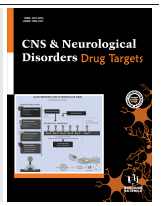
CNS & Neurological Disorders - Drug Targets, 2018, *17*, 3-5

COMMENTARY



Let the Time Fly: Dopamine is the Arbiter

Xiaodong Liu[1], Changzheng Zhang[1,2], Oscar Arias-Carrion[3,*] and Ti-Fei Yuan[4,5,*]

[1]*School of Psychology, Nanjing Normal University, Nanjing, China;* [2]*Department of Psychology & Key Laboratory of Psychological Assessment and Rehabilitation for Exceptional Children, Lingnan Normal University, Zhanjiang, China;* [3]*Trastornos del Movimiento y Sueño, Hospital General Dr. Manuel Gea González, Ciudad de México, México;* [4]*Shanghai Key Laboratory of Psychotic Disorders, Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China;* [5]*Co-innovation Center of Neuroregeneration, Nantong University, Nantong, Jiangsu, China*

Time is crucial to everyone in life. We can know the time by external tools, such as a clock or hourglass, for example. Humans possess an "internal clock" endowed with the ability to compute both physical and subjective timescales [1]. We can estimate time *via* the "internal clock". Further, drugs such as amphetamine and cocaine may affect the "internal clock", suggesting that time perception is plastic. Accumulating data suggest that mesolimbic dopaminergic (DA) neurons contribute substantially to such functions. For example, DA neurons regulate temporal specificity in implementation of reward prediction errors; modulation of brain DA levels can speed up or slow down time estimation [2]; neurological and/or psychiatric changes in DA system result in time judgment distortion, as well [3]. However, two patterns of timing behavior result from amphetamine and haloperidol [2]. Amphetamine may increase or decrease the "internal clock" speed, while haloperidol may decrease or not affect the speed. Nevertheless, the precise mechanism underlying DA-mediated time perception remains largely unknown.

ARTICLE HISTORY

Received: April 07, 2017
Revised: April 19, 2017
Accepted: April 19, 2017

DOI:
10.2174/1871527316999170505110106

A recent study published in *Science* by Soares *et al*. explored for the first time the causal relationship between DA neuronal activity and time sensitivity using pharmacogenetic and optogenetic approaches [4]. The authors designed a temporal discrimination task to evaluate an animal's ability on time estimation, in which mice were trained to discriminate two successive tones at different intervals for water reward, *i.e.* reward for the short intervals of <1.5 s on one side and long intervals over 1.5 s on the other side. Consequently, mice exhibited more failures at intervals closer to 1.5 s. To probe the involvement of the DAergic system in this behavior, Soares *et al*. [4] firstly utilized a pharmacogenetic approach (clozapine N-oxide (CNO) + human M4 DREADD (hM4D) expression) to suppress DA neuronal activities in midbrain, a crucial DAergic region implicated in time perception, during the timing tasks. They found immediate impairment in task performance upon clozapine N-oxide (CNO) treatment.

Considering that midbrain DA neurons are related to reward-dependent behavior [5], and the task of reward prediction error can effectively reflex the temporal judgments when an unexpected reward is obtained, an enhanced DA neuronal cell activity occurs, whereas a missed expected reward corresponds to a suspended neuronal response. With fiber photometry recording of group neuron calcium activities, the authors observed sustained increases in DA neuronal cell firing between the two tones. Response to the second tone represents the reward prediction error, which showed remarkable differences in correct or incorrect choice in the tasks, indicating that DA neuron activity credibly relates to time perception, rather than the actual interval, *e.g.* stronger DA neuronal cell activity corresponds to shorter tone intervals.

Despite the correlation between temporal judgments and DA neuron activity observed in previous and current investigations, it remains uncertain if DA neuron activity simply reflects or sufficiently regulates time perception. The authors then applied optogenetics to accurately activate and inhibit DA neurons. Indeed, activation of DA neurons was sufficient to alter time estimation (Fig. **1**), in agreement with the pharmacological results. Remarkably, the current study focused specifically on time perception and DA neuronal cell activity rather than DA neurotransmission; therefore, the mnemonic effects on time estimation is effectively excluded.

Central DA neurons are found mainly in the substania nigra pars compacta (SNc) and ventral tegmental area (VTA). They are both important for timing behavior; however, their projections innervate different brain regions and generate different effects. On the one hand, Meck [6] found that time discrimination ability in duration discrimination task was compromised by utilizing 6-hydroxydopamine to deplete DA in the substantia nigra or dorsal striatum. Yet,

*Address correspondence to these authors at the Shanghai Mental Health Center, Shanghai, China; E-mail: ytf0707@126.com; and Trastornos del Movimiento y Sueño, Hospital General Dr. Manuel Gea González, Ciudad de México, México; E-mail: arias@ciencias.unam.mx

Xiaodong Liu, Changzheng Zhang contributed equally to this work.

1996-3181/18 $58.00+.00

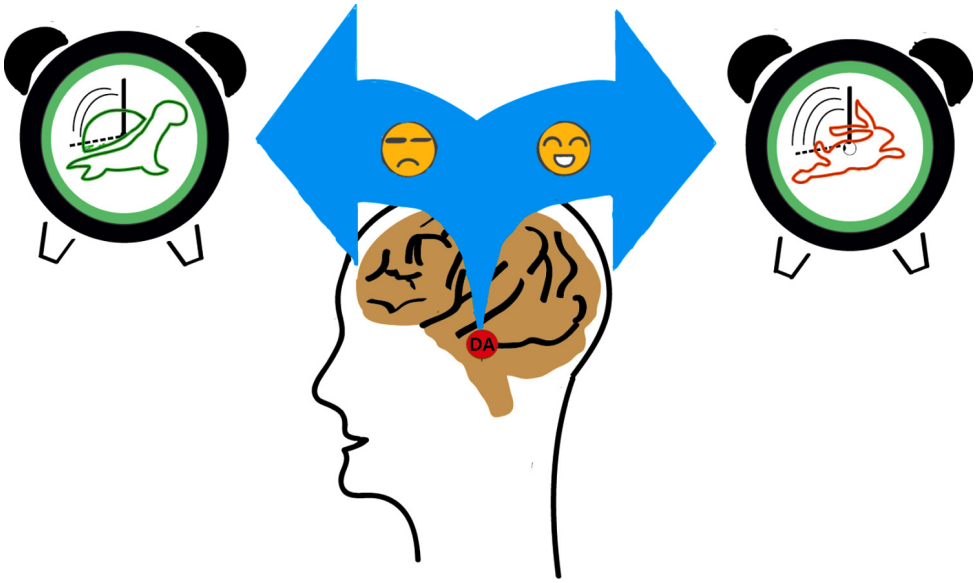


Fig. (1). Midbrain dopamine neurons control judgment of time. Time flies when we are having fun, and it freezes when we are bored.

but the same effect was not found in ventral striatum, suggesting that DA neurons in SNc principally project to the dorsal striatum that is crucial for time estimation.

Parkinson disease is caused by degeneration of DA neurons in the SNc. Indeed, Parkinson's akinesia is often accompanied with inaccurate time perception; for instance, patients with Parkinson disease tend to judge a shorter interval in time estimation task, and patients whose illness was more serious displayed a worsened performance in the task [6], which could be improved by DAergic medication. Huntington disease also displays deficits in striatal DA. There is no doubt that patients with Huntington disease have a worse performance than controls in the interval timing task [7-9], and Teixeira *et al.* [10] proposed that time estimation training may contribute to Parkinson disease. The last authors posited that the cognitive and motor deficits of patients with Parkinson disease would be improved by time estimation training, because training would elicit an adaption change of the pathway.

On the other hand, DA neurons in the VTA also exhibit involvement in time perception, for example, joyfulness-facilitated internal time flow and temporal judgment is frequently distorted in drug abusers [8], who are typically associated with hyperactivities in the VTA DA neurons. Examination of the effect of cocaine and ketamine on timing behavior has shown that cocaine increased "internal clock" speed, while ketamine had no effect. Lipopolysaccharide can produce systemic inflammation. Methylphenidate can elevate the striatal DA, and lipopolysaccharide can enhance the effect of methylphenidate, which suggests that systemic inflammation enhanced stimulant-induced striatal DA elevation [9]. There exists a possibility that time perception is also affected by systemic inflammation. Striatal beat-frequency model may account for time perception [10]. Medium spiny neurons in striatum monitor oscillatory patterns of cortical neurons. When stimulated cortical neurons will change their oscillatory patterns via DAergic projection from the VTA. The current oscillatory pattern will then be compared with the one in memory, which makes MSN begin to estimate time.

We all have the experience that time flies when we sleep and dream. SNc and VTA can interact with neural network that related to sleeping [11]. So we guess it may explain the reason by dopamine in the SNc or VTA, partly. Notably, researchers found that the level of D2 receptor was lower in Methamphetamine abusers than non-drug abusers, and impaired dopamine D2 receptor function was found in chronic drug abusers with altered time perception [12]. It seems that the older we are, the time flies faster. Indeed, elderly adults tended to judge interval shorter than young adults [13]. There was a study which has confirmed that ageing adults report fast time flow, associated with their decreased D2 receptors in dorsal striatum (2.2% decrease per 10 years) [14]. Schizophrenia patients with increased D2 expression in dorsal striatum exhibited distorted time perception [15]. From the above, there exists a possible link between D2 receptor and time perception, in consistent with previous studies investigating time perception with pharmacology approaches.

Apart from pharmacological manipulation, application of transcranial direct current stimulation (tDCS) to the prefrontal area can activate midbrain DA neurons, and such treatment increased the internal perception of facial attractiveness [16]. Conceivably, employing non-invasive brain stimulation approaches, such as tDCS or transcranial magnetic stimulation (TMS) would be helpful in further studies to probe the relationship between the DA system and time perception in humans. There exists a right hemisphere dominance in temporal processing [7], and it may be possible to test if there is a difference between right and left hemisphere by tDCS or TMS.

Optogenetics has been employed recently to stimulate DA D1 receptors on neurons in the medial frontal cortex, which can restore the deficits in temporal control of action caused by VTA DA depletion [17]. We know that the cere-

bellum is related to cognitive function. Parker *et al.* [16] found that schizophrenia patients tended to judge intervals shorter than controls in the interval timing task. They utilized an optogenetic technique to stimulate lateral cerebellar nuclei projections to the thalamus of schizophrenic rats, which resulted in restoration of time estimation ability. It is worth considering whether tDCS or TMS can also produce the same effect.

Collectively, Soares *et al*. [4] point to a possible mechanism whereby DA signaling maintains the "internal clock". This discovery sheds light on how the reward system participates in time perception and internal reconstruction of different dimensions. So, to some extent, these novel findings can explain why time flies when we are having fun and freezes when we are bored!.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The study is supported by the National Natural Science Foundation of China (31771215, 81501164 and 81611130224. The study is also supported by grants from the Postdoctoral Foundation of Jiangsu Province (No. 1601180B), China Postdoctoral Science Foundation Funded Project (No. 2016M601841) and China Postdoctoral Science Foundation Specially Funded Project (No. 2017T100382). TFY is also supported by Young Elite Scientists Sponsorship Program by CAST (YESS).

REFERENCES

[1] Allman MJ, Teki S, Griffiths TD, Meck WH. Properties of the internal clock: first- and second-order principles of subjective time. Ann Rev Psych 2014; 65: 743-71.

[2] Lake JI, Meck WH. Differential effects of amphetamine and haloperidol on temporal reproduction: dopaminergic regulation of attention and clock speed. Neuropsychologia 2013; 51(2): 284-92.

[3] Allman MJ, Meck WH. Pathophysiological distortions in time perception and timed performance. Brain 2012; 135(3): 656-77.

[4] Soares S, Atallah BV, Paton JJ. Midbrain dopamine neurons control judgment of time. Science 2016; 354(6317): 1273-7.

[5] Hollerman JR, Schultz W. Dopamine neurons report an error in the temporal prediction of reward during learning. Nat Neurosci 1998; 1(4): 304-9.

[6] Pastor M, Artieda J, Jahanshahi M, Obeso J. Time estimation and reproduction is abnormal in Parkinson's disease. Brain 1992; 115(1): 211-25.

[7] Jahanshahi M, Jones CR, Dirnberger G, Frith CD. The substantia nigra pars compacta and temporal processing. J Neurosci 2006; 26(47): 12266-73.

[8] Cheng RK, MacDonald CJ, Meck WH. Differential effects of cocaine and ketamine on time estimation: implications for neurobiological models of interval timing. Pharm Biochem Behav 2006; 85(1): 114-22.

[9] Petrulli JR, Kalish B, Nabulsi NB, Huang Y, Hannestad J, Morris ED. Systemic inflammation enhances stimulant-induced striatal dopamine elevation. Trans Psych 2017; 7(3): e1076.

[10] Meck WH, Penney TB, Pouthas V. Cortico-striatal representation of time in animals and humans. Curr Opin Neurobiol 2008; 18(2): 145-52.

[11] Ficca G. What in sleep is for memory. Sleep Med 2004; 5(3): 225-30.

[12] Volkow ND, Chang L, Wang GJ, *et al.* Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. Am J Psych 2001; 158(12): 2015-21.

[13] Carrasco MC, Bernal MC, Redolat R. Time estimation and aging: a comparison between young and elderly adults. Int J Aging Human Dev 2001; 52(2): 91-101.

[14] Seeman P, Bzowej NH, Guan HC, *et al.* Human brain dopamine receptors in children and aging adults. Synapse 1987; 1(5): 399-404.

[15] Ward RD, Kellendonk C, Kandel ER, Balsam PD. Timing as a window on cognition in schizophrenia. Neuropharmacology 2012; 62(3): 1175-81.

[16] Chib VS, Yun K, Takahashi H, Shimojo S. Noninvasive remote activation of the ventral midbrain by transcranial direct current stimulation of prefrontal cortex. Trans Pysch 2013; 3: e268.

[17] Kim Y-C, Han S-W, Alberico SL, *et al.* Optogenetic stimulation of frontal d1 neurons compensates for impaired temporal control of action in dopamine-depleted mice. Curr Biol 2017; 27(1): 39-47.