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Impaired Timing Precision Produced by Striatal D2 Receptor Overexpression Is Mediated by Cognitive and Motivational Deficits

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Increased striatal dopamine D2 receptor activity is thought to contribute to the pathophysiology of schizophrenia. To model this condition in mice, Kellendonk et al. (2006) generated transgenic mice that selectively overexpress the D2 receptor in striatum (D2OE). Drew et al. (2007) reported that D2OE mice display deficits in interval timing and motivation. The present study further explored the impaired timing in D2OE mice. Experiment 1 assessed the role of motivation in producing timing deficits in the peak procedure and found that performance in D2OE mice was improved by increasing motivation. In addition, performance was impaired in control mice when motivation was decreased. In Experiment 2, we found that D2OE mice have no timing impairment when tested using the bisection task, a procedure in which the measure of timing performance is less influenced by motivation to respond. In Experiment 3, we also used the bisection task and found selective impairment in timing of long durations in D2OE mice. These results suggest that striatal D2 overexpression impairs timing by decreasing motivation and through its impact on working memory and/or sustained attention.

Keywords: striatal D2 receptor overexpression, timing, motivation, attention, working memory

Accurate timing is crucial to the performance of many everyday activities. For example, failure to correctly estimate the time that an approaching car will take to reach an intersection before crossing has serious consequences. In addition, distorted timing of intervals in the seconds to minutes range is symptomatic of a number of neurological/psychiatric conditions, including Parkinson's disease, attention-deficit hyperactivity disorder, and schizophrenia (e.g., Frank, Posada, Pichon, & Haggard, 2005; Levin et al., 1996; Malapani, Deweer, & Gibbon, 2002). Accordingly, considerable research interest has focused on the neurophysiological processes underlying accurate interval timing. This work has consistently demonstrated that dopamine (DA) receptor signaling plays an important role in temporal information processing (e.g., Cheng, MacDonald, & Meck, 2006; Matell, Bateson, & Meck, 2006; Meck, 1996). In terms of localization, evidence suggests the striatal dopaminergic system may be particularly important to timing. Meck (2006) reported that lesions of nigro-

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striatal DA projections profoundly impair timing in rats. In addition, correlational evidence suggests that the DA D2 receptor plays an especially important role in the modulation of timing. Meck (1986) assessed the effects of several D2 antagonists on performance and found that the dose of the drug needed to distort the timing of intervals in rats was negatively correlated with the drugs affinity for the D2 receptor. Together, these results suggest an important role for striatal D2 receptor signaling in interval timing.

Drew et al. (2007) recently confirmed the importance of D2 receptors in timing by studying transgenic mice which selectively overexpress the D2 receptor in the striatum (D2OE; Kellendonk et al., 2006). We assessed the effect of this striatal D2 overexpression on timing in a procedure known as a peak interval (PI) task. On some trials, a cue such as the insertion of a response lever into a conditioning chamber signals that a food reward will be made available for the first response that occurs after a fixed interval (FI; e.g., 24 s) has elapsed. These trials terminate when the reward is earned. On other trials, called peak trials, the cue is presented for much longer than usual and the reward is omitted. On these peak trials, the average rate of responding increases as the time of expected reward approaches, reaches a peak at or around the target duration, and then decreases. The location of the peak provides an estimate of timing accuracy, the spread of the response rate function reflects timing variability, and the height of the peak indexes motivation to respond. In this procedure, D2OE mice showed lower overall response rates, were less accurate in timing the 24-s target interval (the peak in their response function was shifted to the right), and were more variable (broader peak response curves) than controls. In addition to having lower peak heights on the timing task, D2OE mice also displayed decreased motivation on a progressive ratio task in which the work requirement (number of lever presses) is increased after each reward. Thus, striatal D2 receptor overexpression alters both timing and motivation.

Drew et al. (2007) suggested that the motivational deficit might have contributed to the timing deficits in the D2OE mice. If this were the case, it might be possible to improve the timing performance of D2OE mice with a manipulation that improves their motivation to respond. The 24-s target duration used by Drew et al. supported extremely low response rates in D2OE mice. Given that response rates in fixed interval and PI schedules have been shown to be inversely related to the duration of the target interval (the shorter the target interval, the higher the response rate; see Wearden & Lejuene, 2006), one way to increase motivation and to potentially improve timing in D2OE mice might be to decrease the duration of the target interval.

If motivation contributes to the timing deficits in the D2OE mice, in addition to improving timing of D2OE mice by increasing their motivation to respond, it should be possible to mimic the deficient timing profile of D2OE mice in controls by explicitly decreasing their level of motivation through a manipulation such as reducing the probability of reward. Roberts (1981) reported that reducing the probability of reward in the PI procedure lowered response rates but did not affect timing accuracy in pigeons, and similar results were recently reported in rats by Cheng and Meck (2007). Although these studies suggest independence of motivation and timing accuracy, some evidence suggests that more drastic reductions of reward probability may affect timing performance. Though timing remains intact early during extinction when reward is no longer presented (Galtress & Kirkpatrick, 2009; Ohyama, Gibbon, Deich, & Balsam, 1999), Grace and Nevin (2000) reported that extended extinction (at least five sessions) ultimately increased timing variability (but see Guilhardi & Church, 2006). Thus, severely reducing motivation by lowering reward probability could result in impaired timing performance.

Given the modulatory role that striatal DA activity plays in both motivation (Berridge, 2004; Wise, 2004) and timing (Buhusi & Meck, 2005; Drew et al., 2007), it is important to separate specific effects of striatal D2 overexpression on timing from effects that may be mediated by motivational differences. Here we investigate the effects of manipulations designed to both increase and decrease motivation on timing in the PI procedure. First, we asked whether increasing motivation in D2OE mice would improve their timing performance. Second, we asked whether decreasing motivation in control mice would decrease response rates and produce timing impairments similar to those observed in D2OE mice.

Experiment 1

Method

Subjects

Seven control and eight D2OE mice approximately 90 days old and weighing between 17 and 29 g were used. D2OE mice were generated as described previously (Drew et al., 2007; Kellendonk et al., 2006). Briefly, mice expressing the human D2 receptor under control of the tet-operator (tet-O) were generated on a C57BL/6-CBA(J) F2 background. Tet-O mice were backcrossed for at least eight generations to the C57BL/6(J) background and then crossed for behavioral studies with mice expressing the tetracycline transactivator (tTA) transgene under the calcium/calmodulin-dependent kinase IIα (CaMKIIα) promoter (Mayford et al., 1996). CaMKIIα–tTA mice were on 129SveV(Tac)N17 background. Control mice were single transgenic littermates. Six litters were used. All mice were female.

Mice were limited to 1 hr daily access to food in order to motivate them to earn rewards during the session. Water was available ad libitum.

Apparatus

Eight matching experimental chambers (Med-Associates, St. Albans, VT) were used. The chambers measured 22 × 18 × 13 cm, and the floor consisted of metal rods placed 0.87 cm apart. A feeder trough was centered on one wall of the chamber. An infrared photocell detector inside the trough was used to detect and record head entries into the trough. A dipper located inside the feeder trough could be raised, providing access to one drop of evaporated milk. Each chamber was equipped with two retractable levers mounted on the same wall as the feeder trough. A houselight located at the top of the chamber provided illumination and a brief tone (0.5 s) accompanied dipper presentations.

Procedure

Mice were taught to press the lever in two phases. First, mice were taught to consume the liquid reward from the raised dipper. Mice were placed inside the chamber with the dipper raised. The dipper was lowered 10-s after the first head entry in the feeder

trough, followed by a variable intertrial interval (M = 30 s), after which another trial was initiated. The session ended after 30 min or 20 dipper presentations. On the following day, mice received a similar session, except that the dipper was raised for 8 s and then lowered. Sessions of this sort continued until a mouse had made head entries during 20 of 30 dipper presentations in one session. There was no significant difference in the number of sessions of dipper training for control (1.14), and D2OE (1.50) mice [$t_{(13)}$ = 0.36]. During this phase and all other experimental conditions, sessions occurred once per day, 5 days per week.

Next, mice were required to press the lever to obtain a liquid reward (5 s of dipper access). Initially, each mouse received an 8-h session during which the lever was extended and responses were reinforced on a continuous reinforcement schedule. After the 20th reward, the lever was retracted (to familiarize the mice with the retraction of the lever). After a variable intertrial interval (M = 30 s), the lever was extended, and another trial ensued. If the mouse did not earn 100 rewards in this session, this procedure was repeated the following day. Two days after the first successful lever press training session, mice were given a shorter continuous reinforcement training session during which the lever was extended at session onset and retracted after every two rewards. Following a variable intertrial interval (M = 30 s), the lever was extended, and another trial commenced. Sessions of this sort continued until the mice received 36 rewards or 60 min elapsed, whichever occurred first. The number of sessions of CRF training for control (2.43) and D2OE (2.75) mice was not significantly different [$t_{(13)}$ = 0.34]. Mice then moved to FI training.

During FI training, lever presses were only rewarded if they occurred a fixed time after lever extension. Mice began on an FI 4-s schedule, meaning that a response was rewarded if it occurred 4 s or more from the time the lever was extended. Reward was followed by a variable intertrial interval, after which the lever was extended to signal the beginning of another trial. A mouse was trained on a given FI duration until they earned 30 rewards in one session, after which the FI duration was increased. The FI durations were 4, 8, and 12 s. When a mouse had received 30 rewards in one session of FI 12-s training, it was moved to PI training. The number of sessions required to reach the FI 12-s schedule for control (4.00) and D2OE (3.63) mice was not significantly different [$t_{(13)}$ = 0.30].

Peak interval sessions consisted of two types of trials: FI 12-s trials as described above, and peak trials during which the lever was extended for 48 s and responses were not rewarded. Peak trials and FI trials occurred randomly, with the constraint that no more than five peak trials could occur consecutively. Initially, PI training sessions consisted of 12 peak trials and 48 FI trials. Once a mouse received at least 30 rewards, the number of peak and FI trials was changed to 24 and 36, respectively. Sessions lasted for 60 trials (peak and FI) or 90 min, whichever came first.

Following 20 sessions on this procedure, the percentage of reinforced FI trials was decreased from 100%-5% over the course of 25 sessions. Because our goal was to produce a timing phenotype in controls that was similar to that observed in D2OE mice, we titrated reward percentage across sessions rather than randomly exposing mice to each reward percentage condition. Each reward percentage condition was in place for at least five sessions until the response rate data appeared stable. All statistical analyses were conducted with a criterion significance level of $p < .05$.

Results

Accurate timing of the FI 12-s duration is indicated by increased response rate as the 12-s target time approaches, maximal response rate at or around the target time, and decreased responding after the target time. Figure 1 shows the mean response rate in the trial plotted as a function of time in the trial for the control (top panel) and D2OE (bottom panel) mice during all partial reinforcement conditions. The data represent the average of the last five sessions of each condition. The peaks of the response-rate distributions were generally near the target time of 12 s, and the heights of the peaks generally declined as reward percentage was reduced. Finally, during all conditions, the response rates were lower, and the spread of the response distributions was broader for the D2OE mice as compared to control mice.

Because the distribution of responding during peak trials is approximately Gaussian, it is possible to quantitatively characterize performance during peak trials by fitting a Gaussian probability density function to the peak trial response distributions (e.g., Buhusi & Meck, 2000; Drew et al., 2007),

$$y = ae^{-0.5\left(\frac{x-x0}{b}\right)^2}$$

where a is peak height (maximum response rate), b is peak spread (variability of timing), and x_0 is peak location (accuracy of timing). This analysis was conducted on the data from each subject from each reward percentage condition using curve-fitting software (SigmaPlot 10).

Figure 2 shows the best-fitting parameters for each group. Consider first the estimates of peak height (upper left panels). As

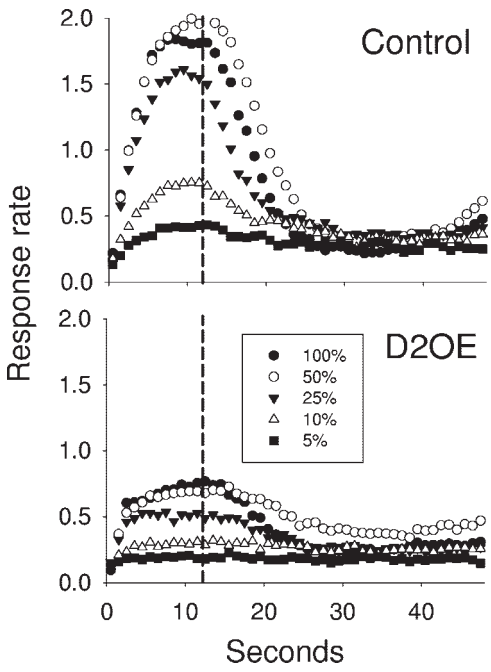

Figure 1. Mean responses per second as a function of time during peak trials during all reinforcer percentage conditions. The top panel shows data from control mice and the bottom panel shows data from D2OE mice. The dotted vertical line in each panel indicates the time at which reinforcement was available during fixed interval trials (12 s).

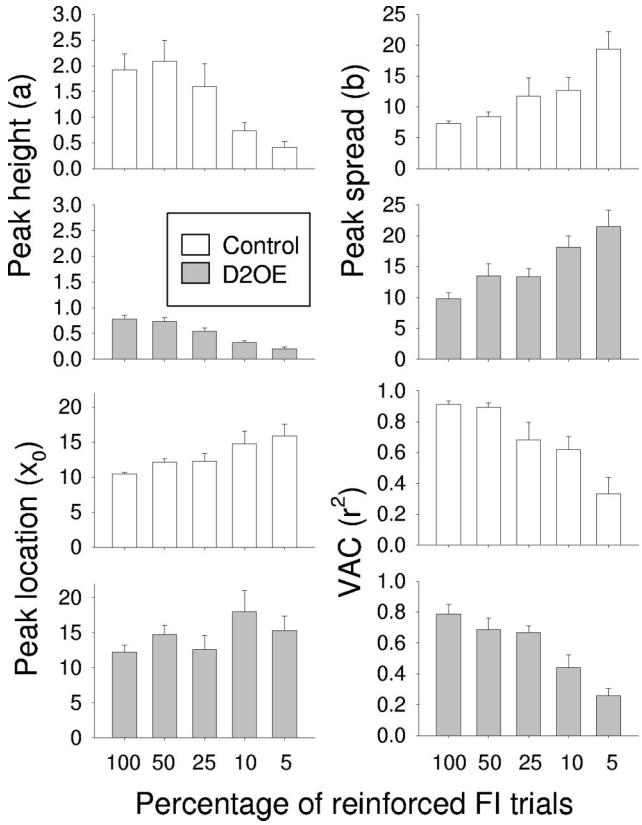

Figure 2. Mean best fitting parameters derived from the fitting of the Gaussian function (see text for details) to the response rate data from the control (open bars) and D2OE (filled bars) mice. The top left panels show estimates of peak height (peak response rate), the top right panels show estimates of peak spread (timing variability), and the bottom left panels show estimates of peak location (timing accuracy). The bottom right panels show the proportion of variance accounted for by the Gaussian function. Error bars indicate one standard error above the mean.

is apparent from the response-rate distribution data in Figure 1, the estimates of peak height at each reward percentage were lower in D2OE mice than in controls. This impression was confirmed by the results of repeated measures ANOVA conducted on the estimates of peak height, with reward percentage as a within-subjects variable and genotype as the between-subjects variable. The ANOVA showed a significant effect of genotype [$F_{(1, 13)} = 16.02$]. There was also a significant effect of reward percentage [$F_{(4, 52)} = 17.08$], and a significant genotype × reward percentage interaction [$F_{(4, 52)} = 4.31$].

Peak spread (upper right panels) increased as reward percentage decreased for both control and D2OE mice, although it was higher during all conditions for D2OE mice. A genotype × reward percentage repeated measures ANOVA showed a significant effect of genotype [$F_{(1, 13)} = 4.70$], and a significant effect of reward percentage [$F_{(4, 52)} = 11.87$], but no significant interaction [$p = .770$]. For peak location (lower left panels), the effect of genotype was not significant [$p = .329$], but there was a significant effect of reward percentage [$F_{(4, 52)} = 3.81$], with no significant interaction [$p = .723$]. In terms of variance accounted for by the Gaussian fits (bottom right panels), there was a significant effect of genotype [$F_{(1, 13)} = 5.05$], and reward percentage [$F_{(4, 52)} = 20.20$], with no interaction [$p = .657$]. Taken together, these results show that although the D2OE mice had significantly lower response rates and showed greater timing variability (broader response distributions), they were just as accurate as control mice in timing the 12-s FI. In addition, decreasing reward percentage decreased response rate and timing accuracy, and increased timing variability in both control and D2OE mice. Finally, in general, the response distributions were better described by the Gaussian function for control mice than for D2OE, but decreasing reward percentage produced response distributions that were less Gaussian in form in both control and D2OE mice. Thus, decreasing motivation in control mice produced a similar profile of results as those seen in D2OE mice.

Discussion

Shortening the FI duration was effective in improving accuracy of timing in D2OE mice. In addition, decreasing motivation by decreasing the percentage of rewarded trials decreased timing accuracy in both control and D2OE mice. Together, these results suggest that the timing accuracy deficit displayed previously by the D2OE mice (Drew et al., 2007) likely has a motivational origin.

Notwithstanding the improvement in accuracy under the shorter FI duration, D2OE mice still displayed significantly more timing variability than controls. Although decreasing the FI duration increased response rates in the D2OE mice nearly fourfold from those reported by Drew et al. (peak height of around 0.2 responses per second), response rates were still much lower in D2OE mice than in controls. The decreased response rates (and decreased peak height) in the D2OE mice suggest that we were unsuccessful in completely equating the D2OE and control mice with respect to motivation. Thus, the persistent difference in timing variability may have been due to a residual difference in motivation between D2OE mice and controls.

Although we were unsuccessful in equating motivation between D2OE mice and controls, it is possible to compare the performance of control and D2OE mice at roughly equivalent levels of motivation by comparing timing variability between control and D2OE mice at similar peak heights in Figure 2 (reward percentage of 50% for D2OE and 10% for controls). This comparison showed no difference in timing variability between D2OE mice and controls [$t_{(13)} = 0.27$]. Thus, when motivation is equated, timing variability is similar between D2OE mice and controls.

Experiment 2

The results of Experiment 1 suggest that the timing impairments in the D2OE mice likely have a motivational origin. In the PI procedure, however, it is difficult to definitively separate timing performance from motivational factors, because the index of timing depends on response rate, and response rate is greatly influenced by motivation (e.g., Roberts, 1981). Thus, it would be useful to assess performance in a procedure which does not depend so heavily on response rate to characterize timing.

In a temporal bisection procedure, a single response to one of two choice options is rewarded based on the duration of a previously presented temporal sample (Church & Deluty, 1977). For

example, at trial onset, a sample (e.g., tone) is presented for either a short (e.g., 2 s) or long (e.g., 8 s) duration. Following sample presentation, choice levers are inserted. Responses on one lever are rewarded following 2-s samples and responses on the other lever are rewarded following 8-s samples. Following acquisition, performance can be tested on trials in which temporal samples of intermediate durations are presented. Once this discrimination is learned, the proportion of responses to the lever corresponding to the "long" sample duration is generally an increasing sigmoid function of sample duration. Performance on this procedure has been found to be sensitive to pharmacological manipulation of DA systems, with a number of aspects of timing performance affected by DA agonists and antagonists (e.g., Maricq & Church, 1983; Maricq, Roberts, & Church, 1981; McClure et al., 2005; Odum & Ward, 2007). Thus, we expect this procedure to be sensitive to any direct effects of D2 overexpression on cognitive processes that underlie timing but to be relatively little influenced by motivation to respond.

Method

Subjects

Ten female control and 12 female D2OE mice from nine litters were used. Mice were approximately 90 days old and weighed between 19 and 24 g.

Apparatus

As in Experiment 1.

Procedure

Mice were trained to drink from the dipper and to lever press as described in Experiment 1, with the exception that both levers were presented during the lever press training sessions. As in Experiment 1, there were no significant differences in the number of sessions required for dipper and CRF training. Following lever press training, mice underwent bisection training in several phases. Half of the mice were trained to press the left lever following a 2-s (short) duration tone and the right lever following an 8-s (long) duration tone. This rule was reversed for the remaining mice. During all of the training sessions, the mice were required to press the lever within 10 s. If a response was not made within 10 s, the levers were retracted and the next trial was presented after a variable intertrial interval ($M = 45$ s). All of the training sessions ended when the mice earned 40 rewards or 70 min had elapsed, whichever came first.

Single duration-single lever training. On Day 1 of training, only one sample duration was presented and it was followed by extension of the corresponding (correct) lever according to the training rule assigned to each mouse. A response on this lever that occurred within 10 s of lever extension was rewarded. On Day 2, the other sample duration and the opposite lever were presented.

Interspersed single duration-single lever training. For two sessions, the previously described single duration-single lever pairings were interspersed within a single session so that both sample durations were presented with each of their respective corresponding levers.

Two duration-single lever training. The mice were presented with the 2-s and 8-s sample durations followed by extension of a single lever. If the presented sample duration corresponded to the lever presented, a reward was provided if a response occurred within 10 s of lever extension. If the sample duration did not correspond to the extended lever, responses were not rewarded. This phase lasted for four sessions.

50% choice response trials. Fifty percent of the trials in each session consisted of a random presentation of a single sample duration (2 s or 8 s) followed by extension of the corresponding lever. The other 50% of the trials were choice response trials, during which the 2-s or 8-s sample duration was randomly presented and both levers were extended. The mice obtained rewards by pressing the lever that corresponded to the presented sample duration. A correction trial always followed incorrect responses during the choice response trials. During correction trials, after an incorrect response, the houselight was illuminated for 1 min and following an ITI, a choice trial with the same sample duration occurred. This phase lasted for three sessions.

75% choice response trials. Seventy-five percent of the trials in a session were choice response trials (as described above) and single duration-single lever pairings were presented on 25% of the trials. This phase lasted for two sessions.

100% choice response trials. All of the trials in a session were choice response trials. Each sample duration was randomly presented with the constraint that both sample durations be presented an equal number of times during the session.

Intermediate tones. After 15 sessions of training with the 2-s and 8-s sample durations, intermediate sample durations (2.6 s, 3.2 s, 4.0 s, 5.0 s, and 6.4 s) were interspersed with the 2-s and 8-s sample durations. Intermediate durations were presented on half of the trials, while the other half of the trials consisted of 2-s or 8-s duration presentations. The mice were not rewarded for responses on intermediate duration trials, but a response on the correct lever following a 2-s or 8-s sample duration was rewarded. The session ended when 60 trials (rewarded or nonrewarded) were completed or 70 min had elapsed. During this phase, the correction procedure was not implemented following incorrect responses.

Results

The top panel of Figure 3 shows acquisition of the 2-s and 8-s tone discrimination in control and D2OE mice. The figure plots the mean proportion of trials on which the mice chose the lever corresponding to a "long" sample duration following presentation of both sample durations. Discriminative performance improved over the course of training for both control and D2OE mice, evidenced by the decreasing proportion of "long" responses following 2-s tone durations, and the increase in the proportion of "long" responses following 8-s tone durations. There did not appear to be differences in performance between the two genotypes. These conclusions were supported by the results of a repeated measures ANOVA conducted on the proportion-long response data with duration and session block as within subject factors and genotype as the between subject factor. The ANOVA found a significant main effect of duration [$F_{(1, 20)} = 385.95$] and block [$F_{(4, 80)} = 5.10$], but not of genotype [$F_{(1, 20)} = .63$]. In addition, there was a significant duration $\times$ block interaction [$F_{(4, 80)} = 28.78$], but none of the other interactions were signif-

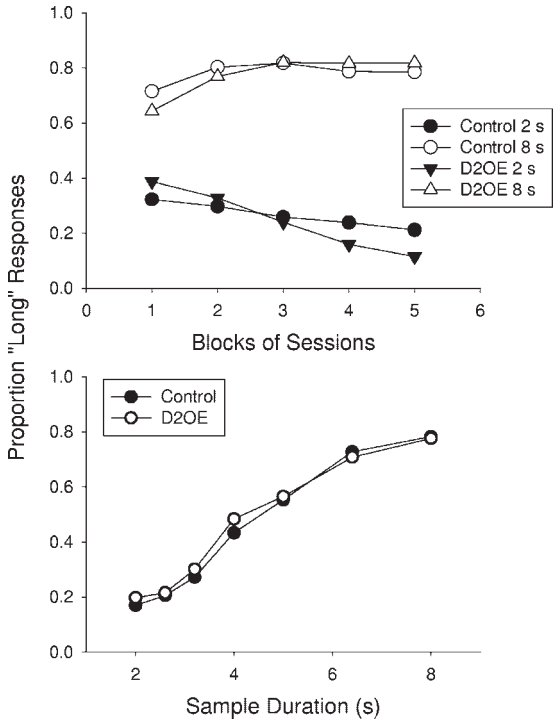

Figure 3. The top panel shows the mean proportion of responses to the lever corresponding to a "long" sample duration on both short and long sample trials across blocks of training sessions in Experiment 2 (2-s and 8-s sample durations). Circles and triangles indicate data from control and D2OE mice, respectively. Open data points indicate data from long sample trials, while closed data points indicate data from short sample trials. The bottom panel shows the mean proportion of responses to the lever corresponding to the "long" sample duration as a function of sample duration during Experiment 2 for control (filled circles) and D2OE (open circles) mice.

icant [$ps > .05$]. These results indicate that discrimination performance improved over the course of the training block, and that performance did not differ between control and D2OE mice.

The bottom panel of Figure 3 shows bisection performance for both control and D2OE mice (averaged across the last five sessions of intermediate duration training). The proportion of long responses was low at the 2-s duration and increased as a function of sample duration, indicating accurate estimation of the passage of time. There was no difference in performance between control and D2OE mice. This interpretation was supported by the results of a repeated measures ANOVA conducted on the proportion-long response data with duration as a within-subjects factor and genotype as the between-subjects factor. The ANOVA found a significant main effect of duration [$F_{(6,\ 120)} = 113.12$] but not of genotype [$F_{(1,\ 20)} = .08$] and no interaction [$F_{(6,\ 120)} = .28$].

To quantitatively characterize bisection performance, we fit a cumulative normal function with two parameters (mean and *SD*) via nonlinear regression to the proportion long response data from each subject and obtained estimates of timing variability and accuracy for each mouse. The standard deviation (*SD*) of the function is a measure of timing variability, with greater values indicating greater variability. The mean is a measure of timing accuracy. Known as the point of subjective equaility (PSE), it is the point on the function that corresponds to a proportion of long choices of .5, and generally lies near the geometric mean of the sample duration endpoints (Church & Deluty, 1977; Gibbon, 1981). Thus, means near the PSE of the short and long duration endpoints (4 s) indicate accurate performance, while increases or decreases in the mean reflect distorted timing. All fits were accomplished using the Solver tool of Microsoft Excel. The function generally fit the data well, accounting for a mean (standard error in parenthesis) of 90.59 (1.23) and 86.45 (3.81) of the variance in the functions from control and D2OE mice, respectively.

Figure 4 shows that the estimates of timing variability (top panel) and accuracy (bottom panel) for control and D2OE mice were very similar. These results were confirmed by independent samples *t* tests, which showed no difference in the estimates of timing variability [$t_{(20)} = .66$] or accuracy [$t_{(20)} = .13$] between D2OE and control mice. We also calculated choice response latencies. The top panel of Figure 5 shows that the mean choice response latency was lower (about 1.5 s) for control than for D2OE (about 2.5 s) mice. This difference was statistically significant when compared using an independent samples *t* test [$t_{(20)} = 2.78$]. The bottom panel of Figure 5 shows choice response latency as a function of sample duration for control and D2OE mice. The choice latencies for controls were around 1 s lower than for D2OE mice at all sample durations. For both genotypes, latencies decreased somewhat as a function of increasing sample duration. A two-factor ANOVA (genotype × sample duration) found significant effects of genotype [$F_{(1,\ 20)} = 7.75$] and sample duration [$F_{(6,\ 120)} = 7.55$], with no interaction [$F_{(6,\ 120)} = .64$].

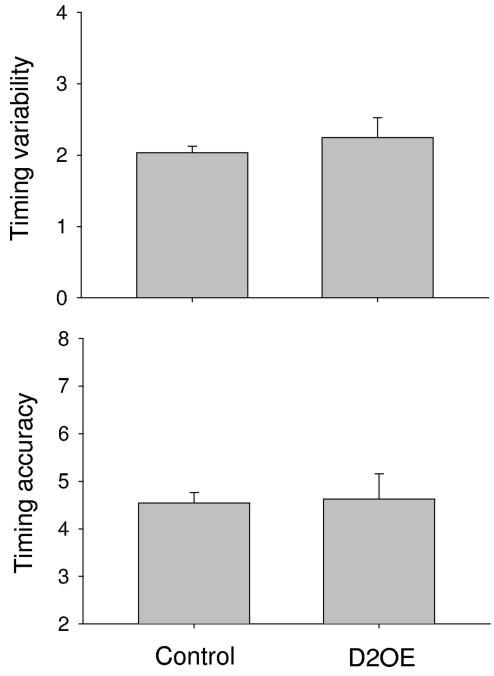

Figure 4. Mean best fitting parameters derived from the fitting of the cumulative normal function to the proportion long data from control and D2OE mice in Experiment 2. The top panel shows estimates of timing variability, while the bottom panel shows estimates of timing accuracy. Error bars indicate one standard error above the mean.

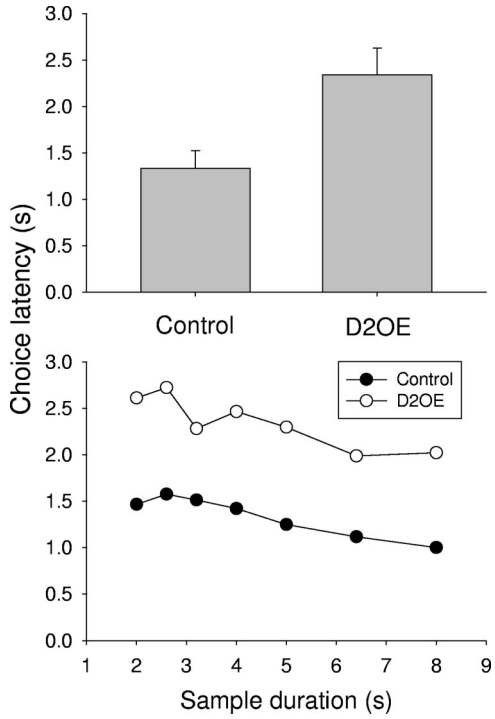

Figure 5. The top panel shows the mean latency to make a choice response (collapsed across sample duration) for control and D2OE mice in Experiment 2. The bottom panel shows the mean choice response latency as a function of sample duration for both control and D2OE mice. Other details as in Figure 4.

Discussion

The results of Experiment 2 suggest that accuracy of timing is not impaired in D2OE mice. The proportion of long responses was similar in control and D2OE mice at all sample durations, and quantitative analysis of the functions indicated that the measure of timing accuracy (the mean of the cumulative normal function) was not different across genotypes. In addition, the acquisition data indicate that there were no differences in learning of the temporal discrimination between D2OE and control mice. Finally, and most importantly, the estimate of timing variability (the *SD* of the function) was not different between D2OE mice and controls. These results were obtained despite the presence of increased choice response latencies in D2OE mice compared to controls. Together, these results suggest that the increased timing variability in D2OE mice in Experiment 1 may have been due to the use of a measure of timing requiring higher response rates that was compromised by a residual difference in motivation between D2OE mice and controls. Thus, the results of Experiment 2 suggest that the D2OE mice do not suffer from a general timing deficit.

Although differences in motivation could account for the differences in timing variability observed in Experiment 1, initial assessments of cognitive performance in the D2OE mice also suggest the possible contribution of a working memory deficit. Kellendonk et al. (2006) found that striatal D2 overexpression resulted in increased DA levels, decreased DA turnover, and greater D1 receptor activation in the prefrontal cortex. Working memory has been shown to be influenced by DA receptor activity in the prefrontal cortex, with too much or too little activity producing working memory deficits (see Seamans & Yang, 2004, for review). In line with this, Kellendonk et al. further reported that D2OE mice displayed acquisition deficits in radial arm and t-maze tests of working memory. These results suggest the possibility of a working memory deficit contributing to the increased timing variability in D2OE mice when they are asked to process a longer duration stimulus (Experiment 1; Drew et al., 2007).

Experiment 3

The range of interval durations used in the bisection procedure in Experiment 2 was shorter than the target interval in the peak procedure in Experiment 1 (and much shorter than the target interval used by Drew et al., 2007). Perhaps the reason we did not see timing deficits when using these comparatively short intervals in Experiment 2 was because the working memory requirement was decreased under these conditions relative to the requirement necessary to time a longer target interval (see Rammsayer, 1999). If this were the case, increasing the duration of temporal samples in the bisection procedure might reveal an increase in timing variability between D2OE mice and controls. Accordingly, we tested the control and D2OE mice again on the bisection task, only this time the anchor durations were 6 s and 24 s. If deficits in working memory contributed to the increased timing variability in the D2OE mice reported in Experiment 1 and by Drew et al., we would expect to see increasingly poor timing of longer sample durations as the working memory requirement is increased.

Method

Subjects

The mice from Experiment 2 were used.

Apparatus

As in Experiments 1 and 2.

Procedure

The bisection procedure remained as described above, except that the two sample endpoint durations were changed to 6 and 24 s. Following 15 sessions of choice training with these endpoints, intermediate sample durations of 7.6, 9.5, 12, 15.1, and 19 s were introduced into the sessions as described above.

Results

Figure 6 shows acquisition of the 6-s and 24-s discrimination in both control and D2OE mice. During the first block, the proportion of long responses was near .5 for both 6-s and 24-s durations. Across blocks, discrimination performance improved for both control and D2OE mice, but in general, D2OE mice exhibited poorer discrimination performance than control mice across blocks. Repeated measures ANOVA conducted on the proportion-long response data with duration and block as within subjects factors and genotype as a between subject factor found a significant main effect of duration [$F_{(1, 20)} = 122.95$] and block [$F_{(4, 80)} = 6.50$], but not of genotype [$F_{(1, 20)} = .24$]. There was a significant

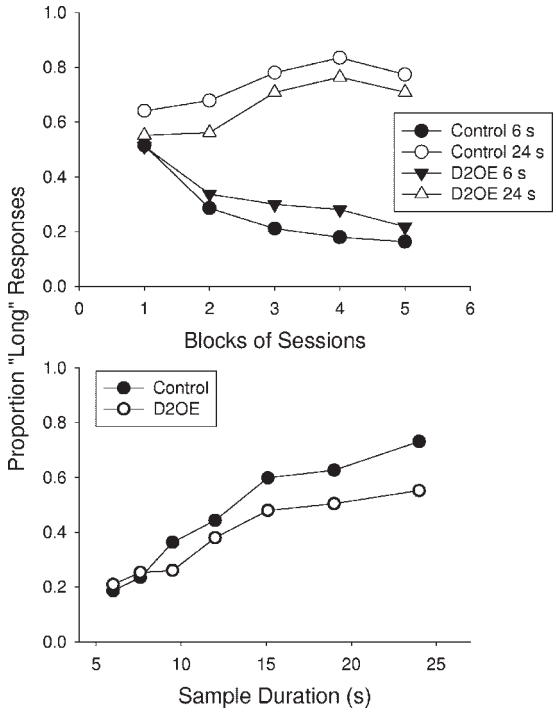

Figure 6. The top panel shows the mean proportion of responses to the lever corresponding to a "long" sample duration on both short and long sample trials across blocks of training sessions in Experiment 3 (6-s and 24 s sample durations). The bottom panel shows the mean proportion of responses to the lever corresponding to the "long" sample duration as a function of sample duration during Experiment 3 for control and D2OE mice. Other details as in Figure 3. Mean proportion of responses to the lever corresponding to a "long" sample duration on both short and long sample trials across blocks of training sessions in Experiment 3 (6-s and 24-s sample durations). Other details as in Figure 3.

duration × block interaction [$F_{(4, 80)} = 45.90$], and the interaction between duration and genotype approached conventional levels of significance [$F_{(1, 20)} = 3.83$, $p < .07$].

The bottom panel of Figure 6 shows bisection performance for control and D2OE mice (averaged across the last five sessions of intermediate training). The proportion of long responses is low at the shortest duration, and increases as sample duration increases for both control and D2OE mice. The function, however, is flatter for D2OE mice than for controls, indicating more incorrect categorization of long durations as "short." The results of a repeated measures ANOVA conducted on the proportion long response data with duration as a within subject factor and genotype as the between subjects factor revealed a significant main effect of duration [$F_{(6, 120)} = 393.54$], but not of genotype [$F_{(1, 20)} = 3.00$], with a significant interaction [$F_{(6, 120)} = 3.30$]. These results indicate that differential responding occurred following presentation of short and long sample durations in both control and D2OE mice, but that responding was less differentiated in D2OE mice at the longer sample durations.

The proportion long data were subjected to quantitative analysis as in Experiment 2. One of the D2OE mice showed a substantial bias for the lever corresponding to the short sample duration regardless of the presented sample duration, and the function failed to fit the data from this mouse. Therefore, this subjects' data were not included. As in Experiment 2, the function fit the controls data well, accounting for a mean (standard error in parenthesis) of 90.99 (1.60) percent of the variance. The fits were somewhat lower for the D2OE mice, accounting for 78.92 (4.41) percent of the variance, excluding the one mouse whose performance seemed unrelated to the sample durations. The top panel of Figure 7 shows that the estimate of timing variability was higher in D2OE mice than in controls. The difference was statistically significant [$t_{20} = 2.43$]. The bottom panel of Figure 7 shows the estimate of timing accuracy for control and D2OE mice. Timing accuracy was significantly different for D2OE mice than for controls [$t_{20} = 2.89$]. Note, however, that the increase reflects the disproportionate decrease in accuracy of categorizing long sample durations (the locus of the increased timing difficulty).

The top panel of Figure 8 shows that choice response latencies were again lower for controls than for D2OE mice as in Experiment 2. The difference was statistically significant [$t_{20} = 2.33$]. Also similar to the results of Experiment 2, the bottom panel of Figure 8 shows that choice response latencies for control mice were around 1 s lower than for D2OE mice at all sample durations, and choice response latencies decreased somewhat for both genotypes as a function of increasing sample duration. This impression was confirmed by the results of a two-factor (genotype × sample duration) ANOVA, which found significant effects of genotype [$F_{(1, 20)} = 5.42$] and sample duration [$F_{(6, 120)} = 6.92$], with no interaction [$F_{(6, 120)} = .05$].

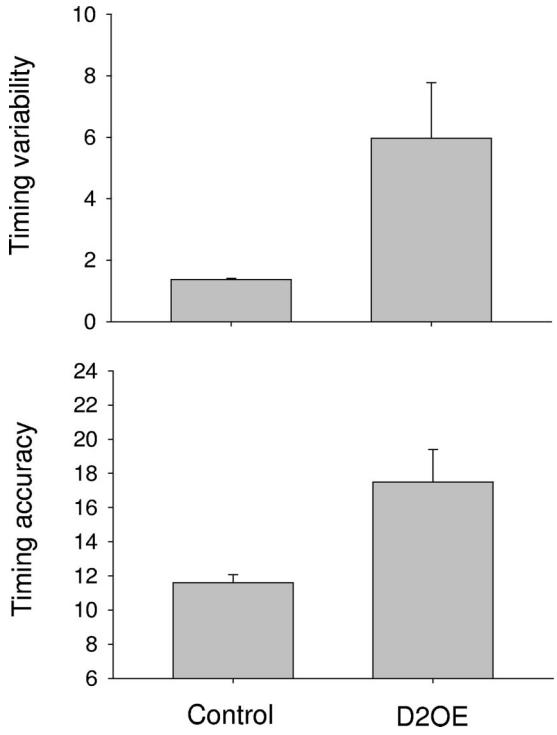

Figure 7. Mean best fitting parameters derived from the fitting of the cumulative normal function to the proportion long data from control and D2OE mice from Experiment 3. Other details as in Figure 5.

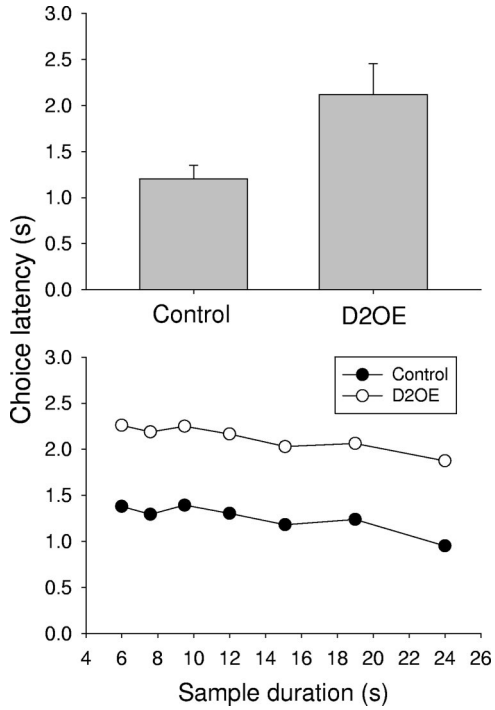

Figure 8. Mean latency to make a choice response for control and D2OE mice in Experiment 3. Other details as in Figure 5.

Discussion

The results of Experiment 3 indicate that D2OE mice have significantly greater variability in timing, and that this greater variability is mediated by selective deficits in timing long sample durations. These results are consistent with the results and interpretation of a study by Radonovich and Mostofsky (2004) that assessed timing in children diagnosed with attention-deficit hyperactivity disorder (ADHD), a condition that is associated with abnormal DA tone (e.g., Ilgin et al., 2001). They found no deficit in timing of short intervals (550 ms) but a significant deficit in timing of long intervals (4 s). Similarly, Mangels, Ivry, and Shimizu (1998) found that patients with frontal lobe lesions were selectively impaired in timing of long duration samples. Based on these results, they suggested that the timing impairments in ADHD and those resulting from frontal lobe lesions resulted from deficits in the utilization of temporal information in working memory, rather than a general deficit in timing ability. Given the alterations in DA turnover and D1 receptor activation in the prefrontal cortex of D2OE mice, the present results are consistent with this interpretation.

General Discussion

The present experiments clarify the nature of the timing deficit in the D2OE mice. Experiment 1 found that accuracy of timing could be improved in D2OE mice by increasing their motivation to respond. In addition, Experiment 1 found that the timing profile of D2OE mice obtained by Drew et al. (2007) in the PI procedure could be mimicked in controls by decreasing the motivation to respond. Experiment 2 used the bisection procedure, a task in which the assessment of timing is not so heavily dependent on motivation to respond, and found no difference in timing accuracy or variability between control and D2OE mice. Experiment 3 found increased variability as a result of poor timing specifically of long intervals by D2OE mice in the bisection task. Differences in motivation (as assessed by choice response latencies) were present between D2OE mice and controls in both Experiments 2 and 3. However, differences in variability occurred only in Experiment 3, suggesting that any residual motivational deficits in D2OE mice does not account entirely for the differences in variability.

The present study is the first to report an effect of reinforcer probability on accuracy of timing in the peak procedure. The difference in our results and those reported previously was likely due to the extremely low reinforcer probabilities studied in the present experiment. Indeed, consistent changes in peak time were observed only when reward percentages were 10% or less. Caution must be taken in interpreting these results due to the fact that the response rate data were less accurately described by the Gaussian function at these lower reward percentages. Nevertheless, the present results call into question the independence of peak rate and peak time, and suggest that accuracy of timing in the peak procedure *can* be affected by *severe* reductions in reinforcer probability (and presumably motivation). These results are in accord with reports of disrupted timing following other manipulations that target motivation (e.g., Galtress & Kirkpatrick, 2009; Plowright et al., 2000; Roberts, 1981; Ward & Odum, 2006, 2007).

The working memory deficit interpretation of the results from Experiment 3 is supported by the results of Kellendonk et al. (2006) showing that (1) striatal D2 overexpression impacts PFC DA levels and D1 receptor activity in a manner consistent with conditions under which working memory is impaired, and (2) D2OE mice show a deficit in acquisition during working memory tasks. In addition to increasing D1 receptor activation in the PFC, striatal D2 overexpression may impair working memory by affecting acetylcholine (ACh) release in the PFC. Acetylcholine is widely known to affect performance on a number of cognitive tasks, including tasks that require working memory. Interestingly, it has recently been shown that striatal DA receptor activation has a modulatory effect on ACh release in the PFC, (Brooks, Sarter, & Bruno, 2007; see Sarter, Nelson, & Bruno, 2005, for discussion). Specifically, Brooks et al. demonstrated that perfusion of the D2 receptor agonists quinpirole and quinelorane into the nucleus accumbens decreased *basal* ACh levels in the PFC. These results suggest that D2 overexpression in the striatum could influence ACh activity in the PFC, thus acting in concert with increased D1 receptor activity to produce decrements in working memory in the D2OE mice. Further experiments are necessary to assess this possibility.

The selective impairment of performance on long-sample trials in Experiment 3 is reminiscent of a robust behavioral phenomenon known in the timing literature as the choose-short effect. This effect is manifest as a selective decrement in long-sample trial accuracy when delays are inserted between sample presentation and the choice point. The general finding is that accuracy on long-sample trials decreases with increasing delays, while short-sample accuracy remains high across increasing delays (e.g., Spetch & Wilkie, 1982, 1983; see Spetch & Rusak, 1992, for review). One prominent theoretical interpretation of this effect focuses on a process of "subjective shortening" of the memorial

representation of the sample over the course of the delay. If increased latency to make a choice response functioned as a delay between sample presentation and the choice point, we might expect results similar to those obtained in Experiment 3. However, given that increased latencies were also present in Experiment 2 and there was no selective decrement in long sample accuracy, this interpretation is less appealing.

Although a deficit in working memory could produce the profile of results obtained in Experiment 3, the poor timing of long sample durations by D2OE mice is also consistent with a decrement in sustained attention. At the behavioral level, due to the continuous nature of temporal samples, if D2OE mice were unable to sustain attention for the duration of the long samples, it could result in incorrect categorization of the long samples as short, thereby producing the asymmetric flattening of the psychophysical functions apparent in Figure 6 (see Ward & Odum, 2007, for discussion). Like working memory, sustained attention also appears to be influenced by an interaction between DA and ACh (Brooks et al., 2007; Sarter et al., 2006).

The present results illustrate a more general issue when comparing cognitive performance across different mouse lines. Differences in performance on cognitive tasks can be mediated by motivational differences in addition to any differences in cognitive capacity. Experiments 1 and 2 show that the timing impairment in the D2OE mouse is largely due to a motivational deficit. This result emphasizes the importance of using cognitive assessment procedures such as the bisection procedure that are less susceptible to disruption by motivational factors if isolation of specific cognitive processes is desired. It should be noted, however, that performance on all cognitive tasks is modulated by motivation (e.g., Steckler, 2001) and teasing apart the specific contributions of motivational and cognitive factors is difficult. Because Experiments 2 and 3 used an identical procedure and we could not detect a motivational difference (latency to respond) in the two experiments, we have interpreted the increased timing variability in Experiment 3 as being due to decrements in working memory or sustained attention. However, we cannot completely rule out the possibility of an interaction between motivation and cognition in producing the present results. Any deficits in working memory or sustained attention in D2OE mice could be exacerbated by decreased motivation.

In conclusion, the D2OE mice were generated as a model of one aspect of the pathophysiology of schizophrenia. The mouse appears to model some of the core cognitive and negative symptoms of the disease (Kellendonk, Simpson, & Kandel, in press). Patients show cognitive impairments such as deficits in attention, working memory, and timing. They also exhibit motivational deficits described as anhedonia and avolition. Our results suggest that timing distortions in patients may arise from both types of deficits. Though a few researchers have reported that schizophrenia patients overestimate short intervals (Densen, 1977; Tysk, 1983, 1990), the most consistent result is that patients with schizophrenia are more variable in timing than controls. In time perception and production tasks schizophrenia patients have been found to exhibit more variable (less precise) judgments (Davalos, Kisley, & Ross, 2003; Elvevag, Brown, McCormack, Vousden, & Goldberg, 2004; Elvevag et al., 2003; Todd, 2006; Yang et al., 2004). Thus variability in temporal information processing is reliably associated with the disease. The present results indicate that striatal overexpression of D2 receptors, a condition that is similar to the increased occupancy and density of D2 receptors observed in schizophrenia (Abi-Dargham et al., 1998, 2000; Wong et al., 1986), is associated with a decrease in timing precision in mice, similar to results from human studies. This concordance increases confidence in the D2OE mice as a useful model for understanding the behavioral and neurobiological underpinnings of the cognitive deficits in schizophrenia. The present results suggest that striatal D2 overexpression does not directly produce a general deficit in timing precision. The deficits in timing precision which occur as a result of D2 overexpression appear to be mediated by deficits in motivation and working memory or sustained attention.

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