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Time estimation exposure modifies cognitive aspects and cortical activity of Attention Deficit Hyperactivity Disorder adults

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Abstract

This study investigated whether time estimation task exposure influences the severity of Attention Deficit Hyperactivity Disorder (ADHD), as well as theta band activity in the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex. Twenty-two patients with ADHD participated in a crossover experiment with a visual time-estimation task under control conditions (without exposure to time estimation tasks) and experimental (thirty days exposure to time-estimation tasks) in association with electroencephalographic analysis of theta band. ADHD patients with thirty days of time-estimation task exposure presented a worse performance of the time-estimation task, as revealed by the measurements of the absolute error and relative error (p≤0.05). However, our findings show the improvement of self-reported symptoms of attention, impulsivity, and emotional control in patients after the time-estimation task exposure (p=0.0001). Moreover, the theta band oscillations in the right dorsolateral prefrontal cortex and in the ventrolateral prefrontal increased with thirty days of time-estimation task exposure (p<0.05). We propose that the decrease in EEG theta power may indicate an efficient accumulation of temporal pulses, which could be responsible for the improvement in the patient cognitive aspects as demonstrated by the current study. Time-estimation task improves ADHD cognitive symptoms, with a substantial increase in cortical areas activity related to attention and memory, suggesting its use as a tool for cognitive timing function management and non-invasive therapeutic aid in ADHD.

Keywords: Attention Deficit Hyperactivity Disorder, Time perception, Electroencephalography, theta band
Introduction

In several situations, we complain about the fast passage of time, and we have the impression that hours, days and years pass quickly [1, 2]. This fact is related to events’ relative duration, which serves as a reference to create the idea of present, past and future [3, 4]. Thus, time estimation is a part of the dynamic interaction between personal experience and environment conditions [5]. Accordingly, the Central Nervous System (CNS) processes the sensory stimuli in timescales which vary from the milliseconds (motor control), seconds to minutes (attention, memory, decision making) and hours of the day (circadian rhythms) [6, 7]. Among various cognitive functions related to time interval interpretation, attention is paramount in time judgment [8, 9].

One important cognitive function that has attracted considerable research interest in Attention Deficit Hyperactivity Disorder (ADHD) is time-estimation [9–11]. These studies examine how well patients with ADHD are able to dissociate different durations of presented stimuli or how well they are able to perform motor actions after a particular time interval has passed. Studies show interval-timing dysfunctions in ADHD, which is likely since dopaminergic mechanisms and frontal-striatal networks - which are affected in ADHD - are central for such processes [12–14]. In the current context, the ADHD is a neurological disorder with deficiencies beginning during childhood, and it has main symptoms of inattention, hyperactivity, and impulsivity, which are contributed by the deficits in dopaminergic neurotransmission [15–19]. Additionally, functional magnetic resonance imaging studies in ADHD patients have found hypoactivity in some cortical and subcortical areas, namely, the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), orbitofrontal cortex, parietal cortex, basal ganglia and thalamic nuclei [20–22]. Among these areas showing hypoactivity, it has been known that DLPFC and VLPFC are important for cognition, executive functions and motor inhibition, both inbuilt in the time estimation [10, 23–25]. For this reason, cortical and subcortical changes are implicated in many ADHD symptoms [18]. Furthermore, neuroimaging investigations have shown that ADHD subjects present functional deficits related to interval timing capability [26, 27]. For instance, Noreika et al. [28] has demonstrated that ADHD subjects have dysfunctions in frontoparietal and fronto-striatum-cerebellar networks, which are closely related to dopaminergic neurotransmission and time perception and could be responsible for the timing deficits in ADHD patients.

Neurocognitive factors elucidated by behavioral tests, neuroimage and EEG-analysis studies indicate that individuals with ADHD may have functional deficits in the timing ability of supra-second range [14, 28]. 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 [29]. It is suggested that deficient timing functions are the key to the behavioral profile of ADHD [30]. Abnormal time processing is 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 [27]. Studies by Hwang-Gu and Gau [13] provide evidence that inaccurate timing is associated with the deficiency in the cognitive processing of sustained attention for a potential stimulus, as well as possible deficits in dopaminergic neurotransmission, for example, affecting the fronto-striatal circuits [31, 32].

Neurophysiological studies demonstrated that ongoing brain oscillations are linked to the intrinsic tendency of the perceptual system to process information within different temporal windows. The activity in the theta band (4–7 Hz) range is suggested to be a correlate in neurobiological aspects inbuilt in the time perception (memory, attention, decision making, and visual perception) [33, 34]. This relationship between ongoing oscillations and temporal windows in perception suggests two testable hypotheses. First, there should be a phasic “alignment” between behavior and the oscillation, with performance depending on the ongoing phase of the oscillation.
Phase-dependent perception was demonstrated originally in EEG studies testing simple near-threshold detection or reaction times tasks [35].

According to Minkwitz et al. [36] and Hegerl et al. [37] ADHD is characterized by an unstable wakefulness regulation, as assessed by EEG measures, which indicate that EEG-based vigilance states are associated with cognitive functions, such as time-estimation, ratings of sleepiness and deficits in sustained attention tasks. It has been postulated that in the ADHD, this unstable wakefulness regulation represents a central pathogenetic factor leading to attention and timing deficits and inducing hyperactive, impulsive and sensation-seeking behaviour as an autoregulatory attempt to stabilize wakefulness by increasing external stimulation [37].

Several lines of rehabilitation can improve cognitive and symptomatologic aspects in individuals with ADHD, but so far no time-estimation exposure protocols in ADHD patients. We based the hypothesis based on the ability of the CNS to respond to different time interval oscillations that allow actions that need attention and memory. We hypothesized that thirty days of time estimation exposure will modulate the theta band absolute power in the DLPFC and VLPFC. Moreover, it is believed that after time-estimation task exposure, patients will present a decline of symptoms attributed to ADHD.

Materials and Methods

All patients with ADHD underwent a previous medical evaluation. The patient’s classification for the study had been determined according to the established clinical guidelines and Attention Deficit Hyperactivity Disorder Scale - Adult and Adolescent Version (ADHD-APA). Patients were only included if they fulfilled diagnostic criteria according to ICD-10 (F90.0, F90.1 or F98.8). Patients were excluded if they presented with additional acute and/or severe psychiatric or somatic comorbidities (e.g. tic disorder, depressive episode, autism). Thirty right-handed ADHD patients (mean age 23 ± 1.4 years, age range = 20-30 years) were recruited at the Federal University of Piauí Clinic for this study. All subjects underwent a medical evaluation to exclude those with other neurological or motor diseases that would impair the task performance. In addition, the use of any substance that inhibits or stimulates brain activity (e.g. tobacco, coffee, alcoholic beverages, foods containing caffeine, and use of medications) was banned 14 hours before or during the study period [5, 38]. However, eight participants were eliminated because they did not comply with the necessary time restriction for the use of the substance that could influence brain activities, and due to chronic use of medicaments (Venvanse, Ritalin, Concerta).

Thus, the remaining 22 (16 men and 6 women, with mean age 22.4 ± 0.9 years) were randomized at a rate 1:1, blinded-experiment for the two conditions in the following sequence: 11 patients starting in the experimental condition (thirty days of time estimation exposure) and finishing in the control condition (without prolonged exposure to time estimation) and 11 patients starting in the control condition and finishing in the experimental condition (Figure 1).

All subjects signed the Free and Informed Consent Form. The experiment was approved by the Research Ethics Committee of the Federal University of Piauí (No. 1.609.985) according to the Criteria of Ethics in Research with Human Subjects included in the Declaration of Helsinki.

Experimental Procedure

a) Randomization:
ADHD patients were randomly selected for one of two conditions: The control condition was performed within only one week. At the end of the control condition, a 7-days wash-out was given to start the experimental condition.

b) Experimental procedure:

- The Attention Deficit Hyperactivity Disorder Scale - Adult and Adolescent Version was applied in both conditions, to monitor the possibility of evaluation and changes in phenotype behavioral.
- Participants stayed in a sound and electrically insulated room. They were seated on an arm-rests chair to minimize any muscular artifact during EEG signal acquisition (Figure 1).
- Initially, EEG signal acquisition lasted for 3 minutes (rest). Posteriorly, time estimation task was executed in 1 block of 40 tracks, concomitantly the EEG (EEG-task). A 42-inch monitor was positioned on a table in front of the individuals, and it was turned on only during task execution, with four time-intervals presented randomly.
- For control condition: EEG was acquired during the time estimation task only in a single week. For experimental condition: EEG was acquired during the time-estimation task once a week, during 4 weeks, with follow-up of 15 and 30 days. Only the experimental condition patients performed thirty days of time-estimation task exposure with a time estimation task mobile app, during 15 minutes daily for 30 days (Figure 2).

Time-estimation task

A 42’ inch monitor was placed on a table in front of the participants at a distance of 50 cm and was turned on only during the task. The time estimate was analyzed using a program that records the displayed time interval (e.g. 1s, 4s, 7s or 9s) [39, 40]. The task was performed in two phases. In the first, the display shows the command “enter” to start, then, the program produces a yellow circle in the monitor center that randomly stays for 1s, 4s, 7s or 9s. In the second phase, the software platform Matlab displays an empty field on the monitor to enter the estimated time interval, and then the subject presses the “enter” key to complete the task (Figure 3). Each participant performed 1 task blocks with 40 tracks. The time estimation was analyzed by Matlab program that records the target time interval presented randomly (i.e. 1s, 4s, 7s or 9s) as well as the estimated time for each subject. This software has an additional channel for EEG that records the start and finish of the time-estimation task, allowing time extraction related to the cortical activity during the time-estimation task completion.

For the thirty days of time-estimation task exposure, a mobile app was developed, which was available in the subjects’ cell phones. During 30 days at the time set by the app (8:30 in the morning) was conducted the time estimation task, with a duration of 15 minutes. In the app, the display shows the command to start, then, the program produces a yellow circle in the screen center that remains randomly in 1s, 4s, 7s or 9s. In the second phase, the app displays an empty field on the screen to enter the estimated time interval, and then the patient completes the task. After completing the thirty days of time estimation exposure a screen appears for the patient to send the results to the researchers.

Attention Deficit Hyperactivity Disorder Scale - Adult and Adolescent Version (ADHD-APA)

The ADHD-APA was applied to identify the ADHD level (mild, moderate and severe) and to identify the disorder subtype (inattentive, hyperactive-impulsive or mixed) [41]. ADHD-APA was developed for the Brazilian population, which has 69 items and evaluates 5 factors: 1) Inattention; 2) Impulsiveness; 3) Emotional Aspects; 4) Self-regulation of Attention, Motivation, and Action
Hyperactivity. The instrument validated and standardized for the Brazilian population helps in the reports quantification of ADHD patients, providing the possibility of transforming subjective information into an objective and relevant indicative for a psychological evaluation. To estimate the classification effect of the instrument and to measure the reliability of the internal consistency type of a scale, the Cronbach’s alpha coefficient (α) was analyzed. The minimum acceptable value for alpha is 0.70; below this value the internal consistency of the scale used is considered low. In contrast, the expected maximum value is 0.90.

Behavioral data analysis

Data were acquired from the mapping of neurophysiological activities through the scalp and then processed according to methods performed by Rocha et al. (2018). Cortical modifications analyzes were performed for the times of 1s, 4s, 7s and 9s. For each experiment, the EEG epoch was extracted between the moment and 2 seconds before the subjects estimated the time interval. The behavioral variable was transformed into measures representing the absolute error value (AE) and the estimated proportion of target duration [40]. The AE value is a measure of the difference between the target-time and judged time-intervals, making it useful to assess the timing precision. The AE was calculated by putting in absolute value the difference between the time estimation (Ed) and the target duration (Td) [AE=|Ed – Td|] [42, 43]. The target duration estimation ratio was obtained by dividing each participant’s time performance by the time duration of the interval presented for that trial [Target duration estimation = Ed/Td]. This analysis is similar to the relative error (RE), and a coefficient below 1.0 indicates trial duration less than the real time, while the coefficient above 1.0 represents the trial duration longer than the real duration, an underestimation or overestimation of time, respectively [40, 42].

EEG recording

The Brainet BNT36 amplifiers (EMSA-Medical Instruments, Brazil) was used to capture EEG signals, using a digital-analog converter card (A/D) of 32-channel and a 12-bit resolution, placed on an ISA of Pentium III - with a processor of 750 Hz. 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. The impedance of the EEG electrodes was kept below 5KΩ. The acquired data had a total amplitude of less than 100μV. The EEG signal was amplified with a gain of 22,000 Hz, analogously filtered between 0.03 Hz (high-pass) and 40 Hz (low-pass) with 240 Hz using the Data Acquisition software (Delphi 5.0) developed in the Neuro-innovation Technology & Brain Mapping Laboratory.

EEG data processing

A visual inspection and analysis of independent components were applied to identify and remove all remaining artifacts produced by the task [44]. Data from individual electrodes that showed contact with the scalp or high impedance (> 5KΩ) were not considered. A classical estimator was applied to the spectral power density, estimated from the Fourier Transform, which was performed by MATLAB (Matwords, Inc.). EEG parameters were reduced to different periods, according to the time interval. Analysis of the cortical modifications were performed for the time intervals of 1s, 4s, 7s and 9s. For each epoch, the EEG recording began 2 seconds before the visual stimulus start (preparation for the task) and continued until the time 0 corresponding to the time-estimation task execution. These procedures selected the leads of the electrodes F3, F4, F7 and F8, due to the relationship with the DLPFC and VLPFC (associated with the executive functions, attention, planning and short-term memory, both neurobiological aspects inbuilt in the time estimation). The theta frequency range (4–7 Hz) was used because of its correlation with attention processes and working memory [45–47].
Statistical analysis

Analysis of AE and RE in the time intervals (1s, 4s, 7s and 9s) by paired t-test was performed between the control and experimental conditions. However, correction of p-value for multiple comparisons was required (p≤0.0125), and with the analysis effect evaluated by the Cohen’s d. For the analysis of cognitive aspects and ADHD symptoms during the period of thirty days of time estimation exposure, Friedman test was performed. Electrophysiological data were analyzed by means of three-way repeated measures ANOVA with following factors: condition (control vs. Experimental); Visit (visit 1 vs. visit 2 vs. visit 3 vs. visit 4 vs. Follow-up 15 days vs. Follow-up 30 days); area (right DLPFC vs. left DLPFC vs. right VLPFC vs. left VLPFC). The Mauchley’s test criteria were used to evaluate the sphericity hypothesis and the Greenhouse-Geisser (G-Gε) procedure to correct degrees of freedom. The normality and homoscedasticity of the data were previously verified by the Levene and Shapiro-Wilk tests. The effect size was estimated as partial eta-squared (ƞ²p) in repeated measures analysis. Statistical power and the 95% confidence interval (95% CI) were calculated for the dependent variables. Statistical power was interpreted as the low power of 0.1 to 0.3; high power from 0.8 to 0.9. The effect of magnitude was interpreted using the recommendations suggested by Cohen [48]: insignificant <0.19; small from 0.20 to 0.49; mean from 0.50 to 0.79; large from 0.80 to 1.29. The probability of 5% for type I error was adopted in all analyzes (p≤0.05), with alpha-Bonferroni correction for the interaction analysis, adjusting the value for p≤0.025.

In addition, a binary logistic regression was utilized to investigate the changes in the absolute power of the theta band in the DLPFC and VLPFC in the right and left hemispheres; and AE and RE in each time interval (independent variables) with and without the thirty days of time estimation exposure (dependent variable). The level of significance of p≤0.05 was considered. The analyses were conducted in SPSS for Windows version 20.0 (SPSS Inc., Chicago, Il, USA).

Results

Cognitive aspects results

We described the cognitive aspects of control and experimental conditions using means ± standard deviation (Table 1 and 2). Subsequently, the Friedman test was performed to analyze the possible differences between the control and experimental conditions in ADHD-APA in the domains of inattention, impulsivity, emotional aspects, SAMA and hyperactivity before and after thirty days of time estimation exposure.

The score in the inattention domain showed a statistically significant difference [χ²(4)= 9.92; p=0.0001; Cronbach’s α= 0.83]. Note that high scores on this factor reflect losses in several subdomains of executive functions. The result indicates that the control condition at the time before obtained higher scores (Median= 50), decreasing during the experimental condition (Median= 30), that is, individuals before performing the experimental condition presented a poor developmental performance of the task, however, as they trained, individuals significantly improved attention.

When analyzing whether there was a difference in the measures reached in the impulsivity domain, a statistically significant difference was observed [χ²(4)= 17.28; p=0.0001; Cronbach’s α = 0.85]. Considering that high scores on this factor may reflect a low capacity for impulse inhibition, this study identified that the experimental condition had a higher score (Median= 55) at the time before the thirty days of time-estimation exposure, decreasing at a later time (Median = 39), that is, individuals had a better ability to control impulsivity after thirty days of time-estimation task exposure. Our analysis identified statistically significant difference [χ²(4)= 8.06; p=0.0001; Cronbach’s α= 0.80] in emotional aspects. Considering that high scores reflect the persistence of
emotional difficulties, it was verified that the control condition presented higher scores (Median= 6) in relation to the experimental condition after time-estimation task exposure (Median= 2), suggesting that the individuals who performed the thirty days of time estimation exposure had improvement in the emotional aspect. On the other hand, when the self-regulation of attention, motivation score was analyzed, there was a decrease between the time before for the control condition (Median= 22) and then for the experimental condition (Median= 20), but without statistically significant differences $[\chi^2(4)= 8.62; p=0.413; \text{Cronbach's } \alpha = 0.83]$. However, although the difference was not significant, results for the experimental condition showed a growing improvement, since individuals after the thirty days of time-estimation task exposure were more attentive and motivated. The hyperactivity domain also showed a decrease prior to the control condition (Median= 36) and then to the experimental condition (Median = 34), but without statistically significant differences $[\chi^2(4)= 16.76; p=0.237; \text{Cronbach's } \alpha = 0.84]$.

Behavioral results

AE results for control and experimental conditions are presented in figure 4. A statistical difference was observed for the time intervals of 1s $[t(21)= 27.97; p=0.002; d= 0.51]$, 4s $[t(21)= 34.32; p=0.001; d= 0.62]$, 7s $[t(21)= 51.68; p=0.002; d= 0.94]$ and 9s $[t(21)= 47.62; p=0.02; d= 0.86]$, with experimental condition patients increasing error for time-estimation task by 44.3% in relation to the control condition.

In relation to RE, the results showed a statistically significant difference for time intervals of 1s $[t(21)= 25.28; p=0.001; d= 0.86]$, 4s $[t(21)= 33.65; p=0.0001; d= 0.61]$, 7s $[t(21)= 51.67; p=0.001; d= 0.94]$ and 9s $[t(21)= 44.96; p=0.001; d= 0.82]$, demonstrated that the thirty days of time estimation exposure had a great effect of inaccuracy during performance task, causing the subjects to overestimate the time 38.7% more than in the control condition (Figure 5).

A binary logistic regression was utilized to study the association of the AE and RE with the conditions without and with thirty days of time estimation exposure. The regression model was statistically significant $[\chi^2(4)= 3216.56; p<0.0001]$ and explained 54% Nagelkerke $R^2$ on task performance through thirty days of time estimation exposure, correctly classifying the arrangement of behavioral variables in 81% of cases (Table 3). The sensitivity of the test was 83.2%, the specificity of 81.5%, the positive predictive value of 81.6% and the negative predictive value of 82.4% for the thirty days of time estimation exposure in the task performance in the different time intervals (1s, 4s, 7s and 9s). Both were analyzed to confirm the relation of time estimation task exposure during time judgment.

Neurophysiological results

The repeated measures ANOVA showed interaction for the following levels of analysis: conditions, cortical areas and visits $[F(21)= 6.75; p=0.001; \eta^2 p= 0.13; \text{power}= 80\%]$. When analyzing the interaction, a two-way association between conditions and visits was found $[F(21)= 19.42; p=0.001; \eta^2 p= 0.22; \text{power}= 100\%]$; conditions and cortical areas $[F(21)= 12.44; p=0.001; \eta^2 p= 0.10; \text{power}= 100\%]$; as well as for visits and cortical areas $[F(21)= 17.14; p=0.0001; \eta^2 p= 0.30; \text{power}= 100\%]$.

The interaction analysis between conditions and cortical areas did not present a statistically significant difference between the conditions in the right VLPFC ($p>0.05$), while in the left VLPFC, the first visit $[t(21)= 3.34; p=0.001; d=0.20]$, the second visit $[t(21)= 7.81; p=0.001; d=0.28]$ and fourth visit $[t(21)= 8.18; p=0.001; d=0.22]$ there were significant difference between conditions, with nonsignificant effect on the theta band power decrease in the experimental condition. A statistical difference between conditions and cortical areas was also observed for the left DLFFC at the 30-day
follow-up [t(21)= 9.32; p=0.002; d=0.10], in the right DLPFC between the conditions in the second visit [t(21) = 9.91; p=0.001; d=0.34] and at the 30-day follow-up [t(21)= 9.77; p=0.001; d=0.30] showing a nonsignificant decrease in the theta band power. On the other hand, the theta band power decrease with moderate effect was observed in the left DLPFC in the experimental condition in the first [t(21)= 2.91; p=0.004; d=0.34] and second [t(21)= 5.34; p=0.001; d=0.37] visits, as well as during the follow-up on day 15 [t(21)= 2.26; p=0.02; d=0.44] (Figure 6).

The interaction analysis between conditions and visits did not reveal a statistically significant difference between the conditions during the third visit (p>0.05). On the other hand, statistically significant difference between conditions was observed during the first visit [t(21)= 2.025; p=0.004, d=0.35]; second visit [t(21)= 4.24; p=0.001; d=0.32] and follow-up for 30 days [t(21)= 4.24; p=0.001; d=0.32]; fourth visit [t(21)= 8.18; p=0.002; d=0.32]; follow-up for days [t(21)= 2.24; p=0.001; d=0.44] and follow-up for 30 days [t(21)= 9.23; p=0.001; d=0.38] for the left DLPFC during the second visit [t(21)= 4.24; p=0.001; d=0.32]; follow-up for 15 days [t(21)= 2.24; p=0.001; d=0.38] for the right VLPFC, while the left VLPFC presented statistical difference only for the first visit [t(21)= 3.25; p=0.001; d=0.18] and second visit [t(21)= 8.15; p=0.001; d=0.10], with nonsignificant decrease of the theta band absolute power in the experimental condition (Figure 7 and 8).

The results of the interaction analysis between the cortical areas and visits indicated statistically significant differences for all visits (p=0.0001) (Table 4). The results indicated theta activity variability during visits for both left and right DLPFC, with a theta power decrease at 15-day follow-up and an increase at 30-day follow-up (p=0.0001). In the right and left VLPFC, the theta activity variability was also observed during the visits, however, in the left VLPFC there was a theta rhythm increase during the visits, decreasing at the last visit and in the 15-day follow-up, but increasing again in the follow-up of 30 days (p=0.0001). In the right VLPFC, the theta activity presented variability during the visits, but with the same left VLPFC behavior in the first and second follow-up (Figure 9).

When analyzing the interactions between areas and visits, a statistical difference between all cortical areas was found (p=0.0001), with the highest theta band activity for the right DLPFC during the first, second, third and fourth visit. On the other hand, at the 15-day follow-up, it was observed that the left DLPFC maintained increased theta power in relation to the other cortical areas, whereas in the 30-day follow-up theta rhythm increase was observed for both left and right DLPFC (Table 5) (Figure 9 and figure 10).

The logistic regression results showed an association between thirty days of time estimation exposure and cortical activity changes of the left DLPFC (visit 1 and follow-up 30 days), right DLPFC (visit 1, visit 2, follow-up 15 days and follow-up 30 days), left VLPFC (visit 2 and visit 4) and right VLPFC (visit 3) for both conditions (Table 6). The regression model was statistically significant [χ2(3)= 298.87; p=0.0001] and explained 54% (Nagelkerke R²) of variability of the cortical activity through thirty days of time estimation exposure, correctly classifying neurophysiological variables in 82% of the cases. The sensitivity of the test was 82.9% and the specificity of 81.8% for the time estimation performance in the cortical activity modulation during the visits. The positive predictive value of 81.9% and the negative predictive value of 82.1% were analyzed to confirm the changes in the cortical activity during thirty days of time estimation exposure.

Discussion
The goal of this study is to analyze whether the time estimation training at different time intervals promotes cortical changes and improves cognitive aspects in ADHD individuals. The ADHD-APA findings include inattention, impulsivity and defects of emotional aspects.

Attention covers 23 items related to attentional skills. The high scores on ADHD-APA may be related to the impairments of cognitive and executive functions, such as staying alert to fulfill the requirements of a situation and difficulty to performing tasks [41]. The present findings indicate that the patients before the thirty days of time-estimation task exposure have poor task performance, which is consistent with the predominantly inattentive subtype of ADHD. However, with they time-estimation task exposure, they showed improvement of attention levels. This indicates a positive effect of the thirty days of task exposure in ADHD individuals, which suggests facilitating the central nervous system adaptation and reducing the symptom of inattention.

As reviewed recently, ADHD is found to be associated with deficits of time duration estimation, rhythm perception as well increased variability in motor timing [49]. Moreover, ADHD is found to show alterations in theta frequency range, which is an electrophysiological correlate of musical rhythm timing in addition to various other timing functions [49]. Moreover, the thirty days of time estimation exposure may induce activity-dependent plasticity changes [50], diminishing the deficits of timing mechanisms that are associated with ADHD, which could account for the improvements of symptoms of ADHD [28, 49, 51].

The impulsivity domain was also composed of 23 related items, more precisely a deficit in the inhibitory system, as described by Barkley and Fisher [52]. High scores in this domain may reflect the low capacity for impulse inhibition, self-control deficits, and impairments in social skills and family and personal interactions [41]. This study suggests that the subjects in the experimental condition obtained better results when compared to the control condition due to the improvements in the ability to control impulsive behaviors. This can be argued based on a neuroimaging study conducted by Hart et al. [27], which showed that the dysfunctions of frontal neural networks is associated with the impulsive behavior, which is consistent with the prevailing view that time perception deficits are the key to ADHD clinical behavioral profile.

In addition, Wittman and Paulus [53] have argued that time perception is an essential factor for the decision-making process and for the considerations to consequences associated to choices we make, so the impulsive subjects often have impaired time processing, in general suffer from greater difficulty in discriminating and/or comparing time intervals. This is also in accordance with our findings on RE, according to which subjects underestimated time more frequently in the control condition than in the experimental condition. Thus, AE and RE in a training task modulate the attentional levels of the cortex, which in ADHD, the cortical network that supports the attention is especially related in the right hemisphere involving the inferior parietal cortex, DLPFC and anterior cingulate cortex that aid the attention and the executive function associated to the general adaptation process [[54, 55]. Time representation by modular clocks in the cortex may involve the pulses accumulation emitted by a pacemaker, or the coincident activity detection between oscillators at different time periods, engaged primarily by neural oscillations and dopaminergic mediations in the prefrontal cortex [10]. The timing basis for the AE and RE according to the Scalar Expectation Theory possibly demonstrates an invariance of timing scales assigned to the pacing of the pacemaker and the temporal representations transfer in the short-term memory, in consonance with the information recruitment in long-term memory [40]. Based on the attention level principles to substantiate our behavioral variable findings, the attention level modulates the activity of the cortical area responsible for allowing the information accumulation, reactions to stimuli and motor and cognitive activities performance, which are dependent on the level of neural excitation.

For the domain pertaining to emotional aspects, it was identified that in the experimental condition, that is after time-estimation task exposure for thirty days, there were smaller scores when
compared to the control condition (tables 1 and 2). This demonstrates that the thirty days of time estimation exposure improve one of key neurobiological functions that affect the time interval interpretation. The time estimation exposure increases the cognitive efficiency, and recruits the attention and memory mechanisms for optimizing the internal clock [4], causing acceleration of timekeeping (comparator) and decision-making [1]. An important factor that influences the emotion, since that humans provide a shorter estimate due to the propensity to store a greater amount of information on positively valued stimuli [56, 57]. In this case, the observed time-estimation task exposure effect may represent a positive increase in emotions, which could lead the subjects to know the task, such as a positive valence stimulus [58]. Thus, time estimation exposure action on attention plays an important role in positive valence, with consequent influence on the internal clock acceleration. It demonstrates that more pulses were accumulated on the counter and were not lost during memory storage, so, time estimation exposure showed an improvement in the non-temporal aspects inbuilt in timing.

In recent decades, more research has confirmed that emotion plays a crucial role in time perception distortions [59]. In one study, Droit-Volet et al. [59] investigated the previous effect of emotions (film clips) on posterior time estimation of a neutral event. They found that the time perception did not change after seeing both neutral and sad films. However, with horror films, time was perceived as longer. Accordingly, we believe that the time-estimation task training had positive effects on the emotional aspects of ADHD subjects, and it could be related to the emotional triggers of the ascending reticular activating system, which causes the increase of the internal clock speed [60]. Thus, the thirty days of time estimation exposure may have reduced the internal clock speed in ADHD subjects, which resulted in better time perception and emotional control of these individuals. These study findings indicate the time-perception task, in addition to modifying the theta band absolute power behavior, also promotes the plasticity changes that reorganize the DLPFC and VLPFC to process and interpret the time interval with the optimization of the variables representing information [61]. Performing time estimation tasks seems to reorganize frontal regions to accurately perceive time. Especially, the prefrontal cortex plays an important role in maintaining, monitoring and storage of temporal information [62].

It is known that the prefrontal areas are critical to executive functions, and several studies demonstrate that theta band is involved in a wide range of executive functions, such as attention, working memory, episodic memory, and semantics, as well as spatial aspects related to the ability to imagine objects or actions [63, 64]. Thus, the changes in theta band absolute power may be related to the plasticity changes resulting from training with time-estimation tasks in ADHD individuals. The lower theta band absolute power in the experimental condition in the VLPFC suggests an efficient information processing activities. This indicates that thirty days of time-estimation task exposure facilitates adaptation during the time estimation task. Accordingly, the efficient temporal processing of the information allows the prefrontal areas to adjust memory and attention for greater control and monitoring of time perception intervals.

The finding of lower EEG theta power in the experimental condition for the VLPFC bilaterally is likely related to the participation of the VLPFC in the control of the impulsivity and may signal future reward. For instance, Marco et al. [65] observed that ADHD young individuals present greater variability in decision making, tending to make choices of immediate consequences, which seems to be related to impulsivity. This observation corroborates the evidence that ADHD subjects tend to overestimate and sub produce time intervals in the range of seconds to minutes [19], presenting higher scores for the late rewards [66]. This demonstrates an association between impulsivity and a deficit in the time interval interpretation, supporting the argument that the time estimation task can control impulsivity.

In our findings, the DLPFC bilaterally showed a significant decrease in the theta band absolute power in the experimental condition. This finding agrees with the DLPFC participation in
the identification of relevant behavioral stimuli, in addition to helping focus attention, which is fundamental for the time perception and cognitive control performance [67]. For instance, when subjects underwent a color attention task, it was observed that directing attention to a color increases the occipital cortex activity. However, when attention was directed to time estimation, there was an increase in activity in the DLPFC. This finding is related to the memory stage of the Scalar Expectancy Theory model [68]. From this perspective, the DLPFC is related to reward, sustenance of attention levels and executive processes, which are important for time perception, as demonstrated in a past study by Vallesi, Shallice and Walsh [69], that involved the right DLPFC in temporal processing in an implicit task. Therefore, it has been pointed out that the right DLPFC participation corroborates for the time interval interpretation since it is activated mainly in tasks involving interval timing when compared to other cortical areas.

In the present study, the left DLPFC shows a decrease in the theta band absolute power between the visits [70, 71]. Studies involving the left DLPFC did not observe any direct function of this area with the time estimation behavior, supporting a relation directed with the right DLPFC [72, 73]. However, several studies support the role of the left DLPFC in descending attentional control. Moreover, the left DLPFC is important for the attention focus given based on acquired experiences or from contextual information. Since attentional control is fundamental for the time perception, it is pertinent to investigate the left DLPFC.

This study has some limitations, which include sample size, and non-homogeneity. However, the moderate effects and statistical power in the analyzes decrease the possibility of a type II error. In addition, the follow-up period could provide greater consistency to our results. Another limitation involves non-EEG uptake during all experiments days. The current analysis can reinforce changes in theta rhythm with the time estimation task, and demonstrates further improvement of the cognition in ADHD patients. Another limitation is non-association with sub-second level tasks, since it could provide a broader view of neurophysiology in timing. Instruments may be used in future studies to assess attention and memory in order to relate both time interval interpretation and the activity of the cortical areas. Future studies would also include phenotypes analysis related to dopaminergic activity, which are important for time perception. This study would address to neurochemical effects on time judgment, in addition to controlling interindividual changes at dopaminergic levels in the current study.

**Conclusion**

The current study demonstrates a relation between ADHD, time-estimation task exposure and prefrontal cortex activity. Thirty days of time-estimation task exposure resulted in modulation of DLPFC and VLPFC areas, improving control of attention, impulsiveness and emotional aspects in ADHD individuals. We propose that the increase in EEG theta power following the thirty days of time estimation exposure may underlie an efficient accumulation of temporal pulses, which could be responsible for the improvement of self-reported symptoms of attention, impulsivity, and emotional control in ADHD patients after the time-estimation task exposure.

Furthermore, the above approaches are useful to investigate the neuroanatomical substrates of the time interval, providing a functional overview in mechanisms for time synchronization. Additionally, this study complements the studies dedicated to time perception and distributed neural-clock mechanisms in the brain, since it allows us to help in the elucidation of behavioral phenotypes in the ADHD patients and study the areas of the brain that are involved with the integration of perceptual time mechanisms.

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Author Contributions

Conception and design of the study: RMF, VM, PR, BV, and ST; Acquisition and analysis of data: RMF, VM, and ST; Drafting the manuscript and/or figures: RMF, VM, VC, KR, FM, DSG, and ST; Contributed reagents/materials/analysis tools: VM, VC, KR, FM, IM, PR, DSG, BV, MC, VHB, AST, and ST; Headed the behavioral and electrophysiological analysis: RMF, VM, PR, and ST.

Ethics approval and consent to participate

All subjects signed the Free and Informed Consent Form. The experiment was approved by the Research Ethics Committee of the Federal University of Piauí (No. 1.609.985) according to the Criteria of Ethics in Research with Human Subjects included in the Declaration of Helsinki.

Competing interests

The authors declare that they have no competing interests.

References


Figure 1. Subjects’ position during time estimation task execution concomitantly the EEG signal acquisition [5].
Figure 2. Illustration of the experimental procedure.

Figure 3. Illustration of the time estimation task.
Figure 4. Representation of the absolute error behavior of the participants in the time estimation task. The results are represented by the mean ± error and the statistically significant differences (p≤0.05) are represented by (*).
Figure 5. Representation of the behavior of the relative error of the participants in the time estimation task. The results are represented by the mean ± error and the statistically significant differences (p≤0.05) are indicated with (*).

Figure 6. Representation of the absolute power behavior of the theta band between conditions and cortical areas. The results are represented by the mean ± error and the statistically significant differences (p≤0.05) are indicated with (*).

Figure 7. Representation of the absolute power behavior of the theta band between conditions during the first visit (A), second visit (B) and fourth visit (C). The results are represented by the mean ± error and the statistically significant differences (p≤0.05) are indicated with (*).
Figure 8. Representation of the absolute power behavior of the theta band between conditions during the 15-day follow-up (A) and 30-day follow-up (B). The results are represented by the mean ± SEM and the statistically significant differences (p≤0.05) are indicated with (*).

Figure 9. Representation of the absolute power of the theta band during the visits and follow-up of 15 and 30 days. The results are represented by the mean ± error and the statistically significant differences (p≤0.05) are indicated with an (*).
Figure 10. Representation of the behavior of the absolute power of the theta band between the cortical areas during visits and follow-up of 15 and 30 days. The results are represented by the mean ± error and the statistically significant differences (p≤0.05) are indicated with (*).

Table 1 - The cognitive behavior for condition without prolonged exposure to time estimation using means ± standard deviation.

<table>
<thead>
<tr>
<th>ADHD-APA</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Cronbach's alpha (α)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inattention</strong></td>
<td>34.13</td>
<td>1.96</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Impulsiveness</strong></td>
<td>56.28</td>
<td>2.58</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Emotional Aspects</strong></td>
<td>4.75</td>
<td>1.48</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>SAMA</strong></td>
<td>14.82</td>
<td>1.34</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Hyperactivity</strong></td>
<td>26.67</td>
<td>1.90</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Note:

*aCondition without prolonged exposure to time estimation;


Table 2 - The cognitive behavior for condition condition with thirty days of time estimation exposure using means ± standard deviation.

<table>
<thead>
<tr>
<th>ADHD-APA</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Cronbach's alpha (α)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inattention</strong></td>
<td>28.25</td>
<td>1.83</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Impulsiveness</strong></td>
<td>49.75</td>
<td>2.61</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Emotional Aspects</strong></td>
<td>3.80</td>
<td>1.34</td>
<td>0.80</td>
</tr>
<tr>
<td>Behavioral variables</td>
<td>B</td>
<td>SE</td>
<td>Wald</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------</td>
<td>-------</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AE&lt;sub&gt;1s&lt;/sub&gt;</td>
<td>0.009</td>
<td>0.136</td>
<td>0.004</td>
</tr>
<tr>
<td>AE&lt;sub&gt;4s&lt;/sub&gt;</td>
<td>-0.008</td>
<td>0.062</td>
<td>0.016</td>
</tr>
<tr>
<td>AE&lt;sub&gt;7s&lt;/sub&gt;</td>
<td>1.343</td>
<td>0.056</td>
<td>5.678</td>
</tr>
<tr>
<td>AE&lt;sub&gt;9s&lt;/sub&gt;</td>
<td>1.192</td>
<td>0.061</td>
<td>3.763</td>
</tr>
<tr>
<td>RE&lt;sub&gt;1s&lt;/sub&gt;</td>
<td>0.009</td>
<td>0.146</td>
<td>0.031</td>
</tr>
<tr>
<td>RE&lt;sub&gt;4s&lt;/sub&gt;</td>
<td>-0.032</td>
<td>0.248</td>
<td>0.016</td>
</tr>
<tr>
<td>RE&lt;sub&gt;7s&lt;/sub&gt;</td>
<td>9.938</td>
<td>0.394</td>
<td>5.678</td>
</tr>
<tr>
<td>RE&lt;sub&gt;9s&lt;/sub&gt;</td>
<td>10.728</td>
<td>0.553</td>
<td>3.763</td>
</tr>
</tbody>
</table>

Note: B: Regression coefficient; SE: Standard error; df: Degree of freedom; AE: Absolute error; RE: Relative error. Significant differences (p≤0.05) are represented by the asterisk (*).

Table 3 - The regression model to investigate the association between the conditions without prolonged exposure to time estimation and with thirty days of time estimation exposure (dependent variable) in relation behavioral variables AE and RE in each time interval (independent variables).

<table>
<thead>
<tr>
<th>Visits</th>
<th>df</th>
<th>F</th>
<th>p</th>
<th>Partial Eta Squared</th>
<th>Observed Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>3</td>
<td>19.13</td>
<td>0.001*</td>
<td>0.02</td>
<td>100%</td>
</tr>
<tr>
<td>Visit 2</td>
<td>3</td>
<td>103.06</td>
<td>0.001*</td>
<td>0.01</td>
<td>100%</td>
</tr>
<tr>
<td>Visit 3</td>
<td>3</td>
<td>36.96</td>
<td>0.001*</td>
<td>0.01</td>
<td>100%</td>
</tr>
<tr>
<td>Visit 4</td>
<td>3</td>
<td>122.94</td>
<td>0.001*</td>
<td>0.01</td>
<td>100%</td>
</tr>
<tr>
<td>Follow up 15 days</td>
<td>3</td>
<td>18.85</td>
<td>0.001*</td>
<td>0.02</td>
<td>100%</td>
</tr>
<tr>
<td>Follow up 30 days</td>
<td>3</td>
<td>78.56</td>
<td>0.001*</td>
<td>0.08</td>
<td>100%</td>
</tr>
</tbody>
</table>

Note: df: Degree of freedom; F: F-value in the ANOVA test; p: p-value. Significant differences (p≤0.05) are represented by the asterisk (*).
Table 5 - Statistical result of a one-way ANOVA of repeated measures of the interaction between cortical areas and visits.

<table>
<thead>
<tr>
<th>Cortical areas</th>
<th>df</th>
<th>F</th>
<th>p</th>
<th>Partial Eta Squared</th>
<th>Observed Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLPFC right</td>
<td>5</td>
<td>34.14</td>
<td>0.001*</td>
<td>0.04</td>
<td>100%</td>
</tr>
<tr>
<td>DLPFC left</td>
<td>5</td>
<td>11.67</td>
<td>0.001*</td>
<td>0.01</td>
<td>100%</td>
</tr>
<tr>
<td>VLPFC right</td>
<td>5</td>
<td>46.99</td>
<td>0.001*</td>
<td>0.06</td>
<td>100%</td>
</tr>
<tr>
<td>VLPFC left</td>
<td>5</td>
<td>66.85</td>
<td>0.001*</td>
<td>0.07</td>
<td>100%</td>
</tr>
</tbody>
</table>

Note: DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; F: F-value in the ANOVA test; df: Degree of freedom; p: p-value. Significant differences (p≤0.05) are represented by the asterisk (*).

Table 6 - The regression model to investigate the association between the conditions without prolonged exposure to time estimation and with thirty days of time estimation exposure (dependent variables) in relation to the absolute power of the theta band in the DLPFC and VLPFC in the right and left hemispheres (independent variables).

<table>
<thead>
<tr>
<th>Cortical areas</th>
<th>B</th>
<th>SE</th>
<th>Wald</th>
<th>df</th>
<th>p</th>
<th>Odds Ratio</th>
<th>95% IC for Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>lDLPFC_v1</td>
<td>0.052</td>
<td>0.062</td>
<td>0.709</td>
<td>1</td>
<td>0.004*</td>
<td>1.054</td>
<td>0.933</td>
</tr>
<tr>
<td>rDLPFC_v1</td>
<td>-0.293</td>
<td>0.078</td>
<td>14.028</td>
<td>1</td>
<td>0.001*</td>
<td>0.746</td>
<td>0.640</td>
</tr>
<tr>
<td>lVLPFC_v1</td>
<td>-0.120</td>
<td>0.062</td>
<td>3.735</td>
<td>1</td>
<td>0.053</td>
<td>0.886</td>
<td>0.785</td>
</tr>
<tr>
<td>rVLPFC_v1</td>
<td>0.010</td>
<td>0.063</td>
<td>0.026</td>
<td>1</td>
<td>0.871</td>
<td>1.010</td>
<td>0.893</td>
</tr>
<tr>
<td>lDLPFC_v2</td>
<td>-0.106</td>
<td>0.090</td>
<td>1.408</td>
<td>1</td>
<td>0.235</td>
<td>0.899</td>
<td>0.754</td>
</tr>
<tr>
<td>rDLPFC_v2</td>
<td>-0.583</td>
<td>0.102</td>
<td>32.532</td>
<td>1</td>
<td>0.001*</td>
<td>0.558</td>
<td>0.457</td>
</tr>
<tr>
<td>lVLPFC_v2</td>
<td>-0.141</td>
<td>0.056</td>
<td>6.264</td>
<td>1</td>
<td>0.001*</td>
<td>0.869</td>
<td>0.778</td>
</tr>
<tr>
<td>rVLPFC_v2</td>
<td>-0.079</td>
<td>0.075</td>
<td>1.120</td>
<td>1</td>
<td>0.290</td>
<td>0.924</td>
<td>0.798</td>
</tr>
<tr>
<td>lDLPFC_v3</td>
<td>-0.009</td>
<td>0.057</td>
<td>0.023</td>
<td>1</td>
<td>0.880</td>
<td>0.991</td>
<td>0.887</td>
</tr>
<tr>
<td>rDLPFC_v3</td>
<td>-0.121</td>
<td>0.069</td>
<td>3.075</td>
<td>1</td>
<td>0.079</td>
<td>1.129</td>
<td>0.986</td>
</tr>
<tr>
<td>lVLPFC_v4</td>
<td>0.007</td>
<td>0.045</td>
<td>0.028</td>
<td>1</td>
<td>0.868</td>
<td>1.007</td>
<td>0.923</td>
</tr>
<tr>
<td>rVLPFC_v4</td>
<td>-0.129</td>
<td>0.054</td>
<td>5.698</td>
<td>1</td>
<td>0.001*</td>
<td>0.879</td>
<td>0.791</td>
</tr>
<tr>
<td>lDLPFC_v5</td>
<td>0.007</td>
<td>0.075</td>
<td>0.008</td>
<td>1</td>
<td>0.929</td>
<td>1.007</td>
<td>0.870</td>
</tr>
<tr>
<td>rDLPFC_v5</td>
<td>-0.007</td>
<td>0.073</td>
<td>0.010</td>
<td>1</td>
<td>0.919</td>
<td>0.993</td>
<td>0.860</td>
</tr>
<tr>
<td>lVLPFC_v5</td>
<td>0.185</td>
<td>0.049</td>
<td>14.120</td>
<td>1</td>
<td>0.001*</td>
<td>1.203</td>
<td>1.093</td>
</tr>
<tr>
<td>rVLPFC_v5</td>
<td>-0.095</td>
<td>0.068</td>
<td>1.942</td>
<td>1</td>
<td>0.163</td>
<td>0.909</td>
<td>0.795</td>
</tr>
<tr>
<td>IDLPFC_v5</td>
<td>0.163</td>
<td>0.098</td>
<td>2.741</td>
<td>1</td>
<td>0.098</td>
<td>1.177</td>
<td>0.970</td>
</tr>
<tr>
<td>rDLPFC_v5</td>
<td>0.415</td>
<td>0.103</td>
<td>16.349</td>
<td>1</td>
<td>0.001*</td>
<td>1.514</td>
<td>1.238</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>df</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>-------</td>
<td>----</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>lVLPFC</td>
<td>0.158</td>
<td>0.083</td>
<td>3.606</td>
<td>1</td>
<td>0.058</td>
<td>1.712</td>
<td>1.171</td>
</tr>
<tr>
<td>rVLPFC</td>
<td>-1.00</td>
<td>0.076</td>
<td>1.712</td>
<td>1</td>
<td>0.191</td>
<td>0.905</td>
<td>0.779</td>
</tr>
<tr>
<td>lDLPFC</td>
<td>-0.188</td>
<td>0.066</td>
<td>8.165</td>
<td>1</td>
<td>0.001*</td>
<td>0.829</td>
<td>0.728</td>
</tr>
<tr>
<td>rDLPFC</td>
<td>-0.296</td>
<td>0.066</td>
<td>20.023</td>
<td>1</td>
<td>0.001*</td>
<td>0.744</td>
<td>0.654</td>
</tr>
<tr>
<td>lVLPFC</td>
<td>-0.006</td>
<td>0.038</td>
<td>0.028</td>
<td>1</td>
<td>0.866</td>
<td>0.994</td>
<td>0.923</td>
</tr>
<tr>
<td>rVLPFC</td>
<td>0.019</td>
<td>0.044</td>
<td>0.183</td>
<td>1</td>
<td>0.668</td>
<td>1.019</td>
<td>0.935</td>
</tr>
</tbody>
</table>

Note: lDLPFC: left Dorsolateral prefrontal cortex; rDLPFC: right Dorsolateral prefrontal cortex; lVLPFC: left Ventrolateral prefrontal cortex; rVLPFC: right Ventrolateral prefrontal cortex; v: Visits; B: Regression coefficient; SE: Standard error; df: Degree of freedom. Significant differences (p≤0.05) are represented by the asterisk (*).