Research

Striatal dopamine D1 receptors control motivation to respond, but not interval timing, during the timing task

Taisuke Kamada[1,2,3] and Toshimichi Hata[2]

[1]Organization for Research Initiatives and Development, Doshisha University, Tatara-Miyakodani, Kyotanabe, Kyoto 610-0394, Japan; [2]Faculty of Psychology, Doshisha University, Tatara-Miyakodani, Kyotanabe, Kyoto 610-0394, Japan

Dopamine plays a critical role in behavioral tasks requiring interval timing (time perception in a seconds-to-minutes range). Although some studies demonstrate the role of dopamine receptors as a controller of the speed of the internal clock, other studies demonstrate their role as a controller of motivation. Both D1 dopamine receptors (D1DRs) and D2 dopamine receptors (D2DRs) within the dorsal striatum may play a role in interval timing because the dorsal striatum contains rich D1DRs and D2DRs. However, relative to D2DRs, the precise role of D1DRs within the dorsal striatum in interval timing is unclear. To address this issue, rats were trained on the peak-interval 20-sec procedure, and D1DR antagonist SCH23390 was infused into the bilateral dorsocentral striatum before behavioral sessions. Our results showed that the D1DR blockade drastically reduced the maximum response rate and increased the time to start responses with no effects on the time to terminate responses. These findings suggest that the D1DRs within the dorsal striatum are required for motivation to respond, but not for modulation of the internal clock speed.

[Supplemental material is available for this article.]

Animals, including humans, can regulate their behavior according to temporal information. This suggests animals can perceive the passage of time (i.e., time perception). Without accurate time perception, we cannot speak, appreciate and play music, drive cars, and play sports. The current paper focussed on time perception in a seconds-to-minutes range; i.e., interval timing (Buhusi and Meck 2005). Interval timing is essential for an optimal foraging (Kacelnik and Bateson 1996) and associative learning (Gallistel and Gibbon 2000).

In rodents, interval timing is frequently examined using the peak-interval (PI) procedure (Catania 1970; Roberts 1981). This task consists of randomly ordered two types of trials; i.e., fixed-interval (FI) and probe trials, separated by intertrial intervals (ITIs). During each FI trial, a reward is delivered for the first response made after a criterion time (e.g., 20 sec) has elapsed from the start of the trial, but not for responses made before the criterion time. Probe trials usually last for three times more than the criterion time in FI trials (e.g., 60 sec), and the reward is omitted. During an individual probe trial, rats typically start responding before the criterion time and stop it after the criterion time. The average rate of responses throughout the multiple probe trials in a session increases as the criterion time approaches, reaches a peak around the criterion time, and then decreases. The location of the peak of the response rate function (peak time), the spread of the function (peak spread), and the height of the peak (peak rate) are indices for timing accuracy, timing precision, and motivation to respond, respectively.

Many studies have demonstrated that systemic injections of drugs affecting dopamine (DA) receptors impact interval timing in various ways. Some studies suggest that DA modulates the speed of the internal clock (Meck 1996). Systemic injection of DA receptor agonist decreases peak times, while that of DA receptor antagonist increases peak times. Importantly, the degree to which responding is altered is proportional to the duration being timed (Maricq et al. 1981; Maricq and Church 1983; Meck 1983, 1996; Matell et al. 2006). Therefore, it is necessary to use multiple target durations of a PI procedure (e.g., 20 and 40 sec) while examining the occurrence of any changes in clock speed mechanisms adequately. A recent study showed that transient activation or inhibition of DA neurons in the substantia nigra pars compacta (SNc) was sufficient to induce overestimation or underestimation of time in a temporal discrimination task, respectively (Soares et al. 2016). These results suggest that DA neurons in the SNc and DA receptors modulate the speed of the internal clock ("the dopamine-clock hypothesis"). Other studies, however, suggest that DA is involved in motivation during the interval timing task (Balcı 2014). Systemic injection of dopamine D1 receptors (D1DRs) antagonist SCH23390 reduced the peak rate (Drew et al. 2003), whereas systemic injection of DA agonist D-amphetamine increased the peak rate but reduced peak time and start time of responding without affecting stop time of responding (Taylor et al. 2007). The results of these studies are similar to those of studies that investigated the effect of manipulation of motivation on interval timing (Balcı 2014). Manipulations that decrease motivation (e.g., decreasing reward magnitude, prefeeding, and reward devaluation) reduced the peak rate, and sometimes delayed the start time (Roberts 1981; Ludvig et al. 2007; Galtress and Kirkpatrick 2009; Delamater et al. 2014, 2018). In contrast, opposite manipulations on motivation (e.g., increasing reward magnitude) caused earlier initiation of responding and a higher peak rate (Galtress and Kirkpatrick 2009). These findings support the idea that DA contributes to modulating motivation (Ikemoto et al. 2015). Therefore, DA might modulate motivation also during the timing task ("the dopamine-motivation hypothesis").

[3]**Present address: Medical Innovation Center, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606-8507, Japan.**
Corresponding author: taisuk.kamada@gmail.com
Article is online at http://www.learnmem.org/cgi/doi/10.1101/lm.052266.120.

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DA receptors within the dorsal striatum (dSTR) can be responsible for the effect of systemically injected DA agents on interval timing. Lesioning of the dSTR and damaged DA neurons in the SNc projecting to the dSTR caused the severe impairment of interval timing (Meck 2006b; Gouvêa et al. 2015; Mello et al. 2015), and optogenetic manipulation of DA neurons in the SNc affected the performance of the temporal discrimination task (Soares et al. 2016). These results strengthen the notion that the DA pathway from the SNc to the dSTR and the modulation of DA receptors in the dSTR are important for interval timing. Therefore, systemically injected DA agents might affect interval timing task through the DA receptors in the dSTR. Consistently, the affinity of DA agents for D2 dopamine receptors (D2DRs), but not D1DRs, correlated with the degree to produce the rightward shift of the temporal bisection function (Meck 1986), and systemic injection of D2DR blocker, but not D1DR blocker, affected interval timing in the PI procedure (Drew et al. 2003). These findings suggest that the change in the activity of D2DRs is implicated in the effect of DA on interval timing.

Some studies, however, suggest that also the D1DRs within the dSTR might also play an important role in interval timing. A study showed that stimulation of the D1DR by systemic injection changed interval timing behavior (Cheung et al. 2007). D1DRs, as well as D2DRs, are highly expressed in the medium spiny neurons in the dSTR (Gerfen and Surmeier 2011). Thus, it is the possible that D1DRs in the dSTR also play an important role in interval timing. Notably, a recent study reported that D1DR blockade in the dSTR increased the time of stop responding (De Corte et al. 2019), and the findings cannot be explained by either “dopamine-clock hypothesis” nor “dopamine-motivation hypothesis.” Therefore, further studies are needed to clarify the role of D1DRs within the dSTR in interval timing.

The present study aimed to examine further the role of D1DRs within the dorsal striatum in interval timing using the PI procedure. After a limited amount of training (Cheng et al. 2007), rats were infused with D1DR antagonist SCH23390 into the bilateral dSTR. Our findings support the “dopamine-motivation hypothesis” of D1DRs in the dSTR.

Results

Histology

Figure 1 shows the locations of the injection cannula tips. All the cannula tips were located within the dSTR ($n=12$).

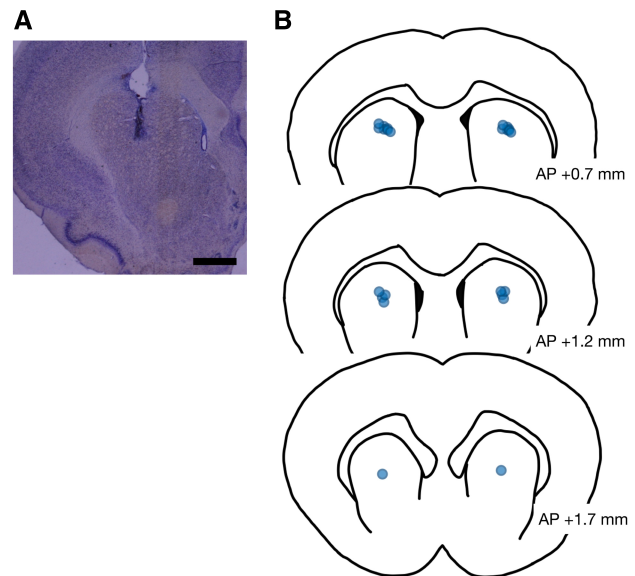

Figure 1. All injection cannula tips were located in the dorsal striatum. (*A*) Representative photomicrograph showing the track of the guide cannulas in the dorsal striatum. Scale bar, 1 mm. (*B*) Placements of the injection cannula tips (blue dots, $n=12$) were in the range from anteroposterior (AP) 1.70–0.70 mm of the dorsocentral striatum.

Behavior

Session-by-session analysis

We analyzed rats’ behaviors during the PI procedure after drug injection (Fig. 2A). First, we conducted a session-by-session analysis. Average peak functions during the infusion sessions are shown in Figure 2B. In all groups, the peak of the function was near 20-sec. D1DR blockade appeared to reduce the height of the response function selectively. Average normalized peak functions are shown in Figure 2C. D1DR blockade did not appear to induce clear effects.

We fitted the Gaussian curve to peak function of each rat (Fig. 3A). D1DR blockade did not affect peak times (Fig. 3B). This observation was confirmed by within-subject Dunnett’s multiple comparison tests, which revealed no significant difference between the control (0.00 µg) and each dose session (0.50 µg: $P=0.93$; 1.25 µg: $P=0.40$; 2.50 µg: $P=0.57$). In addition, D1DR blockade did not affect peak spreads (Fig. 3C). This was confirmed by Dunnett’s multiple comparison tests, which revealed no significant difference between the control and each dose session (0.50 µg: $P=0.91$; 1.25 µg: $P=0.96$; 2.50 µg: $P=0.42$). Notably, D1DR blockade appeared to reduce peak rates dose-dependently (Fig. 3D). Dunnett’s multiple comparison tests revealed that 1.25 and 2.50 µg of SCH23390 significantly reduced peak rates relative to the control (0.50 µg: $P=0.98$; 1.25 µg: $P<0.0001$; 2.50 µg: $P<0.0001$).

Trial-by-trial analysis

Next, we analyzed the response pattern in the individual trials (Fig. 4A). As shown in Figure 4B, D1DR blockade appeared to increase the start times dose-dependently. Dunnett’s multiple comparison tests revealed that 2.50 µg of SCH23390 significantly increased start times relative to the control (0.00 µg; 0.50 µg: $P=0.19$; 1.25 µg: $P=0.09$; 2.50 µg: $P=0.007$). However, D1DR blockade did not affect the stop times (Fig. 4C). Dunnett’s multiple comparison tests confirmed this observation (0.50 µg: $P=1.00$; 1.25 µg: $P=0.93$; 2.50 µg: $P=0.79$).

Supplemental Figure 1a shows coefficient of variation (CV) of start times for each drug condition (0.00, 0.50, 1.25, and 2.50 µg). Dunnett’s multiple comparison tests revealed that SCH23390 did not affect CV of start times relative to the control (0.50 µg: $P=0.99$; 1.25 µg: $P=0.12$; 2.50 µg: $P=0.48$). Supplemental Figure 1b shows CV of stop times for each drug condition. Dunnett’s multiple comparison tests revealed that SCH23390 did not affect CV of stop times relative to the control (0.50 µg: $P=0.99$; 1.25 µg: $P=0.06$; 2.50 µg: $P=0.18$).

Discussion

In the current study, we examined the effect of D1DR blockade within the dSTR on the performance during the PI procedure. Our results showed that D1DR antagonist SCH23390 did not affect peak times and peak spreads but reduced peak rates. Moreover, under D1DR blockade, rats started responding later without changing in the timing to stop responding. These data suggest that the striatal D1DRs are involved in the motivation to respond during the PI procedure.

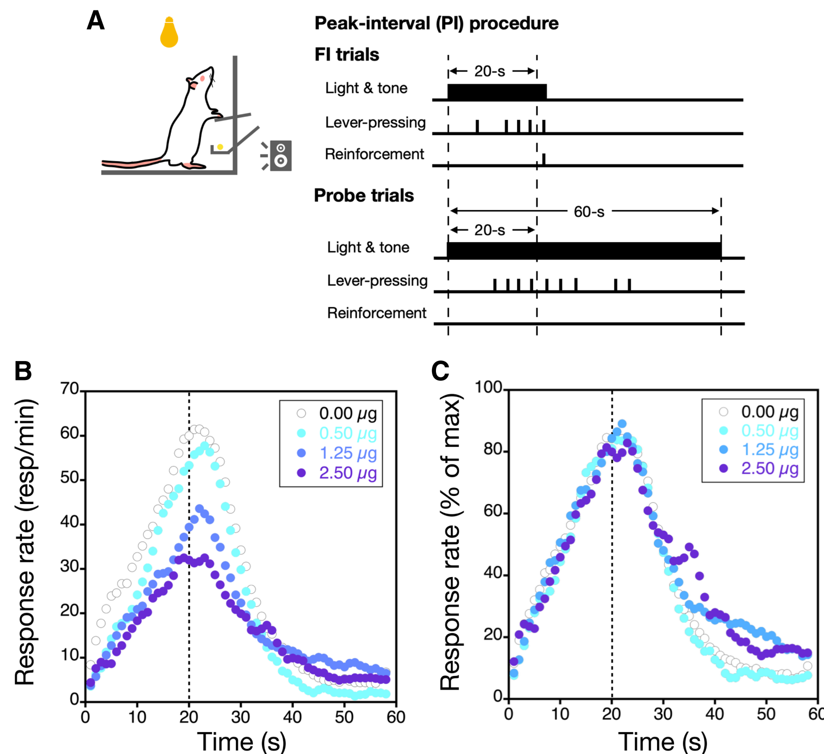

Figure 2. Infusion of D1 dopamine receptor (D1DR) antagonist SCH23390 into the dorsal striatum reduced the maximum response rate. (*A*) Rats were trained with the peak-interval (PI) procedure in operant chambers. This task consisted of two types of trials: fixed interval (FI) trials and probe trials. In FI trials, the first response after 20-sec was reinforced, but responses before 20-sec were not reinforced. On the other hand, probe trials lasted for 60-sec, and reinforcement was omitted. In a typical probe trial, rats started responding before 20-sec and stopped responding after 20-sec. We analyzed data of probe trials. (*B*) Response rates as a function of elapsed time for each drug condition (0.00, 0.50, 1.25, and 2.50 µg) are presented. D1DR blockade reduced maximum response rates dose-dependently. (*C*) Response rates (percentage of the maximum response rate for each rat) as a function of elapsed time for each drug condition are presented. D1DR blockade had no apparent effects. All data are presented as mean. Dot lines indicate the target duration (20 sec).

Our results are roughly consistent with dopamine-motivation hypothesis. To date, two hypotheses have been assumed on the relationship between DA and interval timing: the clock hypothesis and the motivation hypothesis. According to the dopamine-clock hypothesis (Meck 1996), D1DRs tune the speed of the internal clock, and down-regulation of DA function leads to increased values of the accuracy indices in interval timing. If this had occurred in the current study, then all of the peak time, start time, and stop time would have increased at the same time under the striatal D1DR blockade. In contrast, according to the dopamine motivation hypothesis (Balcı 2014), D1DRs contribute to motivation to respond during the timing task. If this hypothesis is correct, then the treatment would reduce peak rates without affecting peak times. As shown in Figure 3, the findings obtained in this study were in line with the dopamine motivation hypothesis. Moreover, the increase in start time shown in Figure 4B is not conflict to the motivation hypothesis because accumulating evidence indicates that operations reducing motivation retarded start times (Roberts 1981; Ludvig et al. 2007; Galtress and Kirkpatrick 2009). Although we have not tried higher doses (>2.50 µg) of SCH23390, these doses may reduce general levels of activity and peak rates in a PI procedure, because one study reported that 5.0 µg of SCH23390 injected in the dorsocentral striatum reduced levels of locomotor activities of pre weanling rats (Charntikov et al. 2011). Taken together, the present results suggest that D1DRs within the dorsal striatum control motivation to respond, rather than the speed of an internal clock.

It is not surprising that D1DR antagonist into the dSTR did not abolish interval timing per se. Some studies have also demonstrated that D1DRs are not involved in interval timing. For instance, affinity for D1DR of dopaminergic agents did not correlate with the degree to produce the rightward shift of the psychophysical function in the temporal bisection task (Meck 1986), and systemic injection of D1DR blocker SCH23390 reduced peak rate at the dose that did not affect the accuracy and precision of interval timing (Drew et al. 2003); D1DR blockade in the dorsolateral striatum did not affect both start and stop time (De Corte et al. 2019). Conversely, cortical D1DR blockade and stimulation impaired ramping activities and oscillatory patterns of cortical neurons during the to-be-timed stimulus, and the optimal performance of a FI task (Narayanan et al. 2012; Parker et al. 2014, 2015). Therefore, our findings extended the previous works by showing that D1DR within the dorsocentral striatum did not affect interval timing per se.

It is not likely that the long term of training history suppresses the potential effect of D1DR blockade on the accuracy of interval timing. Indeed, one study showed that the effect of the DA operation of an internal clock function was only observed when baseline training was limited (>60 sessions) (Cheng et al. 2007). In our study, we trained rats in baseline training for only 18 sessions. Therefore, if our drugs had had any potential effect on the clock function, the peak time would have changed in our experiment; however, this hypothesis was not evidenced by the present data. Thus, the length of the training history cannot explain why SCH23390 did not change the peak time in the current study.

The role of the striatal D1DRs in the PI procedure might be different depending on its subregional locations in the dSTR. Our data showed that D1DR blockade in the dorsocentral striatum reduced peak rates and increased start times. Although normalized response rates after a target duration under 1.25 or 2.50 µg of SCH23390 were somewhat higher than the control condition (Fig. 2C), we did not find any significant differences in stop times between 1.25 or 2.50 µg and control conditions (Fig. 4C). On the other hand, one previous study found that the D1DR blockade in the dorsomedial striatum increased stop times without affecting start times (De Corte et al. 2019). While it is unclear why the effect of D1DRs blockade differed between the the study by De Corte et al. (2019) and this study, one possibility is that the role of striatal D1DRs is different between the dorsocentral striatum and the dorsomedial striatum.

Our data do not violate the prediction of the biologically plausible neural model of interval timing, the striatal beat frequency Morris Lecar (SBF-ML) model (Oprisan and Buhusi 2011). Some models claim crucial roles of the frontal cortex (FC) and the dorsal striatum in interval timing (Oprisan and Buhusi 2011; Simen et al. 2011). In particular, the SBF-ML model (Oprisan and Buhusi 2011)

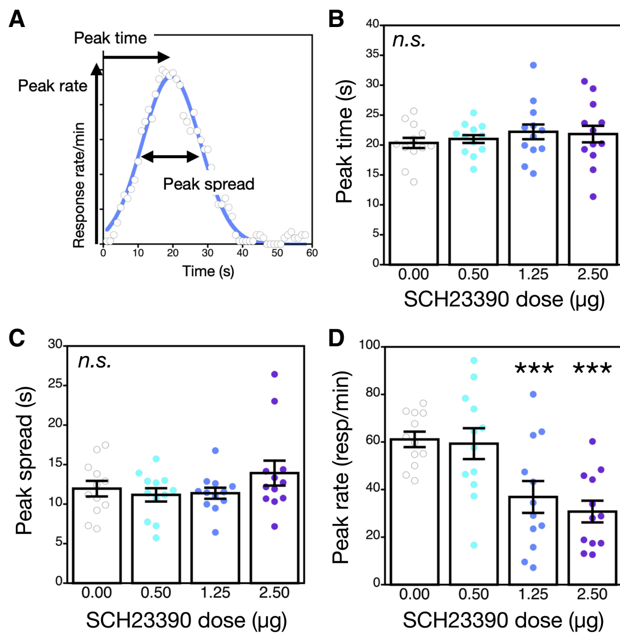

Figure 3. Infusion of D1 dopamine receptor (D1DR) antagonist SCH23390 into the dorsal striatum reduced peak rates without affecting peak times and peak spreads. (*A*) We fitted the Gaussian curve to the response function of each rat. We then calculated peak times, peak spreads, and peak rates from this fitting. This figure shows the response function of the representative rat in the 0.00 µg condition. (*B*) Peak times for each drug condition (0.00, 0.50, 1.25, and 2.50 µg) are presented. D1DR blockade did not affect peak times. (*C*) Peak spreads for each drug condition are presented. D1DR blockade did not affect peak spreads. (*D*) Peak rates for each drug condition are presented. The D1DR blockade reduced peak rates dose-dependently. All data are presented as mean ± SEM. Dots represent the data of individual rats. (***) $P < 0.001$ versus the control condition (0.00 µg), (n.s.) no significant difference between the control (0.00 µg) and other drug conditions, respectively.

assumes that the phasic release of DA from the ventral tegmental area to the FC modulates the firing rate of cortical oscillations. In experiments, systemically injected DA agents induced immediate horizontal shifts of the response rate function in the PI procedure, called "clock pattern" (Meck 1996). The clock pattern was successfully simulated on the model by changing the parameter of firing rate of cortical oscillators (Oprisan and Buhusi 2011). Another experiment showed that effects of a DA agent in the performance of the PI procedure was abolished after the lesioning of the FC (Meck 2006a). Taken together, DA-related mechanisms such as DA receptors in the FC may be essential for the clock pattern change. Therefore, our findings do neither conflict with experimental nor the computational evidences suggesting that DA agents induce the clock pattern change.

One limitation of the current work is the use of a single interval in a PI procedure (20 sec). Multiple durations (e.g., 20 and 40 sec) are needed to interpret the changes in peak times as clock-effects, because the clock hypothesis predicts that DA agents induce proportional shifts in peak times. Some studies have examined the effects of local drug infusion using the multiple durations in between-subject (Kurti and Matell 2011) or within-subject design (Buhusi et al. 2018). In this study, we found that D1DR blockade decreased peak rates and delayed start times, but the same treatment had no effects on peak times. Although the single interval may be enough to interpret the current results as motivational change, multiple target durations can provide more information for drawing conclusions.

In summary, we found that the D1DRs within the dSTR reduced the maximum response rates and delayed the time to start responding without affecting the time to terminate responses. These results are consistent with the hypothesis that D1DRs contribute to motivation to respond (Balcı 2014), but not with the hypothesis that D1DRs control the speed of an internal clock (Meck 1996).

Materials and Methods

Subjects

Twelve male Wistar albino rats (Shimizu Laboratory Supplies), 10 wk old at the beginning of the experiment, were individually housed in stainless steel cages under a 12-h light–dark cycle (light on at 8:00 a.m.), with water provided ad libitum. Rats were maintained at 85% of their free-feeding weight, and target weights were adjusted upward by 5 g/wk to consider growth. All experimental sessions were conducted during the light phase. All animal procedures were approved by the Animal Research Committee of Doshisha University.

Apparatus

Behavioral testing was conducted in eight identical standard operant chambers (225 × 165 × 220 mm). Each chamber was enclosed in a sound-attenuating box with a fan (65 dB), a buzzer (~2000 Hz, 80 dB), and a house light (25 W). Each chamber had an aluminum front wall (all remaining walls were made of Plexiglas) and a stainless-steel grid floor. The front wall was equipped with a stationary lever and a food cup. A 45-mg food pellet (Bioserv F0021-J) was delivered via a pellet dispenser (Med-associates, Inc. ENV-203-45) into the food cup that was 10 mm above the grid floor. Stimuli control and data collection were accomplished by a custom-made software written by Xojo (Xojo, Inc.) running on personal computers (Macbook air, Apple) with a serial I/O controller (Kyohritsu Eletronics RBIO-2U) and a programable controller (SYSMAC, Omron CPM1A-40CDR-A-V1). We acquired data for lever response with a temporal resolution of 0.1 sec.

Surgery

Surgery was conducted before the behavioral experiment. Rats were anesthetized with isoflurane gas (2%–5%). They were then placed on a stereotaxic frame (Kopf Instruments) and a 22-gauge bilateral stainless-guide cannula (Plastics One C323G) attached with a 28-gauge bilateral dummy cannula (Plastics One C323DC) was lowered into the dorsal striatum with the following stereotaxic coordinates: anteroposterior: +0.2 mm to the bregma; mediolateral: ±2.5 mm; dorsoventral: −3.8 mm from the skull surface (Paxinos and Watson 1998). We aimed at the dorsocentral striatum because the silencing of the region produces the severe impairments in interval timing (Meck 2006b; Gouvêa et al. 2015; Mello et al. 2015). The cannulas were fixed using dental cement and two small screws. Rats were allowed to recover for ≥5 d after surgery.

Behavioral procedures

Pretraining

Over 3 d, the rats were trained to press the lever under a continuous reinforcement schedule until they earned 60 reinforcements by lever presses in each session. Each session began with the onset of the house light and ended with its termination.

PI 20-sec training

Rats were then trained on the discrete-trials PI procedure. This training consisted of randomly ordered two types of trials, FI and probe, separated by an ITI ranging between 30 and 50 sec. During this training, rats could freely respond to the lever.

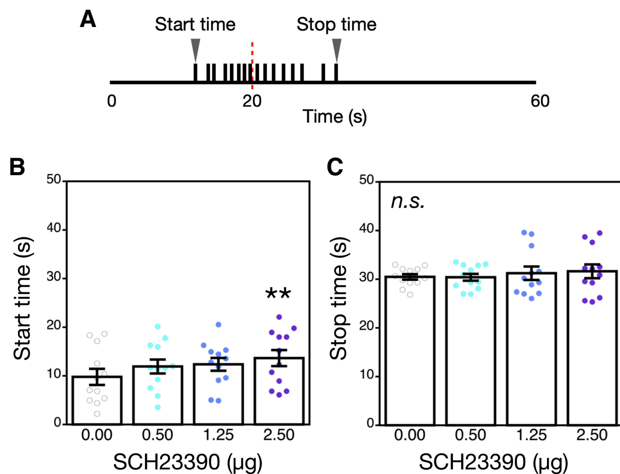

Figure 4. Infusion of D1 dopamine receptor (D1DR) antagonist SCH23390 into the dorsal striatum increased time to start responding in individual trials. (*A*) According to the method of Church et al. (1994), we calculated the time to start responding (start times) and stop responding (stop times) from individual trials. (*B*) Start times for each drug condition (0.00, 0.50, 1.25, and 2.50 µg) are presented. The D1DR blockade increased start times significantly only in the highest dose (2.50 µg) relative to the control (0.00 µg). (*C*) Stop times for each drug condition are presented. The D1DR blockade did not affect stop times. All data are presented as mean ± SEM. Dots represent the data of individual rats. (**) $P<$ 0.01 relative to the control (0.00 µg), (n.s.) no significant difference between the control (0.00 µg) and other drug conditions.

During the FI trials, the first lever response after 20 sec since the house light and tone (signal stimuli) onset yielded one pellet reinforcer, and the trial was finished (signal stimuli were terminated). Probe trials also began with the onset of the single stimuli and terminated at 60 sec, independent of rats' behavior. In the probe trials, any responses, even if they were emitted after 20 sec, were not reinforced. If a rat responded on the lever during the last 5 sec of ITI, the ITI was extended for 10 sec from the moment. Altogether, 18 sessions were conducted, with each session consisting of 60 trials (FI 42 and probe 18).

PI 20-sec training with drug

Before starting each behavioral session, rats were infused with artificial cerebral spinal fluid (aCSF) or SCH23390 (Tocris) solution (0.50, 1.25, or 2.50 µg/0.5 µL: 0.5 µL each side) via 28 gauge bilateral internal cannulas (Plastics One C323I) attached to 100-µL microsyringes (Hamilton 1710N) at a rate of 0.25 µL/min for 2 min using an infusion pump (Eicom ESP-32). Cannulas were then maintained in place for an additional 1 min to allow drug diffusion from the cannula tip. Dummy cannulas were then reinserted into the guide cannulas and after 20 min, rats were placed in the chambers for the PI 20-sec trainings (see "PI 20-Sec Training"). Rats received four times of infusions with different doses in a random order, with a 48-h washout period between successive infusions. PI 20-sec training without drug injection was run in between drug infusion days.

Histology

After completing all behavioral sessions, rats were deeply anesthetized with sodium pentobarbital (130 mg/kg, i.p.) and perfused intracardially with saline followed by ALTFiX (FALMA). The brains were removed and sectioned in the coronal plane (40-µm thickness) using a cryostat (Leica CM1850). Sections were Nissl-stained with cresyl violet to assess the cannula tip locations.

Data analysis

Session-by-session analysis

We divided each probe trial (60 sec) into 3-sec bins that increase 1 sec each, such as 0–3 sec and 1–4 sec. Altogether, 58 bins were included in each trial. For each rat, the number of responses at each bin was summed for each session and plotted as a function of elapsed time (peak function). These peak functions were fitted with the modified Gaussian curve ($R(t) = a \times \exp\{-0.5 \times [(t - t_0)/b]^2\} + c \times [t - t_0] + d$) for each rat using the KaleidaGraph software (Synergy Software version 3.4). Here, t is the current moment, and $R(t)$ is the number of responses in Bin t: parameters a and d are the maximum and minimum values of each fitted curve, respectively: t_0, b, and $a + d$ are defined as peak time, peak spread, and peak rate, respectively (Buhusi and Meck 2000).

Trial-by-trial analysis

As mean peak functions are derived from all of the probe trials pooled together for a given session, the peak function obtained from each probe session does not characterize behaviors on individual trials. During each probe trial, rats started responding before the expected time of reinforcement and then stopped responding after the time (Church et al. 1994). Therefore, the pattern of response rate showed low-high-low. The start time and the stop time were defined as the time of transition from the low to high and from high to low, respectively. We used the algorithms proposed by Church et al. (1994) to extract the times.

The criterion for statistical significance was set at $\alpha = 0.05$.

Acknowledgments

This study was supported in part by the grant from the Japan Society for the Promotion of Science (30844667).

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Received June 29, 2020; accepted in revised form October 5, 2020.