



# Methylphenidate modifies activity in the prefrontal and parietal cortex accelerating the time judgment

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## Abstract

Methylphenidate produces its effects via actions on cortical areas involved with attention and working memory, which have a direct role in time estimation judgment tasks. In particular, the prefrontal and parietal cortex has been the target of several studies to understand the effect of methylphenidate on executive functions and time interval perception. However, it has not yet been studied whether acute administration of methylphenidate influences performance in time estimation task and the changes in alpha band absolute power in the prefrontal and parietal cortex. The current study investigates the influence of the acute use of methylphenidate in both performance and judgment in the time estimation interpretation through the alpha band absolute power activity in the prefrontal and parietal cortex. This is a double-blind, crossover study with a sample of 32 subjects under control (placebo) and experimental (methylphenidate) conditions with absolute alpha band power analysis during a time estimation task. We observed that methylphenidate does not influence task performance ( $p > 0.05$ ), but it increases the time interval underestimation by over 7 s ( $p < 0.001$ ) with a concomitant decrease in absolute alpha band power in the ventrolateral prefrontal cortex and dorsolateral prefrontal cortex and parietal cortex ( $p < 0.001$ ). Acute use of methylphenidate increases the time interval underestimation, consistent with reduced accuracy of the internal clock mechanisms. Furthermore, acute use of methylphenidate influences the absolute alpha band power over the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and parietal cortex.

**Keywords** Methylphenidate · Prefrontal cortex · Parietal cortex · Time estimation · Alpha band · Electroencephalography

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## Introduction

The psychostimulant substance prescription has increased considerably in recent years, whether for therapeutic purposes in the cognitive enhancement [1–4]. Among these substances, methylphenidate (MPH) has been the drug of the first choice for prescription in young people with attention deficit disorder [2, 5–8]. By acting as a central nervous system (CNS) stimulant, MPH promotes an increase in the frontostriatal circuit activation of dopamine and norepinephrine [9, 10]. MPH has a large effect on the prefrontal cortex (PFC) and parietal cortex (PC), which are related, among other functions, to the judgment of temporal perception [6], attention, and memory [6, 8, 11, 12]. Studies have related the PFC in association with PC to the temporal perception processing [13–15] due to its performance in the primordial components of internal clock control, like memory and decision-making [16–18]. Pieces of evidence suggest that the right PFC activity decreases when the time interval is memorized, while in the left PFC, the

activity increases due to the need for the attentive process to interpret the time interval [19]. In particular, there is continuing debate whether the ventrolateral prefrontal cortex (VLPFC) and the dorsolateral prefrontal cortex (DLPFC) participate bilaterally or there is predominance of one of hemispheres [20–22]. In this context, the analysis of methylphenidate actions may answer if an acceleration in the temporal processing phases, or better performance in the task, is associated with the changes in the cortical activity in the left and right PFC.

It has been found that the time interval interpretation precision is directly related to the working memory [23]. Broadway and Engle [24] evaluated the time interval interpretation in 52 healthy individuals previously classified by tasks of low and high working memory capacity at supra-second intervals. They observed that participants with higher working memory capacity present greater accuracy in time interval judgment. In this context, the MPH acute use has shown improvement not only in working memory but also in the attention and memory of short and long term [25–28] with influence on the time interval interpretation [29]. Mehta et al. [5] also studied the MPH effect on working memory in attention deficit hyperactivity disorder subjects and found that MPH improves working memory performance and reduces blood flow in the DLPFC and posterior parietal cortex. In fact, when MPH influences the cognitive functions related to the time interval interpretation, it leads to improved performance in the task and it modifies the cortical activity in the areas related to the time perception [30, 31].

The neurophysiological and behavioral analyses are passive to determine phenotypes associated with the timing [32]. The literature traces an association profile with neurophysiological variables and behavioral performances, for instance, timing tasks by visual, tactile, or auditory stimuli in humans and other species [33]. Differential sensitivity to stimuli has been associated with absolute power activation of electroencephalography (EEG) in the prefrontal cortex, through energy measurements within the alpha frequency [34, 35]. This fact is supported by EEG studies associated with cognitive tasks, since neural oscillations may be important to individual differences in executive actions, cognition, and perceptual ability [35]. For instance, Dockree et al. [36] assessed care in 40 healthy adults under MPH use during a time perception task. The authors showed that there was an improvement in the attentional level with a concomitant reduction in alpha band activity in the PC.

Although papers have examined the MPH effect in PFC through alpha band amplitude to study attentional processes [36–40], memory [1, 41, 42], and time perception [43–45], it is still unclear whether MPH represents changes in temporal information and how it is represented in the PFC and PC activities. To understand the MPH effect on PFC and PC, it would be interesting to examine the time estimation pattern

changes at different time intervals in the supra-seconds scale, demonstrating the attentional demand variation and the participant's working memory recruitment during timing proposed in the study. In this study, we created a behavioral task in which the subjects estimate four time intervals in the supra-seconds' scale, and investigate if the acute MPH use influences the performance and judgment of time estimation as well as alpha band absolute power activity in the prefrontal and parietal cortex.

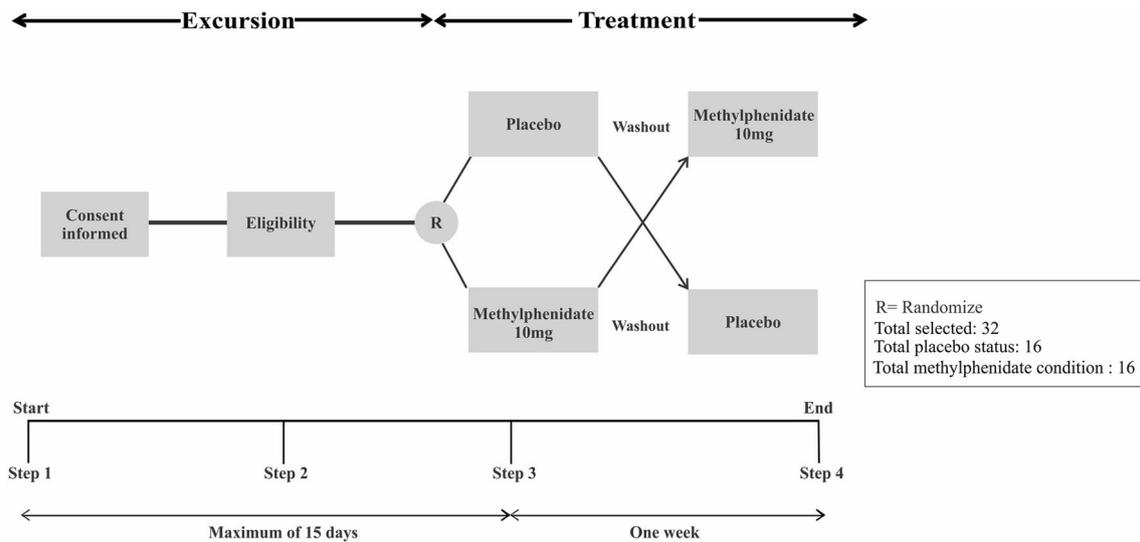
## Materials and methods

### Sample

We recruited 50 healthy male individuals ( $22.6 \pm 1.96$  years, age group = 20–30 years), students of the Federal University of Piauí (UFPI), belonging to a population from Brazilian Northeastern. Only right-handed individuals were selected based on the Edinburgh Inventory [46], and was evaluated the Mini-Mental State Examination (MMSE) of the participants ( $28 \pm 1.5$ ). All participants were not using any substance that could influence brain activities (e.g., tobacco, coffee, alcoholic beverages, caffeine-containing foods, or medications) 14 h before or during the study period. All subjects underwent a medical evaluation to exclude those with neurological or motor diseases that would impair the task performance as well as any contraindications to the MPH ingestion. However, 12 participants were eliminated ( $21.75 \pm 1.71$  years), 10 participants because they did not comply with the necessary time restriction for use of the substance that could influence brain activities and 2 participants because of chronic use of medications (corticosteroids). Therefore, the remaining 38 subjects ( $22.87 \pm 1.97$  years) were randomized to a 1:1 rate, double-blind for two conditions in the following sequence: 19 subjects received MPH (MPH-10 mg) and later received placebo (starch) and 19 subjects received placebo first and followed by drug. Of the 38 subjects, six dropped out from the study for the following reasons: four did not complete the task because they felt discomfort during collection and two subjects refused to ingest the capsule. Finally, 32 subjects ( $23 \pm 2$  years, age group = 20–30 years) completed the study. The experiment was approved by the Research Ethics Committee (no. 1607069/2016), according to the Human Research Ethics Criteria included in the Declaration of Helsinki.

### Experimental procedures

Subjects received 2 days of treatment with 7-day washout. The EEG signal was collected during the resting state (3 min) and at the time estimation task, with 1.5 h after the placebo or MPH capsule ingestion [47, 48]. The time estimation task was performed in 2 blocks with 10 tracks per block



**Fig. 1** Experimental study design

(Fig. 1). This one consisted in the yellow circle presentation, with a ray of 2.5 cm (90 pixels) in a monitor of 20" (1600 × 900 pixels of resolution) with a black background. The circle appeared in the center of the monitor and remained on the screen for four different time intervals (1, 4, 7, or 9 s) in a random sequence. After the circle “disappears,” it is followed up by the question: how much time has passed? The subject then types the answer using the keyboard to provide estimated time interval and presses the enter key to start a new track. Subjects were instructed not to account for the time interval duration while the stimulus was presented (Fig. 2).

**EEG recording**

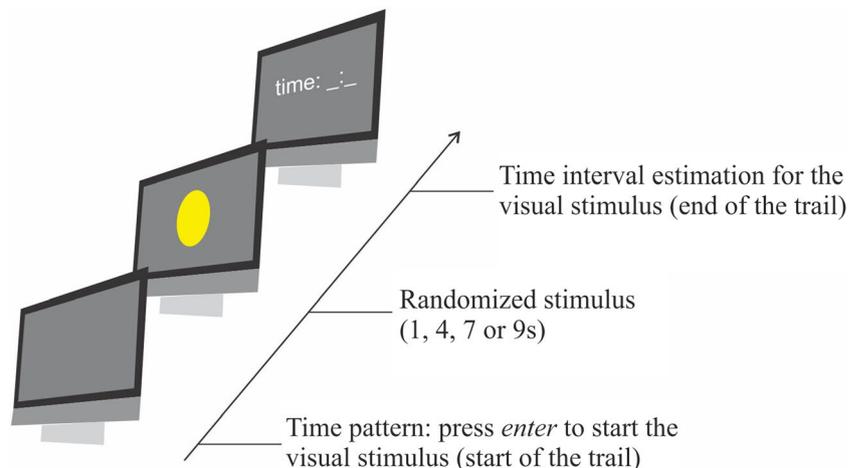
Participants stayed in a sound and electrical insulation room. They were seated on an arm-rest chair to minimize any muscular artifact during EEG signal acquisition. The 20-channel continuous EEG was recorded by Braintech 3000 amplifiers (EMSA-Medical Instruments, Brazil). The silver/silver

chloride electrodes were positioned by an electrode lid equidistant by means of a nylon cap prefixed with the international 10–20 system, including binaural reference electrodes [49]. The impedance of the EEG electrodes was kept below 5 KΩ. The acquired data had a total amplitude of less than 100 μV. The EEG signal was amplified with a gain of 22.000 Hz, analogously filtered between 0.01 Hz (high-pass) and 60 Hz (low-pass) with 240 Hz using the Data Acquisition software (Delphi 5.0) developed in the Neuro-innovation Technology & Brain Mapping Laboratory. Subsequently, the EEG signals were processed by the Neurometrics Program (NxLink, Ltd., USA) and the alpha band absolute power was extracted.

**Electrode spatial location**

The leads of the F3, F4, F7, and F8 electrodes of the frontal region were selected, which corresponds to the PFC because it is an important site of MPH performance [7], in addition to its

**Fig. 2** Time estimation task performance



functions related to the working memory, attention, and time interval estimation [7, 26–28, 50]. The leads of the P3 and P4 electrodes were also analyzed due to their relations with PFC and the involvement with the time interval interpretation in supra-seconds [30, 51].

## EEG data processing

A visual inspection and independent component analysis (ICA) were applied to identify and remove all remaining artifacts produced by the task. The ICA is a routine contained in the EEGLAB software, which was applied to remove other possible artifact sources, such as sweat and muscular tension. The overall rate of removal after ICA was less than percentage 20. Only the remaining epochs were part of subsequent signal processing and statistical analysis. Data from individual electrodes that showed contact loss with scalp or high impedance ( $> 5 \text{ K}\Omega$ ) were not considered. A classical estimator was applied to the spectral power density (SPD), estimated from the Fourier transform (FT), which was performed by MATLAB (Mathworks, Inc.). EEG parameters were reduced to different periods, according to the time interval. Cortical modification analyses were performed for 1 s, 4 s, 7 s, and 9 s. For each time, the EEG time related to 2 s before the visual stimulus start (preparation for the task) and until 0 corresponding to the time estimation task execution was extracted. These procedures were performed for alpha band power in F3, F4, F7, F8, P3, and P4 electrodes due to the relationship with the DLPFC, VLPFC, and PC, respectively [7, 14].

## Statistical analysis

With the aim of achieving a close to normal distribution, the data on alpha band was log-transformed (log 10). The task performance (absolute error) and the time interval judgment (relative error) were analyzed through the paired Student's *t* test on the intervals of 1 s, 4 s, 7 s, and 9 s, after the capsule ingestion. For the neurophysiological variable analysis, two-way repeated measures ANOVA was performed with the condition (placebo vs. MPH) and area (left and right DLPFC and PC and left VLPFC) factors. The possible interactions were investigated with a Student's *t* test. The Bonferroni's correction was considered to interaction analysis with a significance level of  $p \leq 0.025$ . A logistic regression was performed to determine the association between the alpha band absolute power in the DLPFC, VLPFC, and PC in the right and left hemispheres and for the absolute error (AE), and relative error (RE) in each time interval occurred due to the MPH use effect.

The magnitude of the effect was interpreted using the recommendations suggested by Cohen [52]: insignificant  $< 0.19$ , small from 0.20 to 0.49, middle from 0.50 to 0.79, and large from 0.80 to 1.29. The probability of 5% for type I error was adopted in all analyses ( $p \leq 0.05$ ). In order to detect the real

difference in the population, the statistical power was interpreted with 0.8 to 0.9 = high power [53]. All analyses were conducted using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL, USA).

## Results

### Task performance

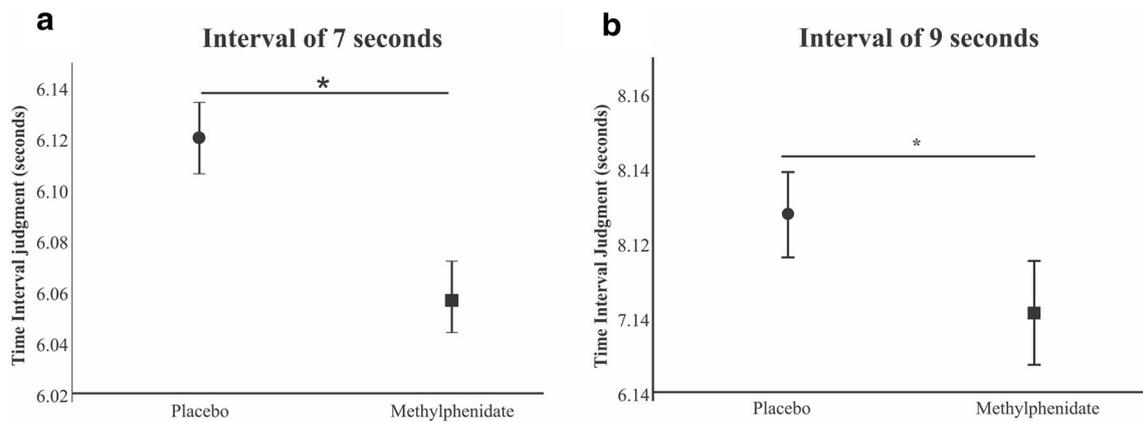
No statistic difference was observed to the AE ( $p > 0.05$ ), but a statistic difference for the RE between conditions was found, with the greatest underestimation to 7 s [ $t(639) = 3.098$ ,  $p = 0.002$ ,  $d = 0.68$ ] and 9 s [ $t(639) = 2.296$ ,  $p = 0.022$ ,  $d = 0.13$ ]. It is found that the MPH had a middle effect to 7 s and insignificant to 9 s (Fig. 3a, b).

### Neurophysiological analysis

A two-way repeated measures ANOVA showed interaction between condition and areas [ $F(4,7970) = 7.067$ ,  $p < 0.001$ ,  $\eta^2 p = 0.04$ , power = 100%]. When analyzed, significant interaction was observed between the conditions in the left DLPFC [ $t(1655) = 8.175$ ,  $p = 0.001$ , and  $d = 0.21$ ], right DLPFC [ $t(1617) = 6.151$ ,  $p = 0.001$ , and  $d = 0.16$ ], right VLPFC [ $t(1613) = 4.892$ ,  $p = 0.001$ , and  $d = 0.12$ ], and left VLPFC [ $t(1733) = 2022$ ,  $p = 0.043$ , and  $d = 0.97$ ]; left PC [ $t(1700) = 6278$ ,  $p = 0.001$ , and  $d = 0.15$ ]; and right PC [ $t(1713) = 5.071$ ,  $p = 0.001$ , and  $d = 0.13$ ]. The results revealed a significant reduction of alpha band power in the MPH condition in the DLPFC, PC, and right VLPFC bilaterally, but only with large effect in the left VLPFC (Fig. 4). In the cortical area activity analysis within each condition, we observed a difference for the placebo condition [ $F(4,4280) = 21.085$ ,  $p = 0.001$ ,  $\eta^2 p = 0.03$ , power = 100%] and MPH [ $F(4,3690) = 46.049$ ,  $p = 0.001$ ,  $\eta^2 p = 0.06$ , power = 100%] with insignificant effect on the conditions. The post hoc test demonstrated that in the placebo condition, the power between DLPFC and left PC decreased and between the DLPFC and right VLPFC increased. However, after the MPH ingestion, the difference between the DLPFC and the left VLPFC are different from the right PC with a decrease in alpha power (Fig. 4).

### Methylphenidate effect probability on task performance and cortical activity

The logistic regression model was statistically significant,  $\chi^2(4) = 9.955$ ,  $p < 0.0001$ . The model explained 13.2% (Nagelkerke  $R^2$ ) of the variation in MPH use and correctly classified 70.0% of the cases. The sensitivity was 24.2% and the specificity was 92.5, with the positive predictive value of 65.8% and negative predictive value of 66.8%. Of the 14 predictor variables, only the DLPFC and VLPFC bilaterally



**Fig. 3** The main effect for the condition, represented by the mean and standard error to 7 s (a) and 9 s (b). The asterisk represents the difference between the conditions

and the right PC, task performance for the 1-s interval and for the time interval judgment for 7 s were statistically significant (Table 1).

The regression results for alpha band power in the left DLPFC ( $B = -1.27, p < 0.0001, CI\ 95\% 0.18-0.41$ ), right DLPFC ( $B = -0.56, p = 0.004, CI\ 95\% 0.88-0.84$ ), right VLPFC ( $B = -0.35, p = 0.029, CI\ 95\% 0.51-0.96$ ), and right PC ( $B = -0.38, p = 0.035, CI\ 95\% 0.48-0.97$ ) indicate the cortical activity decrease associated with MPH acute use. On the other hand, in the left VLPFC ( $B = 1.26, p = 0.001, CI\ 95\% 2.41-5.11$ ), there was no decrease in cortical activity during timing. In the 1-s interval time, MPH is associated with imprecision in AE ( $B = 0.31, p = 0.005, CI\ 95\% 1.09-1.68$ ) and RE ( $B = 0.22, p = 0.033, CI\ 95\% 1.02-1.51$ ). However, to RE in 7-s interval, the MPH may be related to a greater adjustment in the time interval judgment ( $B = -1.02, p < 0.001, CI\ 95\% 0.16-0.1$ ).

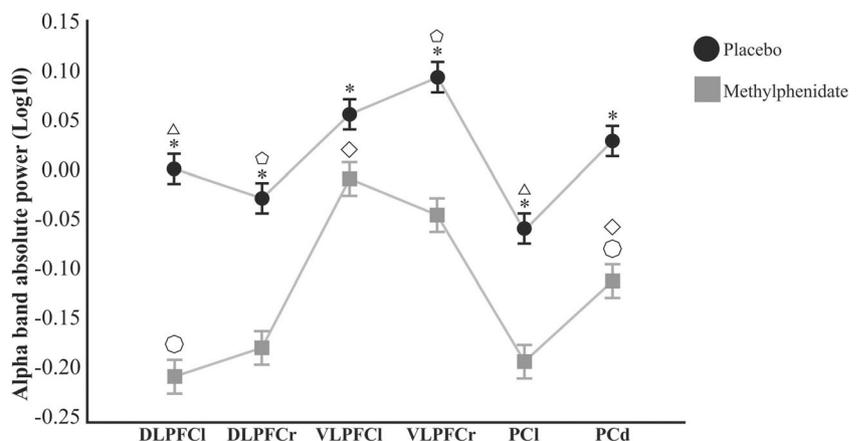
### Discussion

In this study whether the single dose of 10 mg MPH modifies the EEG’s alpha band absolute power in the PFC and PC

during a time estimation task was investigated, with the hypothesis that the MPH modifies the temporal processing phases, leading to improvement in performance in the time estimation task due to greater synchronism between the PFC and PC areas.

Our findings showed that in the intervals of 7 and 9 s, in the MPH condition, in relation to the task performance, showed a greater adjustment regarding the time intervals judgment when compared to the target real time. However, regarding the probability of the MPH effect the time interval performance and judgment, it was observed that in 1 and 7 s there was an association of the MPH administration with AE and RE; in fact, according to Vierordt’s law, people tend to underestimate the longer intervals and overestimate short intervals [54]. This relative variability of time judgment over longer intervals indicates that the MPH effect decreases the visual stimulus interpretation for subjects timing the time interval provided in the task. Longer time intervals are likely to be timed with greater variability than shorter ones, especially when changes in the attentional process occur. Then, the MPH indicates increased attention to the task due to the decrease in the pulse number to the accumulator and causes the subjects to perceive the fastest time [16, 31, 55]. Treisman’s

**Fig. 4** EEG alpha band power in PFC and PC during time estimation task in placebo and MPH conditions. The asterisk represents a statistical difference of  $p < 0.05$



**Table 1** Logistic regression predicting the methylphenidate's use probability to alter the absolute and relative errors and alpha band power in the DLPFC, VLPFC, and PC

Variables	<i>B</i>	S.E.	Wald	<i>df</i>	<i>p</i>	Odds ratio	95% C.I. for odds ratio	
							Lower	Upper
Left DLPFC	−1.277	0.201	40.469	1	0.001	0.279	0.188	0.413
Right DLPFC	−0.563	0.197	8.125	1	0.004	0.570	0.387	0.839
Left VLPFC	1.256	0.191	43.084	1	0.001	3.511	2.413	5.108
Right VLPFC	−0.353	0.162	4.759	1	0.029	0.703	0.512	0.965
Left PC	−0.090	0.168	0.287	1	0.592	0.914	0.657	1.271
Right PC	−0.378	0.180	4.428	1	0.035	0.685	0.482	0.974
AE 1 s	0.307	0.108	8.007	1	0.005	1.359	1.099	1.681
AE 4 s	0.077	0.072	1.135	1	0.287	1.080	0.937	1.244
AE 7 s	−0.024	0.056	0.181	1	0.671	0.976	0.875	1.090
AE 9 s	0.006	0.044	0.022	1	0.882	1.006	0.924	1.096
RE 1 s	0.216	0.101	4.554	1	0.033	1.242	1.018	1.515
RE 4 s	0.039	0.212	0.034	1	0.853	1.040	0.686	1.577
RE 7 s	−1.201	0.313	14.732	1	0.001	0.301	0.163	0.556
RE 9 s	−0.468	0.339	1.905	1	0.167	0.627	0.323	1.217
Constant	10.774	2.360	20.839	1	0.001	7.092		

DLPFC dorsolateral prefrontal cortex, VLPFC ventrolateral prefrontal cortex, PC parietal cortex, AE absolute error, RE relative error

internal clock theory (1963) may also support the finds since it is understood that the time interval judgment has its origin in the activity of the pacemaker which sends pulses to a counter and is assumed to be periodic [56, 57]. The model also involves storage of reference durations and a comparison mechanism; these mechanisms determine the behavioral output. Furthermore, MPH increases the cognitive complexity [6, 58], and recruits the attention and memory mechanisms [4, 5, 25] for greater speed in the internal clock [59], causing acceleration of timekeeping (comparator) and decision-making [31, 36, 60].

Another important factor that influences time estimation is the sex. It is known that men provide a shorter estimate than women [61, 62], because of men's propensity to store a greater amount of information on positively valued stimuli [63]. In this case, the observed MPH effect may represent an increase in concentration, attention, and memory, which could lead the subjects to stimulate the task, such as a positive valence stimulus, and in this way, they perceive the time pass faster [64]. Thus, MPH's action on attention plays an important role in positive valence, with consequent influence on the internal clock acceleration [65, 66]. Thereby, when more attention is given to the time interval, the time subjective duration is increased [67, 68]. It demonstrates that more pulses were accumulated on the counter and were not lost during memory storage. So, MPH showed a decrease in the participants targeting to non-temporal stimuli, leading to less temporal pulses loss, accelerating the time subjective duration [36].

This study results confirm the hypothesis of the research for the PFC and PC changes with MPH, significantly affecting

the alpha power reduction in the DLPFC, PC, and VLPFC bilaterally with larger effect in the left VLPFC. These findings may be directed to the MPH effect in the attention and memory state required in the time estimation task. For instance, Dockree et al. [36] when analyzing the MPH effect (30 mg), atomoxetine (60 mg) and citalopram (30 mg), in the attention in 40 subjects with a temporal expectation task, found an alpha band power variability reduction in the PC. From this perspective, the MPH improves the attention state and decision making [30, 43, 51], facilitating the internal clock acceleration [29]. Rosenberg et al. [39] showed that the MPH effect promotes modulations in the neural networks in the PFC and PC associated with the sustained attention during the cognitive task execution. We argue that MPH, by potentiating dopaminergic and noradrenergic effects in the synaptic cleft [12], promotes working memory functions, which is largely related to the PFC functions [69] and to the time estimation task [31, 70, 71].

Regarding the electrophysiological variable, our findings observed modulations of activity neural in alpha frequency during time perception task. These results demonstrated that the frontal and parietal cortex functions have an effect on timing and coding in time estimation [72] since these areas are closely related to voluntary attention processes and alpha band power is based on the accumulation principle and information processing [73]. In general, electrophysiological records indicate that the alpha band oscillations in the frontal area are associated with fundamental cognitive functions to task performance. We may suggest the cortico-striato-thalamo-cortical (CSTC) loop connections in the information

synchronism relevant to the perceptual capacity in all time domains [74]. The transient alterations of alpha band in the frontal and parietal cortex are considered as an objective correlate of the attentional level [75, 76].

The PC and the right PFC have been related to general processes, such as the attentional resource allocation, coding, and retrieval of information which are essentials in the codification, storage, and retrieval time interval information [77]. Indeed, the results about in the left VLPFC after the MPH acute use [78] can be interpreted according the dopamine transporter blockade due to its increase the extracellular levels of dopamine leading to an unbalancing effect between the right and left cortical areas [10]. This fact was observed in the Volkow et al. [79] study, which associate the MPH acute application concomitant with EEG in healthy individuals. The authors have shown that the change in dopaminergic synapse neurotransmission during acute treatment with the drug is in part a consequence of the extracellular dopamine increase by blocking DAT in the frontal cortex. Thus, the results demonstrated that differences in response to MPH occurred due to individual differences in the dopaminergic release, and this may be associated with the drug biotransformation principles.

A study limitation was not to use other MPH doses to verify the relation between doses to answer our questions. We could also have used instruments to assess attention and memory in order to relate both time interval interpretation and the activity of the cortical areas. Another limitation was that we did not use phenotype analysis related to dopaminergic activity in time perception. This leaves a gap for responding to the MPH effects on time estimation, by not controlling interindividual changes at dopaminergic levels.

## Conclusion

This study reveals the relationship between actions of MPH, the time interval estimation, and the cortical activity. The time interval underestimation was influenced by the administration of MPH, which is likely to be due to effects on cognitive elements—attention and memory processing. The association between MPH administration and the participants' behavior during the time estimation task was detected, which indicates the role of attention level maintenance and the right and left PFC, left VLPFC, and right PC recruitment. The complexity of time estimation task interpretation should be considered more broadly and supported by time perception theories. Thus, this study helps to understand the MPH effect on time perception and its relations with cortical activity, showing a differential involvement of MPH in the timing at supra-second scales. Further studies to better understand the MPH effect on the time interval judgment, using other assessment tools combined with interpersonal phenotypic characteristic analysis, could broaden our knowledge in this area.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethics approval and consent to participate** All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Ethics Committee of the Federal University of Piauí approved all procedures, and participants provided written, informed consent (no. 1607069/2016).

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