$), in which equal preferences were reduced by 0.8 (K) and 1.2 (T) seconds. Unlike with the others, no significant drug effect was found on the choices made by monkey A ($F_{(1,4)} = 1.89$, $P = 0.2$). Despite this, however, the PPX tended to shift monkey A's preferences to the left, with an indifference point reduced by 0.5 seconds (Fig. 2A *bottom*).

Alongside this, intramuscular administration of PPX was found to induce other behavioral impairments. All monkeys made more errors during task execution, especially by more frequently non-initiating their choices and omitting the response when targets were displayed on the monitor ($P < 0.05$, Mann-Whitney U-test; Fig. 2B). In addition, reaction times ($P < 0.05$ for

K and T; $P = 0.2$ for A; Fig. 2C) and movement times ($P < 0.01$) were lengthened overall by PPX, indicating a slowing of the monkeys' responses.

Together, while PPX injections rendered the animals less motivated to perform the DDT, they made more impulsive choices, as evidenced by the leftward shift in their decision curves and their higher sensitivity to delay. Because the PPX administration method, intramuscular injection, was general and nonselective, these various behavioral effects could result from different action sites reached by the drug.

Selective role of the caudate nucleus in impulsive choices

To identify whether the impulsive effect triggered by PPX was selectively supported by one of the striatum subterritories, intra-striatal PPX microinjections were performed on two monkeys. The microinjections were performed alternatively in the right CdN, VS, or putamen at the beginning of different sessions (Fig. 3A). Each striatal territory was tested with the drug during four sessions per monkey, and our analyses mainly focused on effects observed during the earliest period (0-20 min) in order to minimize the effects due to diffusion into other regions. Although only the results from the first period will be presented below, most of the time the PPX-induced effects initiated during the first 20 minutes remained significantly present during the second period (from 20 to 40 minutes post-injection). Figure 3B illustrates the decision curves obtained after distinct microinjections in both monkeys. Importantly, we found that only one territory in the striatum supported a behavioral effect detected during the DDT. PPX administrations in the CdN showed a consistent increase in k values ($F > 47$, $P < 0.001$), while microinjections in the other sites such as the VS and putamen, did not impact choices ($F < 2.6$, $P > 0.05$). Thus, following PPX microinjections in the CdN, monkeys T and A showed

impulsive choices, with increases of 23% and 22% in their temporal discount rates, respectively. These changes in time discounting were accompanied by a decrease in indifference points ($F > 12$, $P < 0.001$), in which equal preferences were reduced by 0.8 (T) and 0.5 (A) seconds. Because the strength of these impulsivity markers was similar between local and systemic PPX administration ($P > 0.5$, Mann-Whitney U-test), it is quite likely that the CdN constitutes one of the main action site reached by the PPX to trigger impulsive choices.

Contrary to intramuscular administrations, no additional behavioral effects during task performance were found when the local microinjections were performed in the three striatal territories. Error rates ($P>0.05$, Mann-Whitney U-test; Fig. 3C), reaction times ($P >0.05$; Fig. 3D) and movement times ($P > 0.05$) were consistently unaltered for both monkeys.

Extent of Pramipexole microinjection in the Caudate nucleus

To check whether PPX action remained local and selective during a microinjection in the CdN, PET scans with coupled (test) or uncoupled (control) [^{11}C]-raclopride were compared with local drug delivery. Specifically, the difference in BP of [^{11}C]-raclopride induced by the microinjection was calculated to visualize the extent of PPX effects on $D_{2/3}$ receptors. A high differential value of BP ($BP_{control} - BP_{test}$) indicated PPX strongly influenced $D_{2/3}$ receptor binding, while a low differential value reflected no interaction. Figure 4 shows the differential imaging results obtained with monkey A (we used a threshold that displays only major effects). Consistent with a local effect, we found high differential BP values (>1) in only the right CdN, in which raclopride binding was reduced by 47%. This result confirmed PPX action on $D_{2/3}$ receptors that was locally limited to the region of interest. Thus, it appears unlikely that the behavioral changes described above were related to an unspecific effect, such as diffusion into other territories.

Discussion

The study aimed to investigate the acute effects of PPX in healthy animal without dopamine lesion and to determine which anterior striatum territory – the CdN, VS or putamen - processes impulsive choices triggered by PPX. To do so, we trained monkeys to perform DDTs and, using intramuscular PPX injections, we found an increase in impulsive choices. Then, using microinjections in the anterior striatum, we showed that the CdN was the only territory to induce impulsive choices. Finally, by pairing microinjection with PET imaging of [^{11}C]-raclopride, we confirmed that the impulsive choices triggered by PPX were due to high dopamine receptor occupancy in the CdN, known to be involved in decision making.

Thus far, the effect of PPX on impulsive choices had been studied with the DDT mainly on Parkinson's patients[40] and rodents[10,11]. Low-dose increased the likelihood of healthy rodents choosing the SIR on DDTs[10,11] but high doses produced omissions[11]. Our results are consistent with these rodent studies, showing that is not necessary to have hypersensitive dopaminergic receptors due to dopamine lesions in Parkinson's patients to produce impulsive choices[41]. This is also coherent with the observation of ICDs triggered by PPX treatment in patients without dopamine lesions such as in restless legs syndrome[4,42] or fibromyalgia[5]. Thus, in our non-lesioned animals, PPX induces changes in the two main impulsive choice markers, the discounting factor and the indifference point, and also induces non-initiated choices. As well, overall slowness was observed in all of our monkeys. These effects may be due to a general decrease in motivation or sedation affecting attentional processes, as already reported in healthy human subjects[43] despite a dose-dependent inconsistency concerning the impact on impulsive behaviors. Our paradigm does not allow dissociating these confounding factors, but together, these results show the difficulty of

characterizing PPX action on impulsivity using peripheral methods such as IM injection or oral administration. Our results also suggest that PPX effects on impulsive choice depend on the basal impulsive trait of each animal. For instance, monkey A was our most impulsive animal in normal condition. This explains perhaps why we had more difficulty in detecting any additional PPX-induced impulsive effect with him. Of interest, impulsive choices were not paired with premature responses in the present study. It would be interesting to further test PPX administration with an adapted version of the 5-choice serial reaction task to investigate more selectively the drug effect on such different impulsive behavior.

Unlike peripheral PPX administrations, intra-cerebral microinjections are advantageous in that they are more specific and selective, without inducing sedative effects that can severely disturb task performance. Although several studies, presented in the introduction, have suggested that the VS would be the most efficient territory for PPX to induce impulsivity, it was only in the CdN that significant modifications in impulsive choice markers were produced. These results are consistent with fMRI studies in healthy subjects[19,21,44,45] and patients[46] performing the DDT, which have shown preferential CdN activation during cue presentation, in a cortico-striatal circuit linking the CdN to the MPFC and the LPFC dedicated to cognitive encoding underlying decision-making processes. Our results also fit well with neuronal recordings in monkeys[13] showing that CdN neuronal activity encodes the difference in temporally discounted values associated with alternatives, giving the CdN a greater role than the VS in value-based decision-making. Thus, by acting on CdN neuronal activity, PPX increases temporal discounting. At a clinical level, ICDs induced by PPX in patients have been attributed to the D_3 receptors mostly located in the VS[41,47,48]. Here, the lack of effects in the VS and the putamen shows that PPX effects on DDT appear to be greater on decision-making processes than on action selection, processed by the

putamen[9], or on motivational states, processed by the VS[17,49]. In the literature, there is also a strong hypothesis regarding a putative balance between two systems controlling impulsive choices[16,50]. McClure et al. (2004) have proposed that a limbic cortico-striatal circuit going through the VS processes the valuation of the immediate reward, while a cognitive circuit including the lateral prefrontal cortex is engaged uniformly by intertemporal choices irrespective to delay[50]. Consistent with the topography of cortico-striatal projections, this second network may involve the CdN, the striatal region where we triggered an increase of impulsive tendencies. Hence, our results could be due to an imbalance between those two functional circuits, caused by the PPX administration into the CdN. Further research is needed to determine how these two systems are involved in the performance of the DDT.

At a pharmacological level, PPX's affinity for $D_{2/3}$ receptors raises the question of the Basal Ganglia pathway underlying the PPX effect. Does PPX trigger an approach behavior towards the small reward or avoidance of the large delayed one? The indirect pathway that expresses D_2 receptors projects to the external pallidum, and is involved in the processes of action inhibition and control of aversive behaviors (escape and avoidance)[51]. Therefore, it is likely that PPX activates the indirect pathway by increasing the temporal discounting of this option and thus making waiting for the large reward more aversive and favoring the search for the small one. This hypothesis is supported by recent research on rodents[52] and monkeys[51]. However, the co-localization of some D_3 receptors with D_1 receptors and the fact that stimulation of D_3 increases the affinity of D_1 for dopamine[53] do not allow us to exclude the activation of the direct pathway, which preferentially expresses D_1 receptors and projects to the outputs of the Basal Ganglia linked to reward seeking.

To conclude, our study on DDT-trained monkeys filled the gap between rodent and human studies, showing that PPX induces impulse choices in healthy non-human primate and that these impulsive choices are supported by $D_{2/3}$ receptors in the CdN. By triggering $D_{2/3}$ receptors, we activated the CdN-PFC loop, reinforcing the involvement of the CdN in decision-making and suggesting the importance of this striatal territory in temporal discounting and impulsive choices.

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Figure legends

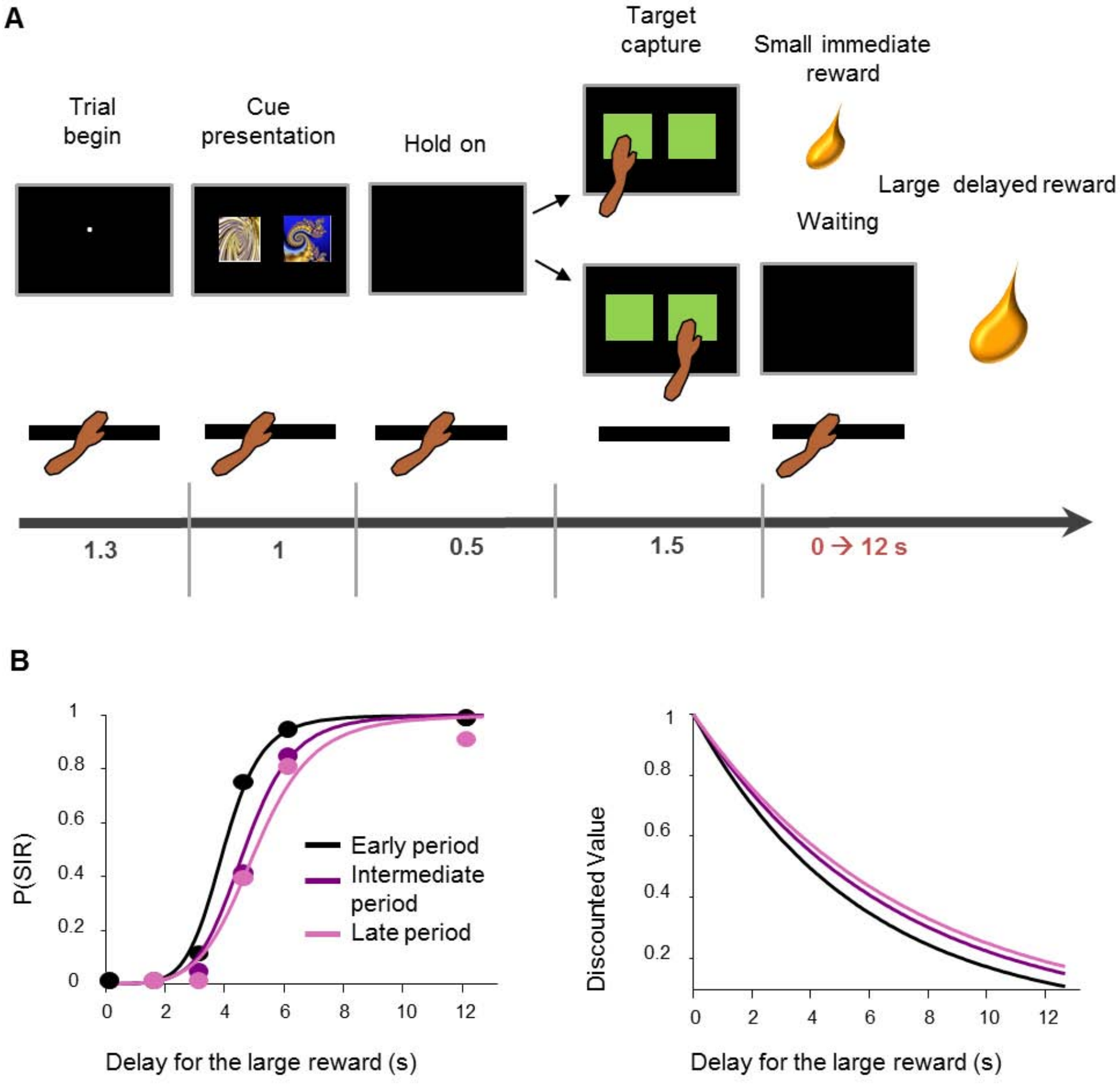
Figure 1: Delay discounting task and choice behaviors. (**A**) Timeline of the instrumental paradigm in which each animal was required to make choices between a small immediate reward and a larger delayed one. (**B**) The decision curves (*left*) show the likelihood that the animal would choose the small immediate reward (SIR) as a function of the delays for the large reward. The lines indicate different periods in the experimental sessions. The temporally discounted value (*right*) was estimated based on the monkeys' choices using an exponential discount model.

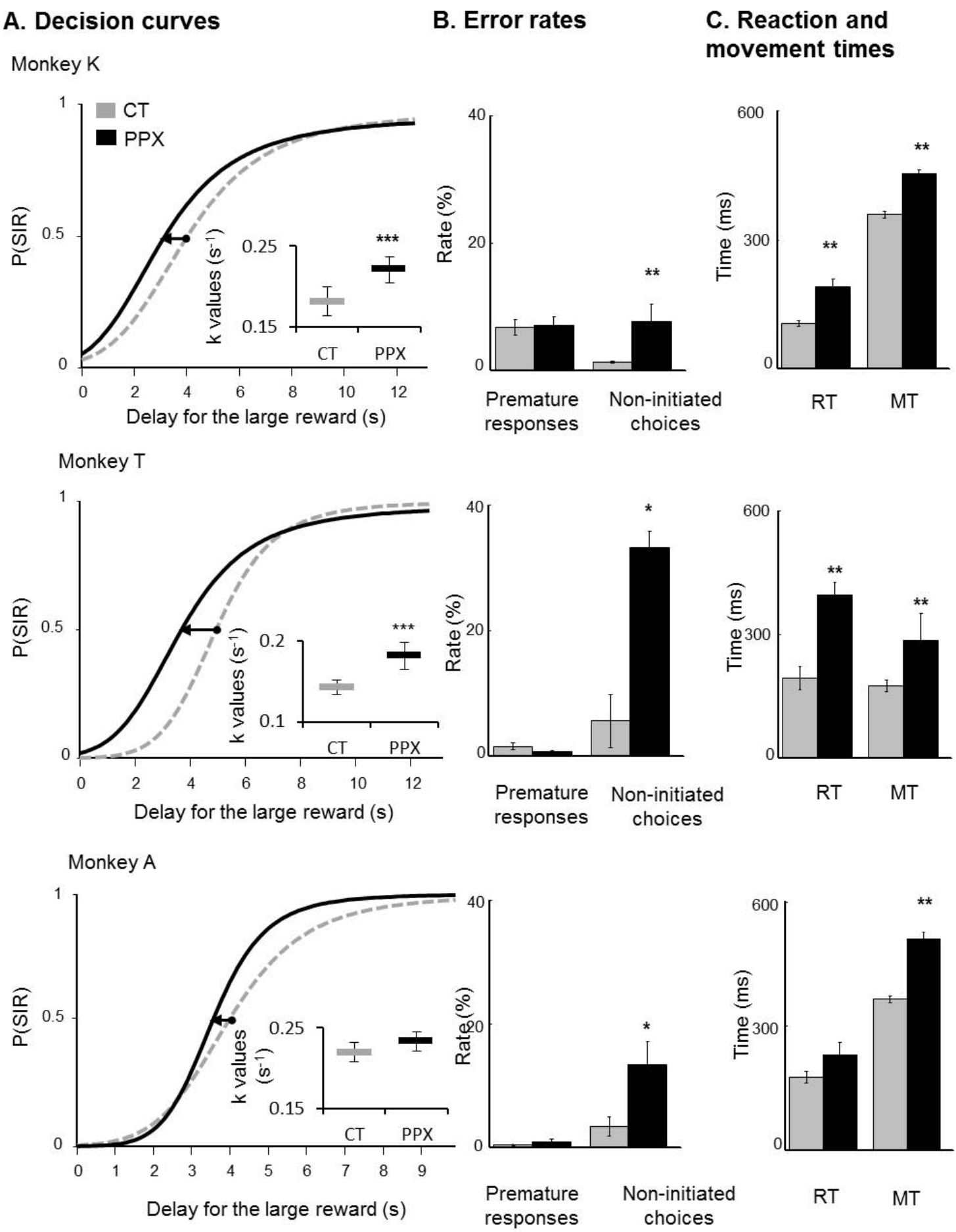
Figure 2: Delay discounting behaviors with intramuscular administration of pramipexole. (**A**) For each monkey**,** four distinct experimental sessions with a PPX injection (*black*) were compared to control days (n=8; *gray*). Following PPX injections, there was a significant increase in discount factor *k* for monkeys K and T (two-way ANOVA; ***$P < 0.001$), while no changes were detected for monkey A ($P = 0.2$). The inserts represent median *k* values ± SEM. The black arrows between decision curves indicate the shift of indifference points (i.e., equal preference between reward/delay conditions) induced by the PPX. (**B-C**) Measures of task performance were averaged (mean ± SEM) across early periods of sessions. (**B**) Error rates, (**C**) reaction times and movement times were increased by the PPX (Mann-Whitney U-test; *$P < 0.05$, **$P < 0.01$).

Figure 3: Delay discounting behaviors after intra-striatal administration of pramipexole. (**A**) Structural MRI and schematic map of intra-striatal microinjection sites in the right caudate nucleus (CdN), the right ventral striatum (VS), and the right putamen (Put). The sites were fairly close between the animals. (**B**) PPX microinjections into the striatum were alternatively tested in different territories. Following PPX injections in the caudate nucleus, there was a significant

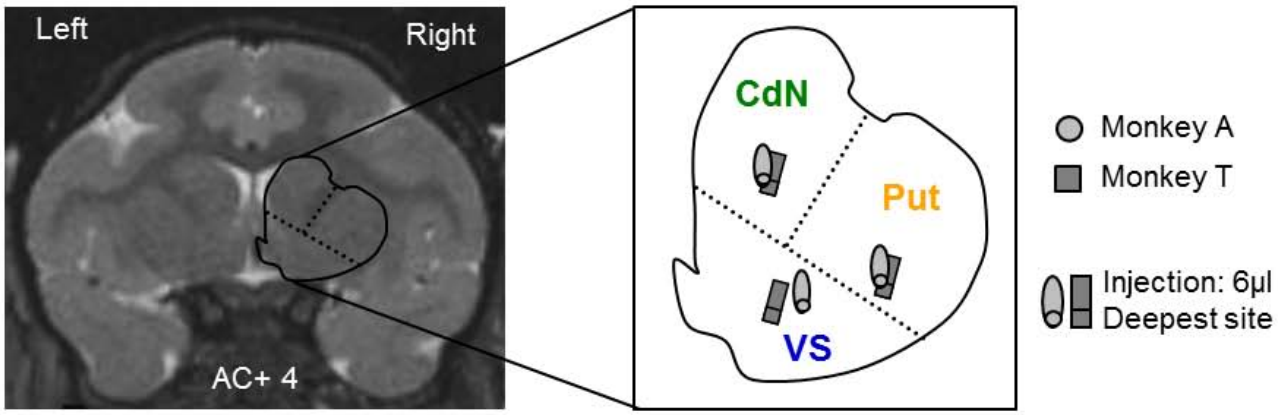
increase in discount factor *k* for both monkeys (two-way ANOVA; ***$P < 0.001$), while no changes were detected for other sites ($P > 0.05$). (**C**) Error rates, (**D**) reaction times and movement times were not altered by the local administration (Mann-Whitney U-test; $P > 0.05$). These figures follow the conventions of Figure 2.

Figure 4. PET scan results. To visualize the local effect of the PPX in the caudate nucleus, we calculated the difference in [^{11}C]-raclopride binding potential ($\triangle BP = BP_{control} - BP_{test}$) between a control condition and when it was paired with a PPX microinjection in the region of interest. Coronal and transverse slices show that the high differential BP values (>1) were selectively located in the caudate nucleus (CdN). [^{11}C]-raclopride binding was marginally modified in the ventral striatum (VS) and the putamen (Put). The histogram (*right*) indicates the mean $\triangle BP$ calculated per territory defined using the MRI template.

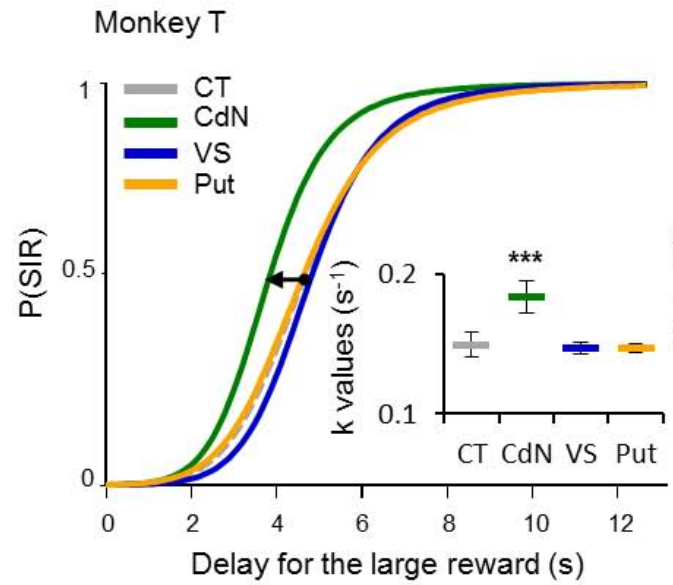

A
Target capture
Small immediate reward
Trial begin
Cue presentation
Hold on
Large delayed reward
Waiting
1.3
1
0.5
1.5
0 → 12 s
B
P(SIR)
Early period
Intermediate period
Late period
Delay for the large reward (s)
Discounted Value
Delay for the large reward (s)

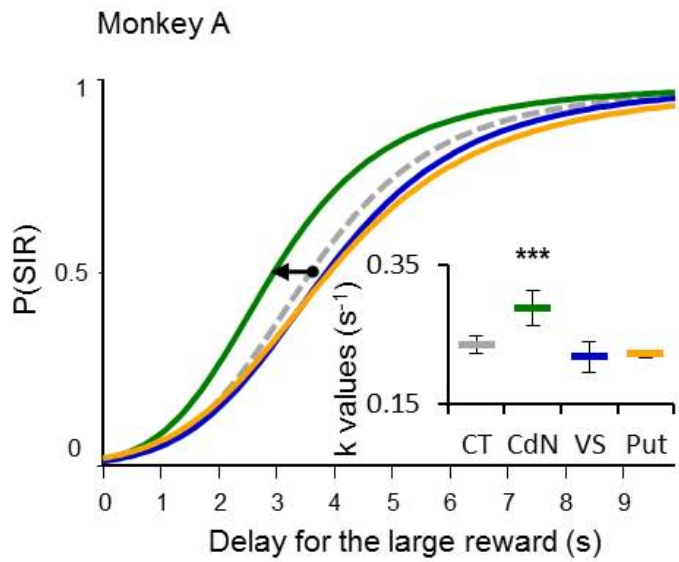

A. Decision curves
B. Error rates
C. Reaction and movement times
Monkey K
CT
PPX
P(SIR)
Delay for the large reward (s)
k values (s-1)
***
Rate (%)
**
Premature responses
Non-initiated choices
Time (ms)
RT
MT
Monkey T
*
Monkey A

A. MRI and sites of PPX microinjections in the striatum

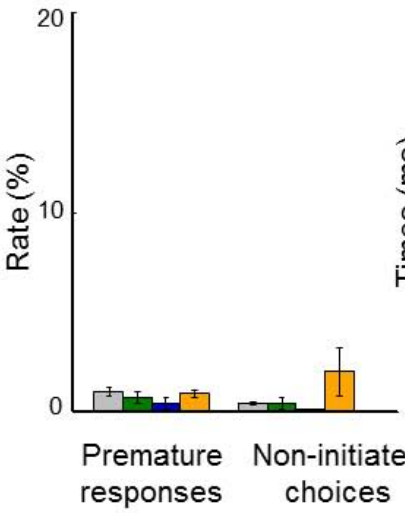


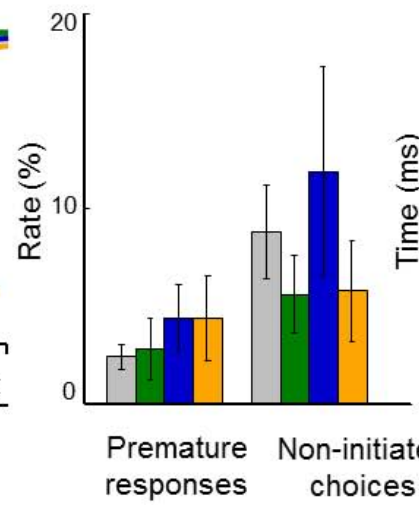
B. Decision curves



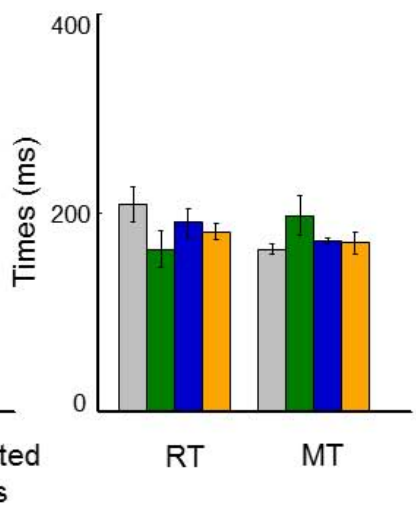


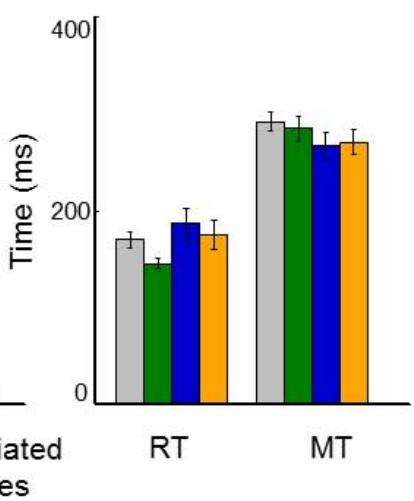
C. Error rates

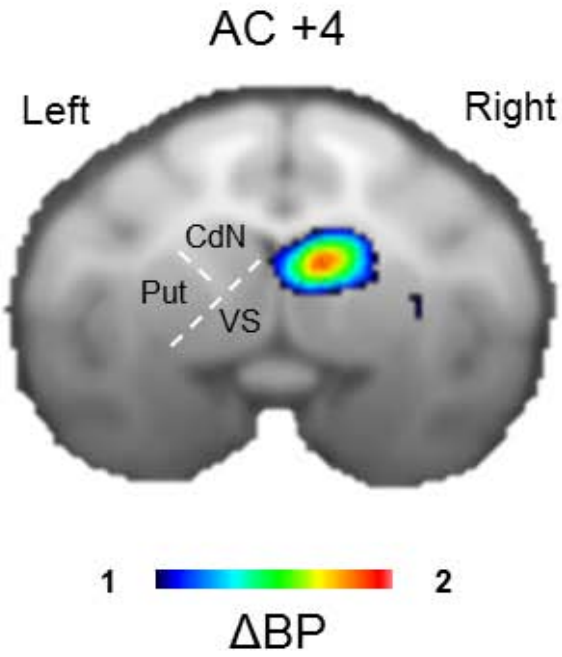


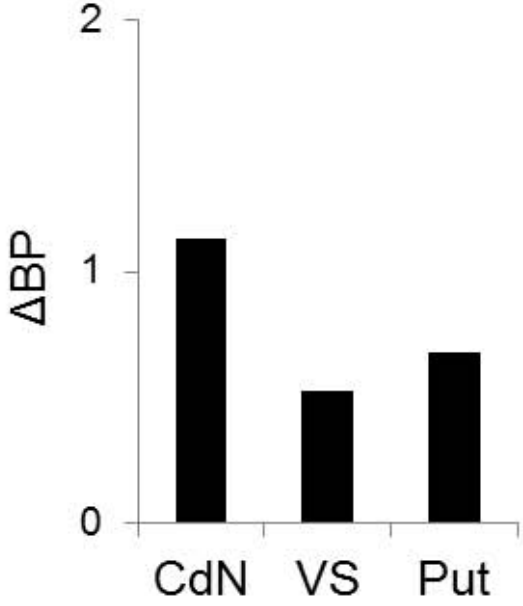


D. Reaction and movement times






AC +4
Left
Right
CdN
Put
VS
1
1
2
ΔBP


2
1
0
ΔBP
CdN
VS
Put