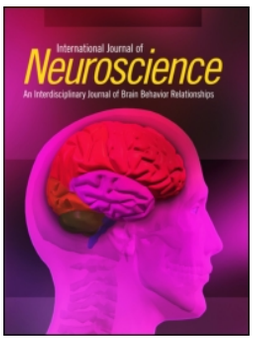

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REVIEW ARTICLE

The dopaminergic system dynamic in the time perception: a review of the evidence

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ABSTRACT

Dopaminergic system plays a key role in perception, which is an important executive function of the brain. Modulation in dopaminergic system forms an important biochemical underpinning of neural mechanisms of time perception in a very wide range, from milliseconds to seconds to longer daily rhythms. Distinct types of temporal experience are poorly understood, and the relationship between processing of different intervals by the brain has received little attention. A comprehensive understanding of interval timing functions should be sought within a wider context of temporal processing, involving genetic aspects, pharmacological models, cognitive aspects, motor control and the neurological diseases with impaired dopaminergic system. Particularly, an unexplored question is whether the role of dopamine in interval timing can be integrated with the role of dopamine in non-interval timing temporal components. In this review, we explore a wider perspective of dopaminergic system, involving genetic polymorphisms, pharmacological models, executive functions and neurological diseases on the time perception. We conclude that the dopaminergic system has great participation in impact on time perception and neurobiological basis of the executive functions and neurological diseases.

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Dopamine; time perception; genetic; executive functions; neurological diseases

Introduction

Time perception (TP) is a part of dynamic interaction between personal experience and environment conditions [1,2]. In this sense, the central nervous system (CNS) processes the sensory stimuli in time scales which vary from the milliseconds (motor coordination), seconds to minutes (time conscious perception) and hours of the day (circadian rhythms) (Figure 1) [3,4]. TP plays a role in coding different environmental stimuli, which depends on dopaminergic systems [5]. In addition to the established role of CNS dopamine (DA) levels with the memory, attention, decision-making and motor actions [6,7], DA is also associated with the time intervals perception in the range of the supra-seconds, and with the internal clock speed, which is consistent with its effect on the rate of internal pacemaker that varies between individuals leading to a 'faster' clock for some and 'slower' clock for others [8,9].

Several studies have analyzed the role of deficits in dopaminergic neurotransmission on executive functions and time interval processing [10–12]. Although several studies have analyzed the role of DA in TP, several issues are inconclusive; among them, how the genetic and neurobiological determinants, modulated by dopaminergic system, influence TP [13,14]. Moreover, several lines of studies based on data from study of genetic factors, pharmacological models, cognitive aspects and neurological diseases indicate that dopaminergic system is important for temporal processing. Genetic studies have demonstrated that timing performance differs between individuals according to dopaminergic levels [15]. There were differences in the expression of dopamine genes in different cognitive domains (i.e. perception, attention, memory and learning) [16] and task switching [17]. Furthermore, differences have also been found for dopamine gene expression in different

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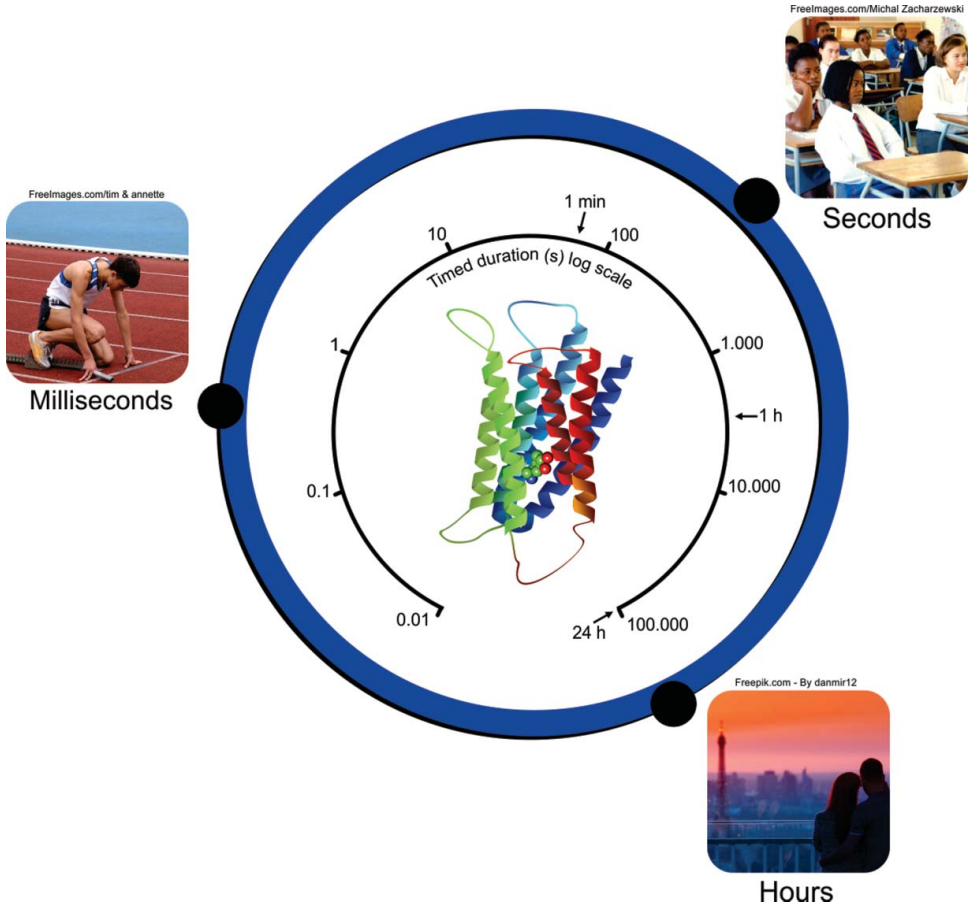

Figure 1. Relation of dopamine levels (DA) and timing across different timescales. Timing on milliseconds is associated with automatic processes (e.g. motor control), timing on scales longer than a second is often referred to as time estimation and thought to rely on conscious and cognitive control (e.g. attention), and hours of the day modulate the circadian rhythms, both mediated by dopaminergic system.

cognitive domains (i.e. perception, attention, memory and learning) [16] and task switching [17]. In addition, differences in genotypes lead to phenotypic differences, such as functional magnetic resonance imaging (fMRI) responses to a variety of cognitive tasks [18]. These differences may be used as intermediate phenotypes between genetic differences and the behavioral manifestation of different neurological disorders.

Thus, the study of the role of the dopaminergic system in TP is not without limitations since analyzing the pattern of dopaminergic modulation due to depletion or increase is complicated by inter-individual changes in DA levels. Therefore, studies analyzing the timing and daily rhythmicity, for example, time estimation and sleep–wake cycle are fundamental to understanding of behavioral phenotypes and neurobiological aspects related to the dopaminergic activity in TP [4,19–22].

Present studies do not completely address the association between dopaminergic levels and TP functions of the brain. Accordingly, in this paper, a systematic process is applied to synthesize findings on the impact of dopamine among genetic factors, pharmacological models, neurobiological bases in executive functions and neurological diseases on the TP. This study is intended to guide the search for a better clarification in respect of the alterations on the dopaminergic mechanisms in TP, supported by the following databases: Pubmed/Medline and HighWire. Therefore, the objective of this study was to conduct a review of the influences on the TP mediated by the DA action.

Methodology

The systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. This study consists of a review of English language research articles about the following: genetic aspects, pharmacological models, cognitive aspects (memory, attention), motor control, schizophrenia, Parkinson's disease (PD), attention-deficit/hyperactivity disorder (ADHD), depression and autism in combination with the terms dopamine and time

perception. Case reports, meta-analysis, original papers and reviews were included in this systematic review. No publication date or publication status restrictions were imposed. Criteria for exclusion were: dissertations, book reviews, conference proceedings or editorials. The results were analyzed, and papers that were deemed to be relevant and of an acceptable quality were included in the analysis.

Information sources

Online searches in the databases Pubmed/Medline and HighWire (1991–2016) were initially performed in January 2017 and repeated in June 2017 using relevant search terms (e.g. [Dopamine and timing], [Genetic and time perception], [Pharmacological models and time perception], [Cognitive aspects with time perception], [Motor control and time perception], [Neurological diseases and time perception]. The search strategies for the database are summarized and presented in Figure 2. Due to the broad nature of the review, the search was focused on dopaminergic system and TP. Abstracts were examined for references to the research question and if the study appeared relevant, then the full text was retrieved. Reference lists of identified articles were searched for additional studies.

Study selection and data extraction

Three reviewers (V. Marinho, T. Oliveira and F. Magalhães) independently read the titles and/or abstracts of the identified papers and eliminated irrelevant studies. Studies considered eligible for inclusion were read in full and their suitability for inclusion was determined independently by three reviewers (V. Marinho, T. Oliveira and F. Magalhães). Disagreements were managed by consensus. However, if this was not successful, the consensus was sought by a fourth reviewer (S. Teixeira). Data were extracted based on study design and setting. Some authors were contacted to provide supplementary information when insufficient data were provided in the study. The authors of three studies were contacted for further information after reading the titles and abstracts. Two replied; since it bases the review of literature fulfilled the inclusion criteria.

Study selection

Studies were included if they met the following inclusion criteria: Initially, retrieved papers from each database were compared to remove duplicate records. Papers were then screened for eligibility based on the title and abstract, and if necessary the full text publication was reviewed.

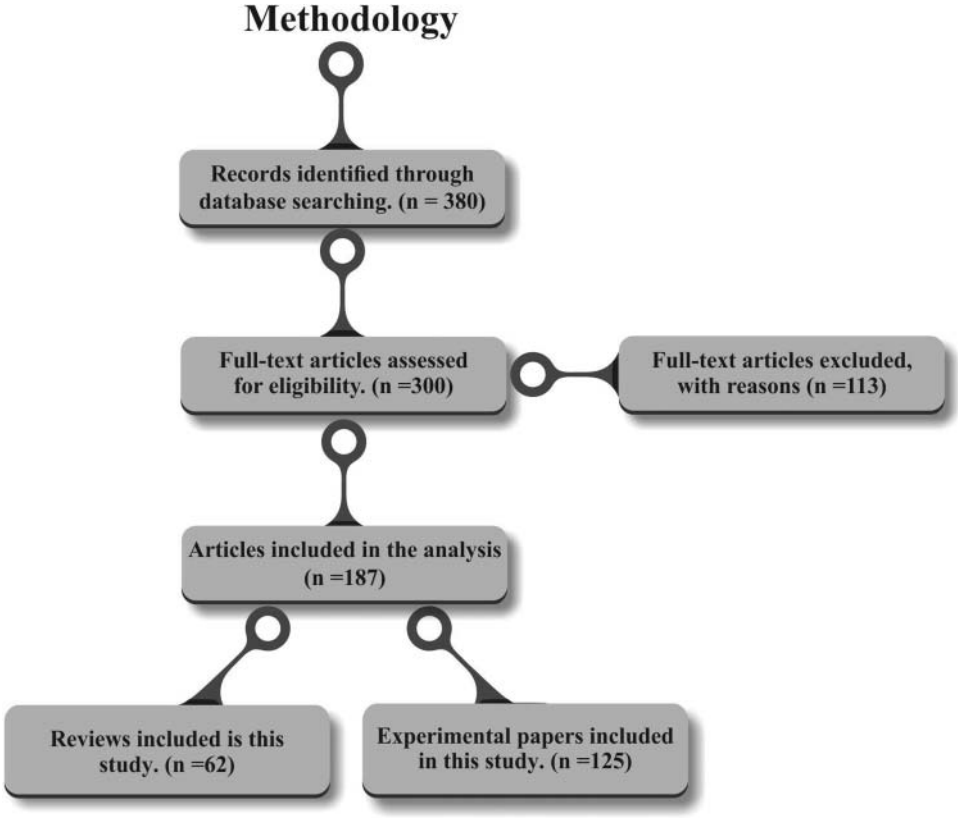

Figure 2. Procedure for systematic review.

Types of neurobiological modalities: Studies were included if they investigated dopaminergic structural connectivity using relationship among TP with genetic aspects, pharmacological models, cognitive aspects, motor control and neurological diseases. Functional connectivity studies based on dopaminergic system with TP were also included. To restrict the focus of the review, we utilize studies with cognitive tasks such as peak interval, interval discrimination tasks, verbal estimation, bisection tasks, time production and timed-motor reproduction.

Types of participants: For results related to development of genetic influences, pharmacological models, cognitive aspects and neurological diseases in time synchronization, studies were included if they contained a sample or subsample of typically healthy participants, individuals with neurological diseases and interval timing experimental using rats.

In summary:

Study design: Case reports, meta-analysis, original papers and reviews articles were included.

Population: Study populations were composed of healthy individuals and individuals with neurological diseases (e.g. children, young adults, middle-aged and elderly). Some studies included experimental models of interval timing in rats.

Intervention: Neurobiological interventions were defined as any intervention that influences the TP mediated by dopaminergic levels (peak interval, discrimination tasks, verbal estimation, bisection tasks, time production and motor reproduction). Whether through genetic polymorphisms, pharmacological models, cognitive aspects and neurological diseases.

Outcome: The primary outcome measure was the change in TP, using a timing task (with auditory or visual stimuli), due to genetic factors, pharmacological manipulations, neurological disease and phenotypes that distort neural synchronism in cognition and time intervals.

Papers were then screened for eligibility based on their title and abstract, and wherever necessary the full text publication was reviewed. These 380 papers were assessed for eligibility based on title and abstract; 300 were classified as meeting eligibility criteria. The next stage involved full text screening of the potentially relevant papers, following which 187 studies were included in the review (Figure 2).

Results

Genetic aspects associated with dopaminergic system on TP

Ten empirical studies of genetic in timing, 2 review papers and 31 genetic studies and risk of neurological diseases investigated the neural regions associated with heterogeneous performance on a perceptual timing. Substantial differences in performance were observed, with some subjects performing well, and others performing close to chance. Furthermore, behavioral and neural data suggest differential processing of TP as a function of interval duration range (sub- and supra-second intervals) [23]. These differences may generate intermediate phenotypes between genetic differences and the behavioral manifestation of different neurological diseases. Thus, in order to demonstrate the contribution of genetic predisposition to the individual differences in brain network recruitment during temporal perception, we study well-known genetic polymorphisms (*COMT* Val158Met, *DRD2/ANKK1*-Taq1A and *SLC6A3* 3'-UTR VNTR) previously implicated in temporal perception. We hypothesized that individual differences in timing abilities would be associated with differences in the activation of brain circuitries, commonly activated in temporal perception [23]. We further hypothesized that this difference in performance would also be associated with a difference in activation within the brain regions we have identified. However, we note that alterations in the dopamine system may lead to either increased or decreased levels of activity during timing along with modulation in performance (Table 1) [9].

Studies with human and non-human participants showed differences in the judgment of time between interval timing and reward processing tasks, and the interaction of this relationship was examined with three different dopamine-related gene polymorphisms. These gene polymorphisms affect the expression of D2 dopamine receptors primarily in the striatum (*DRD2/ANKK1*-Taq1A polymorphism), dopamine transporters (DAT), which clear synaptic dopamine in the striatum (*SLC6A3* 3'-VNTR variant) and (*COMT* Val158Met) results in lower Catechol-O-methyl-transferase (COMT) enzyme activity and higher levels of DA extracellular. The polymorphisms allowed us to investigate dissociable aspects of the dopamine system and their interaction with reward magnitude manipulations in shaping timed behavior and in cortico-striatal information processing that have been implicated for interval timing.

Pharmacological models and TP

Based on 14 studies (reviews and experimental papers) that include terms of dopaminergic drugs on TP in the seconds-to minutes range, it has been proposed that dopaminergic drugs modify the speed of clock-stage processes [24]. Indeed, these drugs can induce systematic changes in the temporal pattern of responding that are amenable to an information processing framework

Table 1. Summary of studies investigating the impact of time perception.

Author	Study	Protocol	Results
[32]	Experimental	Subjects: 52. Cognitive task. Genotyping: *COMT* Val158Met, *DRD4* exon 3 VNTR and *SLC6A3* 3′UTR VNTR.	*SLC6A3* variability showed no difference in study. *COMT* Val158Met and *DRD4* exon 3 VNTR differ in their effects on attentional functions as explicated in long-SOA metacontrast.
[23]	Experimental	Subjects: 25. fMRI associated temporal task. Genotyping: *DRD2/ANKK1*-Taq1a.	A1 carriers of the Taq1a polymorphism exhibited worse performance on temporal task. However, greater activation in the striatum and right dorsolateral prefrontal cortex, as well as reduced volume in the cerebellar.
[70]	Experimental	Subjects: 22. Reaction time task; peak interval. Administration: d-amphetamine, haloperidol or placebo.	Drug-liking scores in response to d-amphetamine administration predicted the direction of shifts in timing functions using the PI procedure, indicating underestimation in task. Haloperidol no difference in this study.
[37]	Experimental	Subjects: 95. 64-channel EEG study. Continuous performance test. Genotyping: *COMT* Val158Met, *SLC6A3* 3UTR VNTR.	Effects of *SLC6A3* and *COMT* on the occipito-temporal activity in CNV. In addition, there was a trend towards an interaction between the two polymorphisms.
[10]	Experimental	Experiment: Phase 1: Group of DAT KD mice and WT mice were tested with a PI. Phase 2: effects of raclopride.	DAT KD mice responded at higher levels in peak trials than WT mice in all conditions, but particularly during the FI 30 peak trials.
[13]	Experimental	Subjects: 44. Genotyping: *SLC6A4* 5-HTTLPR, *MAOA* VNTR, *5HT2a* T102C, *COMT* Val158Met, *DRD2*-TaqIA, *SLC6A3* 3UTR VNTR. Discrimination task.	No differences between time representation and DA genes. However, shows association between 5-HT-related genes and parameters derived from psychometric functions PSE.
[83]	Experimental	Subjects: 6. fMRI associated with PI.	The fMRI data show activation of the frontal cortex, striatum, and thalamus, thus supporting the involvement of frontal–striatal circuits in the timing of supra-second durations.

Note: Stimulus onset asynchrony: SOA; functional magnetic resonance imaging: fMRI; peak interval: PI; contingent negative variation: CNV; dopamine transporter: DAT; knockdown: KD; wild type: WT; fixed interval: FI; serotonin or 5-hydroxytryptamine: 5-HT; point of subjective equality: PSE.

of interval timing. For example, acute administration of methamphetamine, an indirect DA agonist, led to an immediate horizontal leftward shift in the temporal response function that was proportional in magnitude to the duration being timed. Conversely, acute administration of haloperidol, a DA antagonist, led to an immediate horizontal rightward shift, again in a proportional manner. These proportional effects were explained by proposing that dopaminergic agonists increase the speed of internal clock, such that the perceived time (i.e. the output of the clock stage) grows more rapidly than the real time. In contrast, an absolute shift in time estimation might result from drug-induced changes in attentional factors that could alter the latency to begin timing by a constant duration irrespective of the temporal criterion [25]. The results show that pharmacological and anatomical basis of TP are relatively complex. One piece of evidence concerning the neural processes indicate that the specific aspects of this perception process is the observation that humans and non-humans systematically use consecutive reference timing values on opposite sides of the mean criterion time more often than would be expected by chance [22]. Suggestions that operate similar to a feedback-control system to minimize the amount of error in their estimation of the criterion time. This symmetrical pattern of results suggests that clock speed is regulated by the effective levels of dopamine. The result of increased competition and time-sharing between these two dimensions leads to the underestimation/overproduction of temporal intervals.

Cognitive aspects and motor control associated with dopamine on TP

As was the case for the approaches to genetic aspects and pharmacological models, previously discussed, there are 36 studies of cognitive functions and 9 studies with relationship between motor control and dopamine-mediated synchronization of time intervals; however, we refrain from providing a detailed review here. In summary, the papers, which studied cognitive tasks and peak interval timing, highlight areas of the brain whose activity is most correlated with TP. This was done by identifying cortical areas during timing task, which were involved in attention, working memory and motor control. Based on finding same regions in cognitive aspects and motor control, it is concluded that similar brain systems are related to the modulation of TP and the timing of motor acts [25]. It is consistent with the role of involve the association of several brain networks and structures temporal processing [26]. Results from past studies have demonstrated that complex processes involve cognitive aspects and motor control in central structures and peripheral structures with modulations in dopamine levels [27,28].

Neurological diseases associated with dopaminergic system vs. TP

We selected 85 studies about neurological diseases associated with the dopaminergic system and TP. The ability

of human subjects to estimate time is considered a relatively stable function that can be affected by neurological diseases [29]. From a clinical perspective, the examination of timing ability in patients with certain psychiatric or behavioral disorders – particularly those that are (at least in part) defined by characteristic changes in the apparent temporal organization of cognition or behavior (e.g. schizophrenia, PD, ADHD, depression and autism) – may help to improve the understanding of the psychological experience of these disorders and their potential amelioration. In this regard, we show how pathophysiological distortions in timing in the seconds-to-minutes range may improve our understanding of neurological diseases, developmental and childhood disorders, as well as behavioral and cognitive tendencies (Table 2). It is useful to bear in mind that there is no human clinical condition that can be defined solely as a disorder of timing and TP per se (in fact, a complete inability to estimate time is likely incompatible with life) [30]. However, distortions and perturbations in timing ability are present, to varying degrees, in many patient populations, and may or may not accompany differences in other aspects of sensory processing, as well as developmental, cognitive and behavioral profiles [22]. Studies involving individuals who suffer from neurological diseases have revealed that individuals with such conditions often have an impaired TP. Moreover, subjects with neurological and psychiatric damages have difficulty in perceiving and organizing the time, frequently due to disorders on attention, memory and neurotransmitters action as dopamine and acetylcholine [29].

Discussion

Genetic aspects associated with dopaminergic system on TP

TP is a consequence of the subjective experience of how fast or slow is the passing of time after the occurrence of certain events [31]. This way, an individual's capacity to estimate the time objective has been treated as a stable function, however, influenced by neurochemistry cerebral factors, in particular the dopaminergic mediation [32]. DA modulates the internal clock speed and acts as a neurochemical substrate for pulses from the pacemaker-accumulator according to the Scalar expectancy theory. Thus, a series of pulses are produced by an internal pacemaker in the presence of an event. These pulses are collected, counted and then compared with the representations stored, in order to allow the time judging [33,34].

Neurochemical differences in function of cerebral activity predispose the individuals to different behavioral phenotypes; this can be associated with inadequate recruitment, reduction or increase of the levels of DA resulting from differentiated genetic expression, and this induces people to underestimate or overestimate the time [35,36]. In addition, the changes in gene expression generated by polymorphisms influence the involvement ability of the stimuli perceptive mechanisms, modifies the proportion of interferences in neural impulse to concentrate more activity in specific brain areas (i.e., frontal and parietal cortex), which relate to the attention, memory and perception (Figure 3) [37,32].

Studies that associate genetic factors with neurophysiologic variables and TP have used genetically knocked out rats for the *COMT* and *SLC6A3* gene in order to observe the peak time interval in experimental paradigms of exploratory behavior in maze-task. It was observed that rats that were knocked out respond with greater time intervals than the rats that were not genetically knocked out [10,38–40]. The authors attribute genetic influence as the cause of performance differences observed in different strains, as well as to different methodologies, among them, the aquatic maze of Morris, fear conditioning, radial arm maze and the environment exploratory behavior [41]. These studies have increased the understanding of the role of genetic influence in TP [42].

In its turn, in CNS, DA is regulated by important proteins, in particular the COMT and the DAT, expressed by *COMT* and *SLC6A3* genes, respectively [43–45]. The dopaminergic system in the CNS is modified by several genes, mainly *COMT*, *SLC6A3* and *DRD2*, which changes the neural bases chemistry [46]. In particular, performance in discrimination tasks and time estimate differs between the individuals with single nucleotide polymorphisms of the genes that are responsible for the DA regulation [15,23,32]. These genetic differences were also found in various neurobiological studies of cognition, namely, the working memory [16], learning and repetition motor tasks in relation to a visual stimulus [17].

Past studies have also examined how the neural and genetic mechanisms contribute to TP [34,37]. Sysoeva, Tonevitsky and Wackermann [13] have investigated the differences of the neurobiological basis in Russian and right-handed individuals, through polymorphisms analysis (*SLC6A3* 3'-UTR VNTR, *DRD2/ANKK1*-TaqIA and *COMT* Val158Met), concomitant to time discrimination tasks with auditory stimuli. However, the results of this study do not demonstrate modulation in the concentrations of the DA the CNS in TP tasks in intervals from seconds to minutes.

COMT gene located on the 22q11 encodes the enzyme catechol, and has the capacity to catalyze the methyl group transfer from S-adenosilmetionine to

Table 2. Time perception in neurological diseases.

Author	Methods	Stimulus	Standard duration	Result
Schizophrenia				
[126]	Schizophrenia: 60 and Control group: 60. Discrimination task. EPQ questionnaire.	Auditory	50 ms, 1.2 s, 1 s.	Incorrect responses in the discrimination of time intervals, except in the conditions standard in schizophrenia group.
[119]	16 patients with Schizophrenia: 16 and Control group: 18. Discrimination tasks and fMRI.	Auditory	200, 70, 100, 300, 500 ms.	No differences in temporal processing both groups 'easy' and 'difficult'. Schizophrenia group reduced activation in SMA, insula/opercular cortex and DLPFC according to fMRI.
[125]	Schizophrenia: 23 and 22 Control group: 22. Time estimation task.	Auditory, visual	300, 600, 350, 400, 450, 500, 550 ms.	Schizophrenia group exhibited overestimation in both auditory and visual durations (overestimation).
[121]	Schizophrenia: 17 high risk; 16 high risk for major affective disorder; Control group: 34. Time estimation task.	Auditory, visual	3, 3.67, 3.78, 4.24, 4.76, 5.34, 6 s.	HrSz group showed more difference between auditory and visual in timing task than in the NC or HrAff groups. The HrSz participants showed underestimation in time.
[89]	Schizophrenia: 15. Control group: 16 Time estimation task.	Auditory	500 ms,1 s, 3s.	Patients with schizophrenia exhibited overestimation in temporal task.
Parkinson's disease				
[135]	Groups: Patients Parkinson's disease, elderly participants and healthy young participants. Bissection and Cognitive task.	Visual	−134, −100, 67, −33, 0, 33, 67, 100, 134, 167 ms.	PD patients showed underestimation compared with healthy elderly and young participants.
[129]	Parkinson's disease: 19 and Control group: 19. Motor reproduction and Medication On/Off.	No	Seconds range, varied for each participant.	Unfilled: no impairment filled (simple motor task during encoding phase): underestimation (off only).
[128]	Parkinson's disease: 19 and Control group: 19. Medication On/Off.	Auditory	250 ms, 500 ms, 1 s, 2 s.	PD in the off condition of therapy (off stimulation/off medication) is impaired in their ability to reproduce the duration of actions. Violation of Scalar property.
[90]	Parkinson's disease: 10 and Control group: 14. Medication On/Off. Time reproduction task.	Visual	400, 450, 500, 550, 600 ms. 1.6, 1.8, 2, 2.2, 2.4 s.	PD patients do not show abnormalities in cognitive time processing in the millisecond range, however, showed underestimation of the supra-second time intervals after L-dopa medication.
Attention-deficit/hyperactivity disorder				
[159]	ADHD: 10. Motor task.	No	15, 80, 100, 120 s.	Overestimation on children with ADHD showed greater variation in time between the foot jumping and the rope whirling tasks.
[161]	ADHD: 223 Siblings: 105 and Youths: 88. Temporal task.	Verbal, visual	5, 12, 17 s.	ADHD probands tended to overestimate in verbal estimation more than their unaffected siblings and TD youths.
Depression				
[171]	Depression: 18 and Control group: 18. Time discrimination task.	Visual	$<$300 ms, $>$1s.	Depressed group produced a higher discrimination (underestimation) than the control group.
[166]	Major depression: 32, Manic episode: 30 and Control group: 31. Trail Making Test A. Time production task.	Visual	3, 4, 7, 8, 10, 35, 43, 90, 109 s.	Depressed subjects overestimated the longer time spans, with the manic patient group overestimating even more prominently.
[176]	Depression: 15 and Control group: 20. Discrimination task	Visual	80 ms, 120 ms, 450 ms, 550 ms, 1.12 s, 1.28 s.	No difference between groups for discrimination task.
[169]	Depression: 12 and Control group: 8. Psychometric avaliation. Motor task.	No	Seconds range, varied for each participant.	The results showed shorter units longer in patients with melancholic depression. Patients with depression have motor underestimation in the task
Autism				
[187]	Autism: 20 and Control group: 22. fMRI study with the behavioral task.	Visual	9–31 s.	Autism spectrum did not show differences in neural activity within classical mentalizing regions. However, they showed reduced amygdala activity and underestimation.
[184]	Autism: 64. Temporal task.	Auditory, visual	0 ± 10 s, 20 ± 50 s, ±80 s, 100–300 ms.	Relationship between multisensory temporal function and speech processing in autism and underestimation.
[182]	Autism: 19 and Control group: 13. Temporal bisection task.	Auditory	1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7 s.	Autism tended to produce a greater proportion of long responses, displayed a flattening in their timing functions, and greater difficulty discriminating between longer durations.

Note: Eysenck Personality Questionnaire: EPQ; functional magnetic resonance imaging: fMRI; supplementary motor area: SMA; dorsolateral prefrontal cortex: DLPFC; high risk for schizophrenia: HrSz; high risk for major affective disorder: HrAff; normal control: NC; Parkinson's disease: PD; attention-deficit/hyperactivity disorder: ADHD; typically developing: TD.

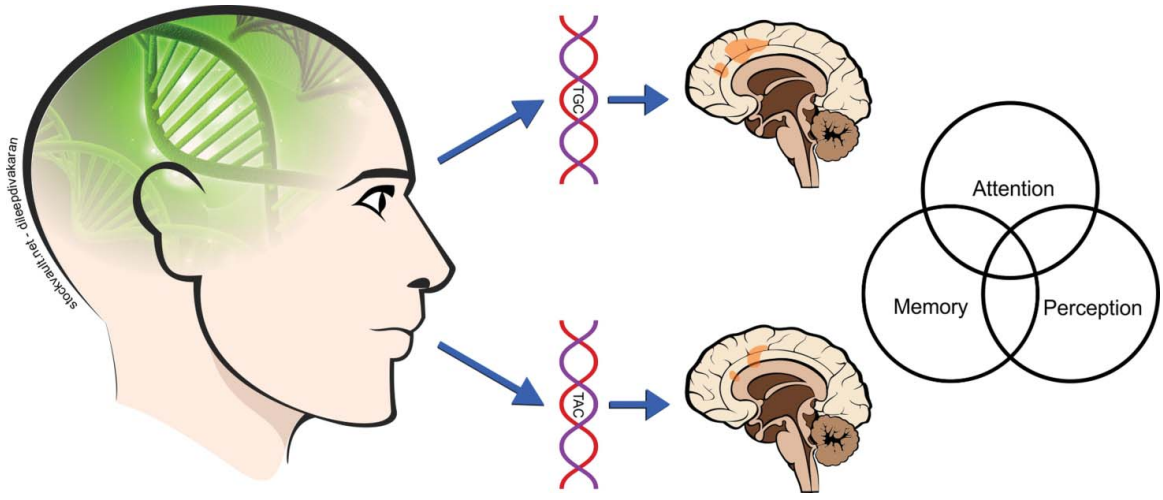

Figure 3. Genetic polymorphisms modulate the functions of the parietal, prefrontal cortex and the role of striatal oscillations in the representation of time intervals in the brain. Thus, it decreases the efficiency in coding the time intervals and cognitive aspects.

catecholamines, including the DA neurotransmitter [47]. The single nucleotide polymorphism *COMT* Val158Met, characterized by the valine replacement for methionine at codon 158, results in lower enzyme activity and higher levels of DA extracellular. Carriers of allele Met (L) have catechol activity relatively low in relation to Val (H) variation, and presumably, reflect in the dopaminergic levels in the dorsolateral prefrontal cortex (DLPFC) [18,48]. The change of *COMT* gene expression may lead to a wide spectrum of changes that affects the perceptive time ability, such as sadness and bad mood in individuals [12], changes in attention level [32], development of schizophrenia and bipolar disorder type II [49,50].

In a review, Green et al. [18] have presented genetic and cognitive data to clarify the mechanisms underlying the human behavior. Variations in the genes lead to differences in protein expression, which is responsible for differences in phenotypic expression such as behavior. The difference in molecular function could be reflected at different levels or activity of neural circuits during a cognitive task. Moreover, neurogenetics seeks to identify variations in the genome that can be linked to the perceptual and cognitive functions through the intermediary neural characteristics.

DRD2 gene with location 11q23.2 encodes a receptor coupled to G protein located in post-synaptic neurons, which plays an important role in the locomotion and hormones production [51]. The polymorphism *DRD2/ANKK1*-TaqIA leads to the replacement of glutamate by lysine residue (Glu713Lys). Before this, two alleles have been identified (A1 and A2), and the presence of one or two alleles A1 is associated with the reduction of the receptor D2 in areas of striated body, with higher observation in the caudate nucleus and putamen [13]. Phenotypes related to the *DRD2/ANKK1*-TaqIA are common in chemical dependence on cocaine and other illicit drugs [52], ADHD [53] and emotional deregulation in children [12]. In relation to TP, it has shown connections with different performances in timed activities [10,23,54]. This way, they demonstrated that D2 receptors are crucial for the neural mechanisms mediating both direct and indirect activation pathways of the prefrontal cortex (PFC), in the motor and pre-motor area, whose transitional expression of D2 receptors in the striatum hinders the temporal control, and leads to time underestimation [13]. Wiener et al. [23] verified the influence of polymorphism *DRD2/ANKK1*-Taq1A in different recruitments of brain structures for the nerve impulses synchronization in perceptive activities of time. In addition, the genetic results demonstrated that individuals with genotypes (A1/A2 or A1/A1) presented a reduction of 30%–40% in density D2 of the striated part, as well as inaccurate performance in perception activities.

SLC6A3 gene with location 5p15.3 encodes the DAT, which modulates the synaptic concentration of the presynaptic terminals of dopaminergic ion-dependent neurons [55]. Variation in exon 15 in region 3' not translated (3'-UTR) contains a repetition in series of 40 pb, designated by a variable number of tandem repetitions or VNTRs, which contains the copies of 9-repetitions (9R) and 10-repetitions (10R) are the most common alleles. Soon, carriers of 9R show less DAT activation than homozygous 10R counterparts in PFC, pre-motor cortex and caudate nucleus [56], underlying impairment of planning and execution processes of working memory tasks [57], the association with ADHD [58], the Alzheimer disease [59], the susceptibility to PD, schizophrenia [60] and the bipolar disorder [61]. In addition, the suppression of the *SLC6A3* gene in homozygous animal models for 9R abolishes the ability to discriminate durations of supra-seconds and increases

the internal clock speed, impairing the temporal integration [62].

Therefore, to substantiate the genotypic contributions to the performance and cortical mechanisms behind the timing ranges, as a means of elucidating the physiology of the internal clock, it will require combinations of tools, such as genotyping analytical tools, neuroimaging and psychophysical evaluations [63].

Pharmacological models vs. TP

Human beings and animals process the temporal information with internal timer mechanisms that can be interrupted, reset or have its speed adjusted [64]. DA has a key role in the temporal processing and in the cognitive processes modulation. Additionally, the maintenance of the DA levels is fundamental to synchronization and TP. The chronic dysregulation may contribute to timing deficiencies observed in normal aging and neurological diseases [30]. Before this, it is of considerable interest to note that TP is influenced by pharmacological manipulation with dopamine agonists and antagonists leading to the increase or decrease of the internal clock speed [65,66].

In experiments of pharmacological manipulation in animals, drugs that increase the DA concentration as the methamphetamine and cocaine have led to a horizontal displacement to the left in the response curve to reward stimuli, which suggests an underestimation of the interval [10,67–70]. In contrast, administration of antagonists of dopaminergic receptors, such as haloperidol, leads to temporal intervals overestimation are produced, with changes to right horizontal in timing functions [64,70,71]. The administration of DA agonists may lead to underestimating the target range. In contrast, the antagonists may result in an overestimation of the interval [64,70].

An important characteristic of dopaminergic drugs for the time interval processing is that the magnitude of the horizontal curve displacement is proportional to the time interval being processed [11]. These effects are consistent with the Scalar expectancy theory [65]. Then, if a drug affects the clock speed, it induces changes in timer functions in the first session. With repeated administration of the drug, individuals should gradually reprogram their timer functions in such a way that the functions would return to the base level, regardless of the continuous drugs administration. The gradual renormalization, like this, is due to the resizing of the stimulus duration, and is not as a result of the tolerance development. Finally, an end must be seen in relation to the drug administration when it is interrupted, produces horizontal displacements in temporal responses to the difference between the temporal stored reference and the change in the clock speed after the drug removal [11].

Also in agreement with the Scalar expectancy theory, the dopaminergic modulation has different effects depending on the context of the activity, increasing the internal clock speed mediated by DA agonists, for example, leads to time underestimation during temporal tasks production, however they cause temporal interval overestimation during of the time estimation tasks. [72]. Taken together, the evidences of pharmacological manipulation and lesions show that clock speed seems to be more related to the dopaminergic transmission in nigrostriatal pathway. This differs clearly from the manipulation of other pathways, as the cholinergic front-hippocampal circuits that show associated with the memory temporal and not with the clock speed, not taking, therefore, the immediate changes, but gradual due to loss of temporal referential stored [11].

Dopaminergic antagonists distort TP in the range of milliseconds to seconds, assigning these effects to dopaminergic modulation of the basal ganglia, which are important structures playing role in synchronization process and regulation of the clock speed [70]. In addition, patients with PD may exhibit different temporal processing deficits when tested with or without medication [73]. These effects may be dependent on the dose and other factors that alter the DA levels [30]. Similar effects of pharmacological manipulation with L-dopa on temporal behavior were observed in rats with lesions in substantia nigra of the midbrain, indicating that the increase of the dopaminergic transmission can reduce the effect of lesions in regions of high dopaminergic connectivity [11,74]. The interval time is also regulated by executive functions such as working memory and attention, which are dependent on the PFC [42]. The dopaminergic modulation can also cause distortions in temporal perception through cortical–striatal connectivity encodings. [11,30].

Experiences with DA agonists and antagonists show indirect effects that show individual variations [70]. Lake and Meck [70] observed that subjects who reported low taste for drugs obtained horizontal displacement to the left in timing responses consistent with the increase of the clock speed mediated by (d-amphetamine) agonists. On the contrary, individuals who reported the use of d-amphetamine showed displacement for right in timing functions, which may be due to the distribution of resources between attention to timing and other aspects related to non-temporal effects of drugs, such as euphoria [70]. Matell and Meck [62], in an experience with continuous or intermittent cocaine administration, showed that sensitization can play a considerable role in the changes induced by drugs in TP. Other factors such as

the training bases lines of a particular activity of TP can also change the performance during the job.

Cheng, Hakak and Meck [75], in different interval peak tasks in groups of rats, observed that the rats that had received a prolonged training level did not present the typical effect of changes to left in horizontal timer functions, but instead they exhibited a disturbance of temporal, dose-dependent control after the administration of methamphetamine. Such experiences show how the familiarity baseline with the task or with the drugs can lead to different performances during the temporal processing [75].

In addition to classic DA agonists and antagonists, L-dopa, a DA precursor, increases the DA levels in the brain [76]. In healthy adults, its administration during the tasks execution of peak range has the effect of lengthening the reproduction of seconds intervals previously learned [77]. From previous models, the increase of the DA levels promotes an increase of internal clock speed and consequently a shorter reproduction of a time interval. However, unlike the effects of DA agonists, which are proportional to the increase in the interval duration, the size of the error was similar in the different durations, which does not suggest a direct effect on the clock speed. Instead, it was suggested that the changes occurred from the directed attention to time, which was reduced [77]. In the same way, DA agonists and antagonists affect attention levels for the time intervals, this, seen in experiments with rats through tasks of peak interval, in which the signal that is being timed is underestimated or overestimated due to attention modulations, this way promotes the adjustment in order to restart their internal timing mechanism [64].

Cognitive aspects (memory and attention) associated with dopamine

Temporal information processing and the prediction of future events are abilities needed for the performance of many everyday activities. The concept of TP refers to the more passive and perceptive aspects of cognitive time management such as perceiving temporal intervals and the ability to estimate temporal delays [78]. Brain mechanisms involved in the awareness of the passage of time have been studied by several researchers (Table 1) [74,79]. Moreover, in the striatal dopaminergic system and PFC are believed to be involved in attention, working memory and impulse control [25,80]. These brain systems are related to the modulation of TP and the timing of motor acts [25].

Processing of temporal information is a complex and distributed function of the cognitive domain, engaging multiple brain regions, including basal ganglia, the frontal cortex and the cerebellum [26,79]. Modern functional imaging studies using fMRI and positron emission tomography (PET) have shown that the processing of time, motor timing and time estimation are associated with activation in right prefrontal regions [25,81,78]. In most of these studies, the prefrontal activation during timing functions is in the right hemisphere. A fronto-striatal network is thought to be the neural basis of the internal clock [82,83]. According to Coull et al. [82], the striatum has been proposed as the neural substrate for the 'beat frequency' model of timing. Mesocortical and mesostriatal dopaminergic pathways, also known to modulate interval timing, are of major importance for action planning and decision-making [75].

Lewis and Miall [79] proposed that in addition to the mesostriatal dopaminergic pathway projecting from the substantia nigra to the striatum, the dopaminergic system includes a mesocortical pathway with projections from the ventral tegmental area to the PFC. This could provide an evidence that mesocortical dopamine might influence cognitive TP by the anatomical overlap between the prefrontal regions innervated by this pathway and those known to be involved in time measurement [79].

Attentional processes may influence each stage of temporal information processing [84]. The more we attend to an event's duration, longer it seems to last. Increased attention to time allows more accurate processing of temporal pulses throughout the stimulus duration by enhanced neural activity in functionally specialized regions [82]. It has been proposed that the less attentional resources are allocated to timing, the more the on-line accumulation of temporal 'pulses' throughout the stimulus duration may be compromised [82,85]. Coull et al. [82] suggested that the parietal and prefrontal activations are unlikely to be due simply to attentional load, and pointed that these regions may thus contribute more specifically to the process of temporal attention.

Memory functions are needed for the perception of the passage of time. The processing of time is thought to be done using the same dorsolateral prefrontal cells that are known to be involved in working memory [79]. Watanabe et al. [86] showed an increase of prefrontal dopamine levels during working memory tasks. Numerous neuroimaging studies evidenced that the right hemispheric DLPFC is strongly associated with working memory [87]. This region seems mostly involved in time abilities influenced by cognitive functions, like attention and working memory, and may be crucial for encoding, storage and retrieval of time information [26].

Individuals with lesions on frontal lobes can show substantial impairments in the estimation of time intervals [88]. Different neurological diseases have shown

impairments in time estimation and motor time, characterized by a dysfunctional connectivity between basal ganglia and PFC due to altered dopaminergic transmission, such as PD, schizophrenia and ADHD [89–92]. Drug abuse [25] and brain lesions [78,93] also provoke deficits in temporal information processing. In PD, whenever there is a decrease of dopaminergic activity in the basal ganglia, patients show deficits in motor timing, duration discrimination [25], work memory, attention and strategic processes [84].

In summary, we found that the temporal information processing is affected by dopaminergic system. Memory and attention are cognitive abilities intrinsically related to the perception of time duration and the passage of time. Impairments of the dopaminergic transmission as well as the cognitive functions can produce changes in TP.

Relationship among motor control, dopamine and TP

TP is involved in several executive functions [94], and has been widely correlated with the control strategy [95], which relates to the neural recruitment process, which human beings and animals use to coordinate the muscles involved in a particular motor performance [96]. In this way, the motor control is a complex process, which involves central and peripheral structures [27]. Therefore, TP for being built into this ability needs an integration of sensory information (i.e. environment information) with internal physiological information, to promote appropriate timing to generate movement or desired action [96].

At present, it is believed that the motor coordination in addition to involving structures considered as macro-structures, the micro-environments adjustment is also needed, such as, specific cerebral areas, network connections, time and appropriate concentration of neurotransmitters in synaptic clefts [28], and a supposed efficiency in these multiple micro communications [97]. The implementation of the motor action also involves feedback mechanisms (or feedback), either during the implementation when there is time to do so, or in preparation a priori, in cases of ballistic movements. That is, movement control is associated with several temporal landmarks, which in practice reflects an almost infinite repertoire of moves [98].

This way, the movement production is a combination of temporal and neural aspects resulting from a dynamic and complex sequencing. Among the neural aspects involved in motor coordination, neurotransmission is one of the fundamental elements. To maintain an integrated relation with the environment during the execution of a specific task, this coupling process at chemical synapses is performed in fractions of milliseconds [99]. Thus, the communications between the nerve cells must meet this basic premise. DA is a neurotransmitter that, together with other neurotransmitters, assists in the control and regulation of various brain functions [100], which belong to the monoamines class, especially to the catecholamines group. Tyrosine hydroxylase enzyme activation transforms the amino acid tyrosine to L-dopa, which is later decarboxylated producing DA. DA participates in varied functions including reward, pleasure, emotional aspects in general and adjustment of motor behavior. DA produces effects in the basal ganglia, which has a fundamental role in regulating and movement control [11]. This supposed regulation involves certain DA optimum amount in the maintenance of the function integrity. Dopamine acts via several receptor-subtypes (D1-5). In addition, dopaminergic levels inhibit the indirect pathway activity and produce an increase in the direct pathway of basal ganglia circuitry [101]. In PD, DA deficiency occurs, which causes delayed, slow and uncoordinated motor actions. Conversely, the excess of neurotransmitter in question produces excess of movements, and repetitive tics.

Relationship between TP, dopaminergic concentration and motor control is established by neural timing mechanisms in a modular fashion [27]. In the control of motor activity, the outcome must be correct in milliseconds range, which distinguishes the effectiveness of implementation, or not, of the action. This temporal accuracy in milliseconds range is fundamental since coupling between task, environment and performer in complexity of producing a motor gesture is constrained to milliseconds range. The coherence between three elements (task, environment and performer) enabled by learning processes and neuroplasticity is responsible for construction of an internal model of the external surroundings. This internal model is hierarchically represented by different levels, namely, genetic, molecular, cellular, circuits (synapses and neurons), systems, behavior and cognition. These different levels interact dynamically and temporally, in the construction of the internal model [18]. The importance of the internal model, or reference system, is that it contains information of the three aspects (environment, the task and the individual) in a very complex way. That is the brain throughout the development process incorporates, depending on who we are and through our practices, different aspects of the environment and the task [102]. Via mechanisms that are not well understood, plasticity of neural circuits induced by external tasks, the brain creates a representation of the environment. Thus, this may be responsible for incorporating time-information into

neural circuits during execution of tasks involving external environment via poorly understood mechanisms. The dopaminergic process participates in this process by regulating the mechanisms and patterns of neural circuitry through complex and sophisticated feedback mechanisms [29].

Neurological diseases associated with dopaminergic system vs. TP Schizophrenia

Schizophrenia is a multifactorial and polygenic psychiatric disorder, in which there is a disintegration of the thought processes and emotional response capacity, and it presents hearing hallucinations, delusions and paranoia. [103,104]. It has neuropathological bases attributed to the alternation in DA concentrations in the brain regions [105]. Due to the role of dopaminergic system, this alteration of DA concentrations in schizophrenia also affects the coordination ability and temporal information processing in the brain [106]. In this context, schizophrenic individuals have abnormal temporal perception due to the involvement of ineffective DA recruitment at the mesolimbic pathway [105].

Dysfunction in perceptive time capacity in individuals with schizophrenia is believed to be due to genetic alterations that modifies the DA concentration [59,107–109]. Thus, TP's distorted neurobiology is attributed to genetic alterations and neural communication between the inadequate striated system and PFC. It is noteworthy that Ward [110] postulated that schizophrenia is a functional hypodopaminergic state that affects the PFC and the mesolimbic pathway. Together, the synchronism of deficient frequency bands can contribute to some positive schizophrenia symptoms, such as the disorganized behavior and paranoic delusions [111].

Accordingly, the involvement of neuroanatomical degenerations and the modulation of cerebral chemical composition [112,113] can be related with coordination disturbances and processing of the information underlying cognitive functions [22]. With this, a wide variety of modified cognitive fields have been identified in individuals with schizophrenia, for example, the attention [108] and the memory [114]. These defects in cognitive function execution are related with deficits in perception as well as information processing [115].

Bonnot et al. [116] have combined TP neuropsychological investigations and their association with the dopaminergic system modulation in schizophrenia to investigate cognitive behavior [117]. The approach in this study by Bonnot et al. [116] uses temporal discrimination tasks. Their results showed a tendency of time overestimation for patients with schizophrenia (Table 2). Uhlhaas et al. [118] showed electrophysiological and anatomical abnormalities in the oscillatory neurons activity, and proposed a central role for these abnormalities in schizophrenia pathophysiology. In patients with schizophrenia, activity synchronization of the bands beta and gamma of the electroencephalogram are shown to be abnormal, suggesting a crucial role for dysfunctional oscillations in cognitive deficits and the other classic abnormalities of the disease. Dysfunctional oscillations may result from anomalous networking of cortico-striatal and mesolimbic pathways [118].

In an fMRI study, Davalos et al. [119] compared the performance of a milliseconds-range time comparison task, in patients with clinically stable schizophrenia and healthy subjects, which has two levels of difficulty. The result did not show significant differences between the groups, but in relation to the reaction time, the group with schizophrenia made more categorization errors than the controls at both difficulty levels [108,120]. In general, patients with schizophrenia showed lower activation levels in neural circuits associated with the timing of the time interval [116]. The differences between the groups led the researchers to propose that the discrimination failure of duration of milliseconds range in patients with schizophrenia is consistent with a deficit of temporal processing [30].

Penney et al. [121], in a study of temporal discrimination, verified how groups formed by (individuals at high genetic risk for schizophrenia vs. healthy non-carriers) react through auditory and visual stimulus with intervals of 3 and 6 s. The results show that the psychometric functions for visual stimuli are displaced more to the right in the participants with genetic risk for schizophrenia in comparison to the healthy non-carriers. The location of the psychometric functions to auditory stimulus did not differ between the groups. This is in agreement with notion of the role of internal clock speed in the ability of the subjective timing functions [122], also consistent with the role of dopaminergic system based on genetic data [123,124].

Other studies of temporal discrimination tasks in healthy individuals and patients with schizophrenia showed that patients with schizophrenia performed poorly in the discrimination task, and were inaccurate in sound sequences reproduction and replication tasks [125,126]. Thus, the study by Elvevåg et al. [127] investigated the basis of cognitive alterations, revealing a deficiency in temporal information processing due to neuroanatomical changes in the dopaminergic communication between the PFC and the hippocampus. The results further suggest that individuals with schizophrenia have a distorted subjective perception of time. TP in individuals with schizophrenia is processed by clocks that are slow, which is responsible for reduced accuracy and precision of the interval timing [104]. Despite the

growing interest in timing functions of the brain in the schizophrenia pathophysiology, there are very few studies directly examining the TP by genetic analyzes.

Parkinson's disease

PD is widely known for presenting with chronic neurodegenerative changes affecting the substantia nigra [62,128–130]. The destruction of the nigrostriatal dopaminergic neurons gradually decreases the DA levels, which affects the control of voluntary movements. Nigrostriatal dopaminergic neurons are also implicated in various executive and cognitive functions (i.e. memory, attention, decision-making and perceptive stimuli capacity) in addition to the accuracy and time judgment [131,132]. Accordingly, PD typically exhibits abnormalities, such as bradykinesia, resting tremors, muscle rigidity and postural instability, and thus impairs most of the common daily activities [133,134].

Dopaminergic transmission is correlated with TP, as DA levels predict a modulation in the subjective perception of time (Table 2) [135]. Thus, the reduction or exacerbation of DA concentrations through the modification of the internal clock speed can lead to different changes in synchronization ability and interval timing by the brain. In addition, it may be also due to time intervals perceived as longer or shorter [22,135]. Modulations of the subjective perception of time and dopaminergic levels are related by common areas that are affected by DA depletion, i.e. cortical and subcortical regions, which act jointly in the judgment of time interval [136].

The DLPFC, supplementary motor area, posterior parietal cortex, anterior cingulate cortex, suprachiasmatic nucleus, cerebellum and basal ganglia are found to be important for milliseconds-seconds to minutes [137,138]. The basal ganglia are the most affected regions in PD especially as a network hub in thalamus-cortico-striatal and nigrostriatal, which are important for dopaminergic neurotransmission [139,140]. This way, TP in addition to being modified by environmental interactions, is modulated by dopaminergic levels [141]. It promotes a more elongated TP when there is an increase in the DA levels and to a reduction of the time window when in low concentration [142]. For this reason, several studies are researching the involvement of DA in TP tasks through visual stimuli and/or hearing, with operations of concomitant administration of agonist drugs and dopaminergic antagonists [143]. Wiener et al. [23] observed that individuals with PD without the use of agonist of DA medication showed a deviance to the left in timing tasks, i.e. they underestimated the time while subjects in drug treatment approached closer to the hit, thus strengthening the hypothesis that DA influences the timing.

In spite of this, Parker, Ruggiero and Narayanan [144] did not observe a deficiency in the generalist timing or temporal reproduction of short periods. In the same way that individuals with PD demonstrated inadequacy in the temporal estimation and repetition motor tasks in long intervals. In addition, there was a relationship between short-term memory decline and the accuracy of the time target production. Even though the DA administration in PD did not result in an improvement of the memory impairment, the dopaminergic agonist administration accelerates the internal clock, while the antagonist decelerates. Therefore, it suggests that changes in timing functions depend on the different neural mechanisms involved. Thus, the most common experimental alternative approach is to elucidate the role of DA in timing process and conscious and unconscious perception of time [145].

Attention-deficit/hyperactivity disorder

ADHD is a neurological disorder with deficiencies beginning during childhood, and it has primary diagnosis symptoms of inattention, hyperactivity and impulsivity [146,147]. The disease is multifactorial due to the interaction between genetic factors (i.e. changes in dopaminergic receptors) [148,149], neurobiological and environmental factors that affect the initiation and the severity of the disease [146,147]. Neuroimaging studies in humans and rats suggest that ADHD is related to a deficiency in the concentration and dopaminergic neurotransmission [150]. Thus, changes in DA chemical concentration determine several behavioral phenotypes, ranging from anxiety, impulsivity the difficulty of social interaction [151,152]. As well as a reduction in the volume of the caudate nucleus, and thus, makes it difficult the information transmission to brain areas, as for example, the PFC and nucleus accumbens in striatum, that play a key role in the executive functions [153,154]. Thus, there is an impact on TP due to the deficiency in the ability to interpret stimuli originating from the environment and the capacity to encode time intervals [155].

Neurocognitive factors elucidated by nuclear magnetic resonance studies indicate that individuals with ADHD may have functional deficits in the timing ability of supra-second range [155,156]. Since these neural networks are linked with the impulsivity behavior, which is defined as a premature response and instantaneous gratification, performed before all available information [157]. It is suggested that deficient timing functions are the key to the behavioral profile of ADHD [30,158].

Chen et al. [159] indicated that children with ADHD have perceptive disabilities including TP. In this context, they have inaccurate performance in reproduction task

and motor production. This study, which included groups of 10 children of both sexes with ADHD and without ADHD, revealed that children with ADHD showed abnormal temporal processing and delay in motor response during jumping ropes activities. Zimmer [160] reviewed PET studies that studied mechanisms that lead to dopaminergic deregulation, which suggested abnormalities in relation to DAT. Review of past work by Zimmer [160] also suggests abnormalities of fronto-strial circuitry in ADHD. Hypodopaminergic state is now believed to underlie the pathogenesis of ADHD [146].

Abnormal time processing is now considered as a phenotype characteristic of patients with ADHD. Furthermore, it is now believed that a fast internal clock may be responsible for abnormal temporal processing [156]. Studies by Hwang-Gu and Gau [161] provide evidence that inaccurate timing may be associated with the deficiency in the cognitive processing of sustained attention for a potential stimulus [161], as well as possible deficits in dopaminergic neurotransmission, for example, affecting the fronto-striatal circuits [162,163].

Noreika, Falter and Rubia [155] and Pan et al. [53], in a review, argue that behavioral phenotypes in ADHD are present in relation to the interval timing functions. On the basis of genetic and neurofunctional aspects and the dopaminergic system, respectively. This way, the evaluation demonstrates that ADHD patients suffer losses in different areas of temporal processing (i.e. time engine, time of perception of sound stimuli and visual stimuli), from milliseconds to minutes. The most consistent deficiencies in ADHD are found in sensory-motor synchronization, temporal discrimination tasks and time reproduction. Note that these are executive functions wherein dopaminergic neurotransmission plays an important role. Moreover, molecular alterations in genes that play a role in determining the DA levels, such as for example, *DRD2* and *SLC6A3* gene have attracted the most attention, since the decrease in the expression of these genes is correlated with poor performance in tasks of stimuli perception [164].

In summary, ADHD is strongly correlated with deficits of temporal processing, which is supported by the data from the study of neurocognitive, genetic and functional aspects, mainly associated with the reduction of dopaminergic action, also affecting executive functions and perception of stimuli processes.

Depression

TP is subjective and often depends on the situation lived at a certain moment [165]. In particular, time seems to move more slowly in depressed individuals [166]. Depression is defined as an affective disorder characterized by pessimistic thoughts, feeling of sadness or emptiness, in which the mesolimbic system is involved due to the deficiencies in neurotransmission and neural interconnections [167]. The results of Blewett [168] showed that the reduction of the levels of dopaminergic receptors in cortical regions and the hippocampus frontal plays an important role in this phenomenon.

In depression, the internal clock is faster, leading to the accumulation of more pulses that is responsible for the time interval in relation to a healthy individual [169]. The changes in the rate of the internal clock in depressive may be influenced by changes in the neurotransmitters mechanisms [170]. In particular, the internal clock mechanism depends on the dopaminergic level, in which the DA levels' decrease is related to the deceleration of the clock speed, while speeding up the internal clock is caused by the increase of DA levels [15].

Depression influences the cognition, which is due to the activity of pacemaker-accumulator in the timing ability and time judgment (Table 2) [62]. Several studies in last several years observed the performance in timing tasks between depressive and healthy individuals. Different timing tasks were used in these studies, which included time estimation, time production, time reproduction and discrimination of duration to study the effects of depression on the TP [171]. In one study, depressive individuals underestimated the time interval of 30 s by 6 s, which was accompanied by a greater error in time estimates [172]. Pharmacological experiments showed that the time estimation tasks, in which the duration of time intervals is underestimated, are associated with abnormal DA levels. As a result of the inactivation of dopamine receptors D2, while other receptors, type D1, have no such effect on the TP modulation [173].

In time-production tasks, which produces a specific time interval, marking its beginning and end, depressed patients produce shorter intervals, due to the more rapid pace of internal clock when compared to healthy individuals [166,174]. In addition, in the reproduction task, individuals are required to reproduce a time interval previously presented, by pressing a button to mark the beginning and the end of the interval, and it was observed that the clock speed did not change between depressive and healthy individuals [72].

Cognitive factors such as attention and memory need a timer circuit in the range above seconds, while milliseconds are assumed specifically by the cerebellum, mainly based on sensory mechanisms [175]. Msetfi, Murphy and Kornbrot [171] studied task time discrimination short ($<$300 ms) and long ($>$1000 ms) time in depressed students, which revealed that depression affects the ability to maintain attention in relation to the duration, and thus, students with depression showed impaired

performance in discriminating longer periods, while discrimination of shorter intervals was normal. Sévigny, Everett and Grondin [176] argued that distraction can easily create the feeling in depressive individuals that minutes seem 'a century', this distortion of passage of time is related with the way they control their attention, because of their inability in maintaining the attention focused on an event [167,170].

Autism

Autism is a disorder with huge symptomatic variety within the human development, with changes in their capacity of attention and working memory. Behavioral changes have been shown to impact on the TP (Table 2) [177]. Various cortical and subcortical areas are implicated in autism, such as the PFC, basal ganglia and cerebellum [178]. Moreover, these regions have dopaminergic circuits, which influence the perceptive capacity and time measurement [179,180].

Some of the symptoms of autism are known to be consistent with Scalar expectancy model [181,182]. In addition to TP, the working memory function and voluntary exchange of attention is of paramount importance for this model, hence the interest in research on how autistic realized the passage of time. Allman, DeLeon and Wearden [182] presented to children with autism and without autism a bisecting temporal task, using two pairs of durations (1 s vs. 4 s and 2 s vs. 8 s). Children with autism exhibited the point of subjective equality which was lower than that detected in healthy children. The estimate of the bisecting point was shifted to the left in relation to the autistic spectrum, which suggests a deficit working memory. Thus, the individuals with autism have a predisposition to decrease longer periods of time.

De Boer-Schellekens, Eussen and Vroomen [183] used multisensory stimuli (flashes, simple beeps, claps and expressions with one syllable) to analyze the timing in participants, aged 16–22 years with and without autism. They judged the interval between the visual and auditory stimuli, and found sensitivity to multisensory temporal activities to be diminished in all types of stimuli, presented to the autistic patients, which demonstrates that autistic children have a lower capacity to distinguish multisensory stimuli. In another study, Stevenson et al. [184] investigated the changes of multisensory perception in the presence of simple and complex stimuli, comparing children with autism with high performance in speech production with normal children. It was observed that a temporal processing was less precise with an increase of the complexity of the task in both groups. Soon, the deficit in judging the time triggers changes in the context of language and communication.

Szelag et al. [185] compared the performance of individuals with autism aged between 9 and 16 years. Visual and auditory stimuli were presented. The visual stimuli consisted of a green rectangle displayed on a screen while the auditory stimulus consisted of a tone of 200 Hz with the durations patterns between 1 and 5.5 s. It was observed that autistic children reproduce time intervals shorter or longer, depending on the type of stimulus. In addition, the autistic patients present changes in the executive function areas, which are of great importance for the timing functions [186]. Szelag et al. [185] demonstrated anatomic changes in different brain areas, such as, cerebellum and medial structure of the temporal lobe, which are fundamental to social and emotional cognition, and the DLPFC, which is crucial for the working memory [187].

Limitations of existing research

The majority of the findings are based on cross-sectional methods; further longitudinal studies are needed in order to model within-person change and avoid cohort effects, have been conducted. There are also other sources of variability within the literature that may have limited the conclusions drawn from this review. Some of these factors, such as the sensory modality, intensity, size, complexity and familiarity are not standardized in the various studies of the TP, making it impossible to determine a full association with dopaminergic levels. This plethora of effects poses a serious challenge to researchers seeking time-bound unifying principles. Limitations involved population size and timing phenotypes in relation to sample size in genetic research. In addition to changes in methodologies of neuroimaging analysis on cognitive tasks in healthy individuals or patients with some neurological disease that may affect the judgment of time.

Conclusion

Finally, we must not forget the importance of the dopaminergic neurochemical mediation at the neurobiological aspects of TP in all levels: the molecular and neurofunctional; moreover, psychopharmacology, motor control and neurological diseases are related to the depletion or DA improper recruitment. The above are mutually informative approaches in the study of TP, which are useful to investigate the neuroanatomical substrates of time interval, providing a functional overview neurochemistry in mechanisms for time synchronization. Furthermore, it leads us to complement the studies dedicated to TP and neural timers distributed in the brain. Reciprocally, the approach of the dopaminergic influence in TP is useful in

neurogenetics applied to neurosciences, since it allows us to help in the elucidation of behavioral phenotypes and study the areas of the brain that are involved in the dopaminergic circuit, and their integration with the perceptual time mechanisms.

Authorship contributions

V. Marinho, T. Oliveira, K. Rocha, J. Ribeiro, F. Magalhães, B. Velasques, P. Ribeiro, L. Di Giorgio and J. Bittencourt wrote the initial manuscript.
T. Bento, M. Orsini, G. R. Pinto, D. S. Gupta, V. H. Bastos and S. Teixeira with editing, reviewing, scientific input and final presentation.

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