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Contributions of dopaminergic signaling to timing accuracy and precision

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Existing evidence suggests that interval timing, processing of temporal information in the hundredth of milliseconds-to-minutes range, recruits broad brain regions such as cortico-striatal circuits via dopaminergic–glutamatergic pathways. In this review, we summarize recent findings on the neurobiological basis of interval timing with a special focus on dopaminergic modulations of temporal information. Two properties of interval timing — accuracy and precision — are used to examine recent results from manipulations of dopaminergic signaling and the resulting distortions in temporal processing.

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Dopamine and the clock pattern of interval timing

Dopamine (DA) is one of the major neurotransmitters in the mammalian brain with its projections originating from the midbrain to multiple forebrain regions. Due to these broad neuromodulations, DA plays critical roles in many cognitive functions. Interval timing, one important such cognitive function, relies on cooperation of multiple forebrain regions that most of them are targets of the DA projections. Thus, DA can certainly modulate interval timing, but the underlying sophisticated mechanisms need to be elucidated. The first comprehensive review of interval timing and how DA modulates it was reviewed in [1], in which the term 'clock pattern' was coined. The clock pattern is a phenomenon induced by pharmacological distortion of time that manifests in three stages. In the first stage, an acute administration of dopaminergic drugs, either an agonist (AGO) or antagonist (ANT) into a group of well-trained animals distorts the animal's timing performance by shifting their timing function 10–20% leftward by AGO or rightward by ANT from the baseline (pre-drug) condition. Hence, the accuracy of interval timing is affected by acute injection of dopaminergic drugs (see Box 1 and Figure 1). In the second stage, if the injection continues in daily session as a chronic regimen, this DA drug-induced shift gradually diminishes such that the timing function returns to that of baseline condition. At that point, if the drug injection discontinues, then the third stage emerges — a 'rebound' effect is seen when the timing function, originally showing a shift of 10–20% in one direction, will now be showing the same magnitude of shift, but in the opposite direction. This clock pattern effect can be induced by drugs targeting primarily on the DA systems, not on acetylcholine and serotonin [2]. Since that seminal review, many attempts have been made to investigate the neural correlates of DA modulation on the clock pattern of interval timing. In this article, we will review recent progress on how manipulating the DA signaling can affect the clock pattern of interval timing. Besides manipulation, the concentration of brain DA also naturally fluctuates in conjunction with circadian rhythms. How this circadian modulation of DA affects interval timing will also be reviewed.

Current models of interval timing that involve dopamine signaling

To explain the clock pattern of interval timing, an information-processing model was proposed that involves a clock stage, a memory stage and a decision-making stage (for a recent review, see [3]). Among them, the clock stage is composed of a pacemaker, a gate switch and an accumulator. According to this model, DA primarily participates in the clock stage. An increase of DA signaling (by AGO) accelerates the accumulation of pacemaker pulses in a given amount of time. DA ANT triggers the opposite effect. This explains the first stage of the clock pattern, that is, the acute drug effect on interval timing. As the drug effect diminishes during the second stage of the clock pattern, the animals re-adjust their timing based on the new readout from the clock stage such that their new timing performance gradually returns to normal baseline condition under the influence of the drug. When the drug injection discontinues, the 'out-dated' clock readout forces the animal's timing performance shifted to the opposite direction until it re-adjusts again to normal baseline under drug-free condition. The neural substrates underlying the above three stages of the clock pattern can be inferred by studying the DA targeted regions. Several

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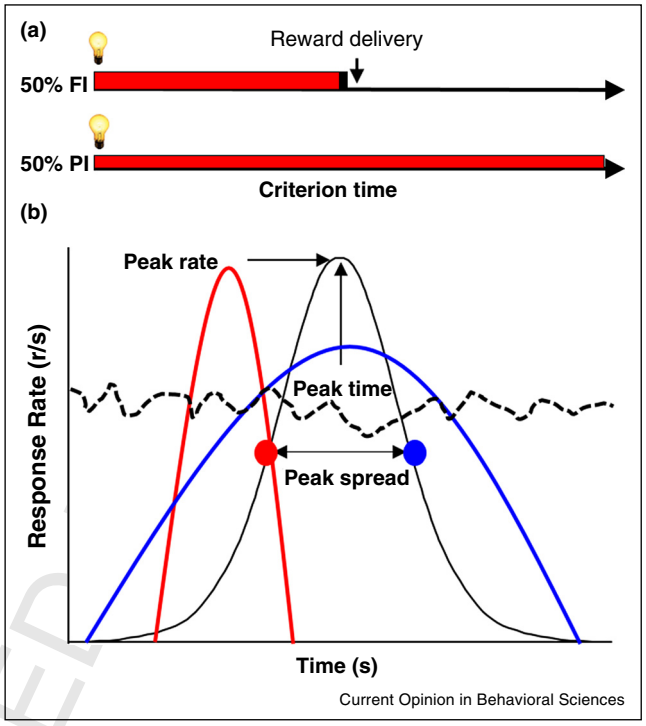
Box 1 Accuracy and precision of interval timing.

In interval timing, accuracy refers to the degree of a match between objective (physical) and subjective (perceived) durations, whereas precision is related to the variance of perceived durations across repeated trials [64]. For example, in the peak-interval (PI) procedure, subjects receive 50% fixed-interval (FI) trials randomly intermixed with 50% non-reinforced probe trials in which the to-be-timed signal remains active two or three times longer than the FI time (Figure 1a). Under probe trials, the time at which the maximal response occurs, that is, the peak time, is taken as an estimate of the accuracy of timing. The maximal response rate is defined as peak rate that reflects the motivation level of the subjects at the criterion time, and the width (or peak spread) of the response function (Figure 1b, black function) is taken as an estimate of the precision of timing. Peak spread is usually taken from the difference of start time (Figure 1b, red dot) and stop time (Figure 1b, blue dot). The ratio between peak spread and peak time, the coefficient of variation, CV, is shown to be constant (i.e., the scalar property) in a large range of durations in several species [4]. In timing tasks, it is possible for subjects to perform in a way that is highly precise but with bad accuracy — a precisely wrong performance (Figure 1b, red function). The clock effect by acute injection of dopaminergic drugs [1–4] is a typical example of good precision but bad accuracy because the peak time is shifted horizontally. Interestingly, mild stress induced by mild electrical shock can also affect the accuracy of timing, probably through modulation of the dopaminergic system in brain structures related to both temporal and emotional processes [65,66]. In contrast, it is also possible to have a bad precision but with good accuracy — a lousily correct performance (Figure 1b, blue function). In the extreme case, a totally imprecise function (Figure 1b, dotted black function) is possible and in such condition, the accuracy (i.e., the peak time) cannot be properly determined. Thus, in order to study the accuracy of interval timing, it is necessary to make sure that the precision of the timing performance is maintained at a proper level. Inherently, both timing accuracy and precision appear to be modulated by the circadian system in mice [45].

Figure 1



Timing accuracy and precision. **(a)** peak-interval (PI) procedure. **(b)** Examples of responses rates averaged across trials in a temporal duration reproduction procedure, such as the PI procedure. In test trials, the level responses distribute normally around the criterion time with a width that is proportional to the criterion time. The red function is an example of a precisely wrong function and the blue function is a lousily accurate function. The black dotted function is an example of poor precision preventing the identification of accuracy.

lines of evidence suggest that striatal medium spiny neurons (MSNs) are crucial to duration discrimination in the seconds-to-minutes range through their participation in large-scale oscillatory networks involving functional links among mesolimbic, nigrostriatal, and mesocortical dopaminergic systems [4,5]. According to the striatal beat-frequency (SBF) model, the proposed neural mechanism of interval timing is based on the coincidental activation of striatal MSNs by cortical neural oscillators [6]. Furthermore, it was recently implemented a modification to this model (SBF–ML) by using biophysically realistic and noisy Morris–Lecar neurons [7]. According to this model's simulation, dopaminergic modulation of the firing frequency of cortical oscillators results in immediate change in timing (first stage of the clock pattern) and gradual recalibration under chronic drug injection (second stage), rebound to the opposite direction and gradual recalibration upon discontinuing the drug (third stage), as well as scalar (proportional) effects. Together, these biologically plausible models can be used to account for DA signaling in temporal processing thus suggesting that manipulation of DA signaling, both presynaptically and post-synaptically, should modulate the timing performance.

Interval timing in animal models with up-regulation and down-regulation in DA signaling

Approach by regulating receptor expression levels

Striatal MSNs are commonly classified according to their expression of two major classes of DA receptors: the D1-like receptors (DRD1 and DRD5) and the D2-like receptors (DRD2, DRD3, and DRD4), together constituting the direct and indirect pathway in the basal ganglia.

D2 overexpression in the striatum

DRD2-expressing MSNs, which form the 'indirect' striatopallidal pathway, lead to inhibition on adenylyl cyclase pathway. These receptors have been shown to be critical for interval timing in both humans [8] and animals [9,10]. Transgenic mice that selectively and transiently overexpress DRD2 in the striatum show impairments in both interval timing and motivation to work for food rewards [9]. Whereas the motivational deficits can be rescued by shutting off DRD2 overexpression in the adult with doxycycline, the timing deficits are not fully rescued,

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indicating that once DRD2 are transiently overexpressed, its effect on timing is not reversible (or re-adjustable), which is in a stark contrast with the drug-induced clock pattern mentioned before. In later reports, it was shown that the deficits in timing precision appear to be mediated by impairments in motivation and working memory or sustained attention [10]. These studies on mouse DRD2 overexpression may explain some of the symptoms characteristic in patients with schizophrenia, including deficits in attention, working memory, and timing. Thus, altering the expression levels of DRD2 uniformly in the striatum does not just affect interval timing, but other functions as well. For example, a recent monkey positron emission tomography (PET) study suggests that eyeblink rate may be used as a biomarker for DRD2 receptor density, which by itself also correlates with reversal learning and sensitivity to positive feedback [11•]. Another example is that chronic injection of quinpirole, a DRD2 agonist induced obsessive-compulsive disorder (OCD-like) behavior in rats as if the reinforcement contingency was sensitized in the temporal domain, which could not be observed in control rats under drug-free condition [12].

D1 signaling in the medial prefrontal cortex

Recently, there were studies reporting that D1 signaling in the medial prefrontal cortex (mPFC) is required for normal temporal control of behavior [13,14]. The earlier study showed that focal infusion of muscimol, a GABA agonist inducing inhibition in the mPFC flattened the 20-sec timing function, a signature of poor temporal precision. In the same study, infusion of SCH23390, a DRD1 ANT, but not sulpiride, a DRD2 ANT, replicated the effect of muscimol. Similarly, photoinhibition of mPFC D1-expressing neurons by optogenetics also replicated the flattening effect [13]. In the later study, ramping activity was seen in the mPFC single units and coincided with an increase of 4 Hz neural oscillations near the target duration (12-sec). In addition, both mPFC ramping activity and 4 Hz oscillations were shown to be sensitive to local DRD1 blockade, further suggesting the importance of mPFC D1 signaling for temporal control (or precision) of behavior maintained under the fixed-interval (FI) procedure [14].

D3 expression in the ventral striatum

Dopamine D3 receptors (DRD3) are highly expressed in the ventral striatum and it has been postulated to mediate emotional behavior in mice. In addition, DRD3 have a significant role in the treatment of many neurologic disorders, like depression, schizophrenia, and Parkinson's disease. Moreover, DRD3 are involved in mediating the effects of DA AGOs on operant behavior in rats [15]. In circadian timing, which mediates regulation of several physiological, metabolic and behavioral functions with periods close to 24 hours, DRD3 expression presents daily oscillations in the mouse ventral striatum [16•]. In fact, molecular components of the circadian clock act as regulators that control the 24-hour variation in the expression of DRD3, suggesting a molecular link between the circadian clock and the function of DRD3. This rhythmicity accounts for pharmacological actions of DRD3 AGOs/ANTs, such as the time-dependent change in the efficacy of the DRD3 agonist 7-OH-DPAT. Whether DRD3 in the ventral striatum or the ventral striatum itself modulates any aspect of interval timing remains to be explored, but a recent study has shown that protein synthesis in the ventral striatum is important for acquiring the stop time (see Box 1) in the peak-interval procedure, which is more related to the precision, but not accuracy of timing [17].

Approach by pharmacological treatments that are non-specific to any DA receptors

Another approach to adjust brain DA signaling is to inject indirect dopaminergic drugs, right before testing the animals in interval timing tasks. In fact, this is what the clock pattern was originally based on [1,7,18]. Although this approach has yielded a vast amount of data regarding the relationship of DA and timing, it is not without exceptions that in the literature, some reports are not consistent (e.g., DA AGO producing no effects or opposite to the clock speed effect [19]). Here, we compare results from both sides and try to highlight the potential differences between the positive and negative results.

Positive findings

Most positive findings from animal studies were reported by using discrete-trials of, either the peak-interval procedure (see Box 1) or the duration bisection procedure in rodents. The commonly used AGO drugs were psychostimulants, or indirect DA AGO, such as cocaine or methamphetamine [18,20–23] while fewer studies were performed using d-amphetamine [24–26•], or estradiol that increases striatal DA release [27]. For ANT drugs, haloperidol, a non-selective, but nevertheless primarily targeting at DRD2 was commonly used [18,26•,28]. In terms of the underlying mechanism, recent work proposes that the effect of DA AGO/ANT may result from reduced/increased putamen-originating beta (15–30 Hz) oscillatory band that by itself can trace phasic or tonic changes of DA in cortico-striatal circuits. It was shown that measuring beta power at the beginning of the timed behavior can predict the subsequent produced interval duration [29••,30]. In this regard, DA AGO would result in reduced beta-band synchronization, while DA ANT would do otherwise, and thus triggering shorter or longer time estimates accordingly. A direct drug test of this proposal will be much needed.

Inconsistent findings

Instead of finding a change of the clock speed (i.e., accuracy), most of the negative drug studies reported a

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disruption of timing performance (i.e., poor precision in [31]) or only a change of the start time but not the stop time or vice versa [32,33]. As mentioned in Box 1, accuracy requires a certain level of precision. When the precision is poor, it is hard to gauge what the drugs really did to the accuracy of timing. When the above inconsistent results are reported, it is necessary to be carefully examining the procedural difference in the studies. There are many sources that could contribute to poor temporal precision that results in bad temporal accuracy. One potential source, just to name a few, is the use of relatively short ITIs in studies that report negative results. Using shorter ITIs that are equal or shorter than the to-be-timed duration brings in factors, such as motivation or impulsive responding [34] that are interfering with timing itself that we want to study. An extreme case of using no ITI (i.e., non-discrete trials) can be seen in [13], in which the response was quite high even at the beginning of the FI trials. When the ITI is too short, the animals may still be in the process of consuming the rewards (e.g., food or sucrose solution), thus it is hard to infer when the animals start timing from the beginning of a trial. That is, if the start time varies from trial to trial, it is hard to determine the overall accuracy of timing because the timing function will appear flat (i.e., bad precision). Using discrete-trials with long and random ITIs (at least longer the criterion time) helps the animals to have a clear starting time point in the trial. This will contribute to better precision of timing by reducing premature responses. In addition to short ITIs, overtraining (e.g., extensive use of the same research subjects) may contribute to habit formation, which is a functional characteristics of the striatum that may 'blunt' the effects of DA drugs on timing precision [35,36]. Brain damage may also block the observation of the clock speed effect by DA drugs, either by acute brain lesion [37] or chronic drug treatment at toxic dose [38]. Sex difference in timing precision and accuracy also needs to be considered when comparing studies across labs [27,39]. It is a trend and a new requirement in the biomedical research to consider potential sex differences in preclinical behavioral studies.

On the drug itself, it is also possible that the drug has lost its potency over time because the storage condition for the drug bottles may not be the same across labs (e.g., was it capped tightly and kept in a dry safe?) and no drug can maintain its potency forever. If no drug effect is obtained in the timing task, it becomes necessary for the experimenter to test the same drug in a second non-timing task to verify whether the drug is still potent on any behavior in general. Finally, it should not be overlooked that there are potential non-specific effects of using indirect DA AGOs in behavioral studies because there are many types of indirect DA AGOs, each of which may exert slightly different pharmacological effects in the brain. Once the DA levels are universally increased in the brain, the subsequent activation of different DA receptors subtypes may vary across different brain regions by different indirect DA AGOs. Together, these may contribute to DA drug effects that are not restricted to timing accuracy per se (e.g., for a recent discussion on how DA modulation of motivation can be intertwined with timing, please see [40]). To disentangle the two (timing and motivation), a finer-grain approach needs to be developed.

Approach by altering DAT

Once DA is released in the synapse, its reuptake is mainly in charge by dopamine transporter (DAT) from the presynaptic side. Mice with DAT gene deletion were shown unable to develop temporal control of behavior, that is, a flattened response function [41], another case of poor precision. Instead of knocking out the DAT gene, knocking it down in adult mice, thus reducing DAT expressions has been shown to alter timing functions, but mainly in the start time (see Box 1) of the function [42]. The same group later tested human subjects to examine DAT gene polymorphism and found no change of timing performance, possibly due to procedural differences between animal and human research in this set of studies [43•]. Overall, with a global change of DAT expression before training the animals, the resulting effect does not resemble the clock speed effect induced by acute DA drug injections right before testing the animals when they are trained under drug-free conditions. Although most indirect DA AGOs (e.g., cocaine and methamphetamine) target at DAT, the time point when the DAT manipulation takes place seems to be critical. In this regard, an inducible and reversible technique [e.g., in Ref. 9] will be more desirable in future studies on manipulating DAT expression levels on timing.

Interval timing and daily rhythms of dopamine levels in the dorsal striatum

It has been reported that DA levels in mice present 24-hour rhythms in the dorsal striatum, with lower levels during the day and a peak during the night [44•]. Moreover, higher dorsal striatal DA levels during the night coincide with better performance on interval timing (i.e., peak location closer to the target time, higher peak amplitude and reduced peak width) in the nocturnal phase of the light/dark cycle in mice [45]. Both interval timing and DA oscillation — as well as DA synthesis and turnover — in the dorsal striatum are affected by inducing circadian disruption under constant light conditions. In addition, circadian regulatory elements have been found in the promoter region of components involved in DA metabolism, like DAT, D1A receptor (DRD1A), tyrosine hydroxylase (TH) and monoamine oxidase (MAO), demonstrating that the expression of these components is under circadian regulation [46,47]. It was recently reported that melatonin-depleted rats by pinealectomy (i.e., removal of the pineal gland, a brain structure that releases the circadian hormone melatonin) showed impaired learning in the peak-interval timing task. Furthermore, lack of melatonin increased

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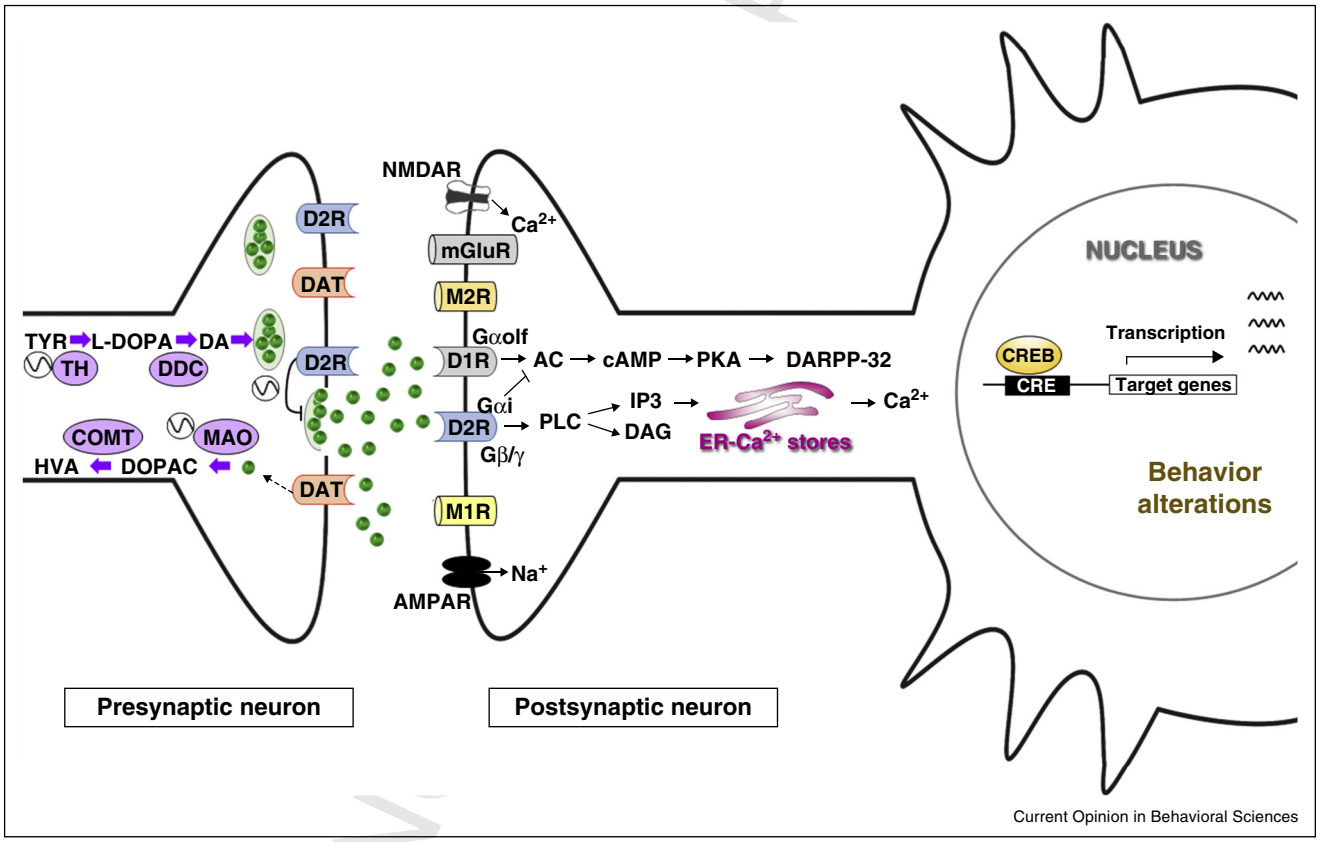
striatal DA availability — which was reversed by external melatonin administration — indicating that this hormone may modulate interval timing on a circadian base [48].

DA signaling has been linked to circadian clock components such as Per2. In this regard, mouse PER2 is involved in the circadian regulation of DA metabolism and mood-related behaviors [44•,46]. Both *mouse per2* (*mper2*) mRNA and mPER2 protein oscillate in the dorsal striatum and substantia nigra pars compacta (SNpc). Therefore, PER2 may regulate striatal DA rhythmicity by acting as a transcription factor through E-box sequences in key dopaminergic enzymes such as TH and MAO. In fact, in humans Per2 has a role in regulating striatal DRD2 availability and its vulnerability for cocaine addiction [49]. Thus, the data suggest a circadian regulation of dopaminergic transmission in striatal circuits that can be seen at both sides of the synapse, such as TH (for synthesis), DAT (for reuptake), MAO (for break down) as well as DRD2 (for postsynaptic signaling). This could be in part responsible for the interaction between the circadian system, which is 24 hours, and the interval timing, which is at a 'shorter' time scales. Figure 2 summarizes the main dopaminergic signaling pathways in MSNs in the dorsal striatum.

Temporal processing in humans with dopaminergic deficits

Interval timing is altered in several disorders associated with pathological dopaminergic function, including

Figure 2



Schematic illustration showing the principal signaling pathways in MSNs in the dorsal striatum. The effects of DA in MSNs are mediated by G-protein-coupled receptors. DA signaling via DRD1, which are coupled to AC through Golf, increases cytosolic cAMP levels leading to the activation of PKA and phosphorylation of various intracellular targets, such as DARPP-32. DRD2 activation leads to inhibition of AC through Gαi subunits. In parallel, released Gβ/γ subunits stimulate phospholipase Cβ isoforms, generating DAG and PKC activation as well as IP3 release and the mobilization of intracellular Ca^{2+} stores. Integration of these signaling pathways leads to changes in behavior such as learning, reward and timing. The circadian system is able to regulate daily rhythms in components related to dopaminergic neurotransmission. Some examples involve rhythmic DA synthesis by TH, rhythmic DA release — under the control of D2 autoreceptors — or rhythmic degradation mediated by MAO. *Abbreviations*: AC, adenylyl cyclase; ACh, acetylcholine; AMPAR, AMPA receptor; COMT, catechol-o-methyl transferase; CRE, cyclic-AMP-response element; CREB, CRE binding protein; DA, dopamine; DAG, 1,2-diacylglycerol; DARPP-32, cAMP-regulated phosphoprotein of 32 kDa; D1R, dopamine D1 receptor (DRD1); D2R, dopamine D2 receptor (DRD2); DAT, dopamine transporter; DDC, DOPA decarboxylase; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; IP3, inositol 1,4,5 trisphosphate; M1R, muscarinic acetylcholine receptor 1; M2R, muscarinic acetylcholine receptor 2; MAO, monoamine oxidase; mGluR, metabotropic glutamate receptor; NMDAR, NMDA receptor; PKA, protein kinase A; PKC, protein kinase C; TH, tyrosine hydroxilase; TYR, tyrosine. The symbol ∿ indicates circadian oscillation.

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schizophrenia, Parkinson's disease (PD), Huntington's disease (HD), attention-deficit hyperactivity disorder (ADHD), and Multiple System Atrophy (MSA) [50–56]. For example, PD patients exhibit important deficits in accuracy and precision on temporal reproduction tasks, which are attenuated by levodopa administration [51]. Interestingly, PD patients show a 'migration effect' when they are trained and tested OFF medication with multiple target durations across the session. This effect results in overestimation of the shortest durations and underestimation of the longest ones, and it has been related to a DA-dependent dysfunction of retrieving temporal memories [51–53]. This effect, which is equivalent to the Vierordt's Law, was not reproduced in healthy volunteers with reduced DA levels resulting from acute phenylalanine/tyrosine depletion (APTD) [57], indicating that the underlying intrinsic pathology of PD contributes to the migration effect. PD patients also display greater deficits in timing tasks that are dependent on controlled attention, such as cross-modal auditory/visual tasks [58]. In addition to the above mentioned disorders, several dopamine-related gene polymorphisms–such as DRD2/ANKK1-Taq1a, COMT Val158Met and DAT 3′ VNTR–have been associated to timing functioning [43•,59,60], see Table 1.

Recent human pharmacological studies corroborate the effect of indirect DA AGOs on producing proportional leftward shifts of the timing functions while DA ANTs producing proportional rightward shifts, both are a shift in accuracy of timing. For example, ketamine, which increases prefrontal DA levels, impairs accuracy on a perceptual timing task [61]. Moreover, indirect DA ANT manipulation (acute phenylalanine/tyrosine depletion, which causes reduced striatal DA release) decreases correct response in a temporal discrimination task (shorter, longer or the same) in human volunteers [62]. Indeed, these temporal distortions are correlated with drug-induced euphoria, which has important implications for the study of temporal processing and drug addiction [26•]. These results point to the clinical relevance of research on temporal processing and the U-shaped functions relating levels of dopamine to the control of clock speed, memory, and emotion [63].

Conclusions and future directions

Although we are still far away from a complete understanding of exactly how DA affects the activity of cortico-striatal circuits and how this drug-induced neural activity change modifies timing behavior, there are a few tentative conclusions that can be drawn: (i) Dopaminergic pharmacological modulation affects mainly the clock speed of interval timing, although the experimenter should carefully rule out the motivation effect on timing or at least take that account into consideration; (ii) The clock speed effect may be due to DA modulation of the firing frequency of cortical oscillators that project to MSNs in the dorsal striatum. (iii) Cortico-striatal DRD1 or DRD2 alteration impacts on interval timing, although there are some inconsistent results partly due to poor precision preventing a direct observation of temporal accuracy. Studying both systematically will be imperative in the future. (iv) DA metabolism in the dorsal striatum is subjected to circadian control, explaining in part the day/night differences observed in timing behavior. (v) Interval timing is profoundly affected in human pathologies with DA dysfunction, and

Table 1

Interval timing in animal models and human polymorphisms with changes in dopamine levels.

Genotype	Physiological and behavioral alterations	Interval timing	Dopamine levels
Animal models			
$DAT^{-/-}$ mice	Hyperactivity and learning impairment; insensitive to psychostimulants.	Complete loss of temporal control; altered sensitivity to drugs [41].	Increased extracellular DA levels.
$DAT^{+/-}$ mice	Insensitive to psychostimulants.	Altered sensitivity to drugs; effects on clock speed [41].	Increased extracellular DA levels.
Knockdown DAT mice	Hyperactivity; impaired response habituation in novel environments.	Lower threshold for initiating responding in the timing task [42].	Increased extracellular DA levels.
DRD2 transgenic mice	Deficits in tasks that require working memory and behavioral flexibility, and in motivation for food reward.	Impairment in timing accuracy and precision [9].	Reduced dopamine-induced adenylate cyclase activity in the striatum.
DRD1 optogene-tics inhibition	Alterations in psychostimulant-mediated behavior.	Impaired performance in the fixed-interval timing task [13].	Reduced VTA dopaminergic transmission.
DRD2/ANKK1-Taq1a	Deficits in reversal learning and attention.	Increased timing variability for sub-second time durations [59].	Decreased DRD2 density in the striatum by 30–40%.
Humans			
COMT Val158Met	Disruptions in working memory and frontal executive tasks.	Increased timing variability for supra-second time durations [59].	Decreased dopamine availability in prefrontal cortex.
DAT 3′ VNTR	Several neuropsychiatric conditions due to decreased DAT expression	Normal [43•].	Increased DA levels.
BDNF Val66Met	Impaired episodic memory. Also associated to eating disorders.	Normal [59].	Increased DRD2/3 availability and lower DA tone in the ventral striatum.

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dopaminergic treatment may ameliorate this affection. Further research in this subject will have a deep impact in our understanding of timing and time perception from behavioral, physiological and clinical perspectives.

Conflict of interest

Nothing declared.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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