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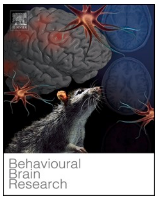

Research report

Time perception in stimulant-dependent participants undergoing repetitive transcranial magnetic stimulation

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ABSTRACT

Background: The dopaminergic (DA) system is an important neural system for the modulation of time perception and the timing of motor actions. Dysregulation of the DA system is related to chronic use of stimulant drugs, which lead, among others, to executive dysfunctions. Little is known instead about the potential deficiencies in temporal processing of stimulant-dependent individuals. The present study aimed to investigate temporal processing using a time bisection task with different temporal intervals in chronic cocaine users undergoing repetitive transcranial magnetic stimulation (rTMS).

Method: Study 1: A time bisection task with short temporal intervals range (480/1920 ms) was administered to 18 cocaine use disorder (CocUD) patients and 20 healthy control before and after the intensive phase of rTMS treatment (5 days apart). Study 2: 22 CocUD participants and 23 control participants completed two temporal tasks (time bisection and time reproduction) with long temporal intervals range (1200/2640 ms) at baseline and immediately after the intensive phase of rTMS treatment.

Results: Study 1: A shift in the psychometric function consistent with temporal overestimation in CocUD patients compared to controls was observed. However, no temporal impairment in CocUD patients at test session was found. Study 2: The analysis of temporal variability indices showed a significant difference between groups at baseline but not at Day 5 due to a significant difference between time points only in the CocUD group.

Conclusions: This study report a temporal overestimation in CocUD patients and a temporal variability reduction after an rTMS protocol in CocUD patients.

1. Introduction

The dopaminergic system and its target neural substrates, e.g., the striatum and the prefrontal cortex, are important neural systems for the modulation of time perception and the timing of motor actions [45,53,54,9]. Dopamine (DA)/glutamate interactions in cortico-striatal circuits have been proposed as a critical factor in modulating the speed of the internal clock accordingly to the internal clock model of timing [9]. Traditionally, the DA has been identified as a neurobiological substrate of the pacemaker pulses. According to this proposal, increases in the level of DA increase clock speed and decrease the uncertainty of temporal estimates, while decreases in the level of DA decrease clock speed and increase the uncertainty of temporal processing [52,66]. In the striatal beat frequency (SBF) model [48,49], temporal processing depends on the synchronisation of oscillatory processes in cortico-striatal circuits. At the onset of an interval to be timed, the model posits that cortical oscillators are phase-reset and, at the offset of the interval, the state of these cortical oscillators is read out by medium spiny neurons located in the neurons of dorsal striatum. DA release from the ventral tegmental area (VTA) at the onset of the temporal interval is believed to play a part in the phase resetting function of cortical neurons [26,49,9]. Specifically, the SBF model poses that tonic DA levels in the frontal cortex are important in setting the tonic firing rate of cortical projections to the striatum. Increases or decreases in this rate could thus result in increases or decreases in the rate of cortical oscillations, resembling a pacemaker-like mechanism [16,49]. Furthermore, this mesolimbic DA neurotransmission can be enhanced through PFC-localized serotoninergic receptors activations (specifically,

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postsynaptic 5-$HT_{2A}R$) [25]. Interestingly, chronic exposure to cocaine results in the upregulation of frontal 5-$HT_{2A}R$ [70] and the modulation of serotoninergic system in the VTA [50], which, as already mentioned, is thought to be a crucial region for phase reset timing.

Patients with Parkinson's disease (PD), who have decreased dopaminergic function in the basal ganglia have been used for a long time as a neuropsychological model for timing [29,30]. Temporal dysfunctions were observed in patients with PD when tested "off medication" with time estimation and temporal intervals between 3 and 17 s [38,62]; time production and temporal intervals between 5 and 30 s [38,89] or time reproduction and temporal intervals between 1.6 and 15 s [34,33,35,62,78,89] and adequate temporal abilities when tested with the same tasks "on medication" [55,65,68,85]. More germane to the present study, Koch and colleagues [33] showed a greater temporal impairment in left hemi-PD compared to right hemi-PD patients. Nevertheless, the magnitude of temporal dysfunction depends on the heterogeneity of PD (both clinical and cognitive characteristics) and the type of temporal task and temporal range used. Indeed, when tested with time comparison tasks and temporal intervals between 200 and 1600 ms, PD patients were as accurate as controls [29,30].

Dysregulation of the dopaminergic system is also related to the chronic use of drugs such as stimulants [81]. In fact, the continuative consumption induces a profound motivational circuits alteration, involving not only DA but other neurotransmitter systems, which leads to a chronic, relapsing, addictive disorder [36] resulting from the convergence of aberrant incentive salience and habit generation [83,82], reduced reward sensitivity [46,84], excessive stress response [71,72,73], and executive dysfunction [24,61] in a three-stage recurring cycle (i.e., intoxication, withdrawal and anticipation phases). More specifically, during the anticipation phase, the craving states and executive control deficiencies, including alterations in response inhibition and error-processing mechanisms [31,74], are associated with abnormal activations in prefrontal regions of the mesocorticolimbic-DA system [32,4,59], whose functioning is crucial for learning, goal-directed behaviour, reward processing and goal-directed attention allocation [19,7]. While these cognitive dysfunctions associated with frontolimbic DA and serotonin-related disruptions are widely reported in stimulant-dependent individuals [21], less is known instead about whether these individuals have fundamental problems with temporal processing as reported in other clinical populations with dopaminergic-related timing deficits [1,2].

Previous research conducted on rats showed cocaine-induced temporal overestimation consistent with the idea of an increased clock speed [14,15]. Mixed results have been reported regarding the clock speed effect of other psychostimulants as amphetamine [8,75]. The few studies conducted with stimulant-dependent users reported conflicting results; Mohs et al. [60][1] revealed relatively shortened temporal production following acute methamphetamine injection after 1, 2, and 3 h, reflecting a continuous acceleration of cognitive processes. Wittmann et al. [88] demonstrated that stimulant-dependent patients exhibited deficits in perceptual and motor timing in temporal intervals around 1–2 s. Zhang et al. [90] reported group differences in a time reproduction task for short-term abstinence but no differences in a time discrimination task, concluding that alteration of time perception in methamphetamine-dependent patients is task-specific and dose-dependent. More recently, Mioni and colleagues [58] reported no differences between patients and controls in terms of perceived time, but patients were more variable (higher *WR*) than controls. The authors reasoned that the lack of difference between groups could have been related to the duration of abstinence in stimulant-dependent patients. Indeed, compared with previous studies patients included in Mioni et al. [58] study were abstinent for on average of 127 days [88] 27.7 ± 5.6 days; [90] 69.74 days ± 35.95.

The present study aimed to investigate temporal processing using a time bisection task with different temporal intervals in chronic cocaine users. Patients were tested on the first day of recovery and they were tested before and after a left dorsolateral prefrontal cortex (-l-DLPFC) high-frequency (HF) repetitive transcranial magnetic stimulation (rTMS) protocol, a novel neuromodulation treatment has been demonstrated to be effective in reducing craving, drug use and withdrawal symptoms [12,40,41,42,76,13].

We predicted temporal overestimation and higher temporal variability in cocaine use disorder (CocUD) patients compared to controls tested during the first day of recovery, consistent with the effect of a stimulant on clock speed [9]. Moreover, since the long-term rTMS-induced neuroplastic effect and the significant improvements in craving and other withdrawal symptoms reached after the first treatment week (when daily sessions were administered in a consecutive manner) we predict attenuated temporal impairment in CocUD patients compared to controls at retest. Patients and controls will be assessed at two different timepoints 5 days apart to test the possible effect of the intensive phase of rTMS treatment on dopaminergic circuits.

2. Study 1 – time bisection task with short temporal intervals range

2.1. Materials and methods

2.1.1. Participants

Eighteen right-handed CocUD male patients and 20 healthy control males age-matched were assessed. CocUD participants were recruited after referral to the clinic for addiction treatment in Padova, Italy. All patients were treatment-seeker participants meeting CocUD diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders – 5 (DSM 5), as ascertained by a clinical psychiatrist with substance use disorders expertise [3]. Exclusion criteria included a prior history of other severe psychiatric diseases, including major depression, bipolar disorder, schizophrenia or other psychosis, other substance use disorder (excluding cocaine, nicotine, and caffeine for CocUD participants), current pharmacological treatment with dopaminergic agonists or antagonists (e.g. quetiapine), personality disorders or sleep disturbances reputed as the primary disorder, current unstable medical status, significant neurological illness, and any contraindication for rTMS (including implanted metal and devices in the body, or history of epilepsy).

The main demographic and clinical characteristics of the sample are summarized on Table 1 divided by group. Healthy participants consisted of 20 male participants aged between 27 and 56 (39.4 ± 9.56). CocUD individuals ($n = 18$) were aged between 27 and 53 (37.06 ± 7.44). The years of education was between 8 and 18. No significant differences were found between groups in age and education (p's > 0.1). The addiction years average referred by the participants was superior to seven years (8.06 ± 5.93) and the self-reported days of cocaine consumption in the month prior to treatment intake was high (22.33 ± 9.21).

2.1.2. Clinical assessment

The core addiction symptomatology (i.e., craving, sleep disturbances, mood, and other negative affect symptoms) was assessed through the following standardized self-report scales:

Cocaine Craving Questionnaire (CCQ): A self-administered questionnaire composed of five questions on intensity and frequency of craving, both currently and in the preceding 24 h that have been shown to possess short-term predictive validity of cocaine use [86]. *Beck Depression Inventory II* (BDI-II): A 21-item self-report inventory assesses the severity of depression [6]. *Self-rating Anxiety Scale* (SAS): A self-report inventory, which assesses the severity of anxiety [91]. *Pittsburgh Sleep*

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[1] Notably, participants were not methamphetamine-dependent patients, but healthy volunteers tested after they had received 10 mg of methamphetamine, 100 mg of secobarbital or a placebo on separate days.

Table 1
Demographic and clinical characterization of Experiment 1 sample.

Variables	Controls	CocUD Patients (test)	CocUD Patients (retest)
n	20	18	
Gender (Female / Male)	0/20	0/18	
Age (years)	39.4 (9.56)	37.06 (7.44)	
Education (years)	13.3 (3.37)	11.66 (2.47)	
Age of first exposure		20.83 (6.69)	
Addiction years		8.06 (5.93)	
Duration of current abstinence (days)		2.39 (1.68)	
CCQ score		22 (12.87)	5.56 (4.48)
BDI-II score*		20 (7.42)	-
SAS score		52 (8.82)	38 (7.23)
PSQI score		10.33 (4.43)	6.06 (3.08)
GSI score		72.84 (18.72)	47.47 (7.99)

Data are presented as mean (standard deviation), unless otherwise specified. *BDI-II* Beck Depression Inventory-II; *CCQ* Cocaine Craving Questionnaire; *GSI* Global Severity Index of the Symptoms checklist 90 - Revised; *PSQI* Pittsburgh Sleep Quality Index; *SAS* Self-rating Anxiety Scale; * The instructions of BDI-II require the participant to consider the last 2 weeks preceding the test; thus, it was not included in the retest at Day 5.

Quality Index (PSQI): A self-report scale to assess perceived sleep quality [10]. *Symptom Checklist-90-R* (SCL-90-R): A brief self-report psychometric instrument to evaluate a broad range of psychiatric symptoms and to measure the progress and outcome of psychiatric and psychological treatments [18]. Moreover, cocaine use was examined through urine drug tests and reports from the patients or from collateral informants (usually patients' relatives).

2.1.3. *Procedure*

CocUD participants were tested in the specialty clinic for Addiction in Padua (Italy) and controls were tested either at the same centre or at the Department of General Psychology (Padova, Italy). During the task, the participants were seated at approximately 60 cm in front of a 15-inch PC monitor screen. PsychoPy3 [64] was used to set up and run the experiments, which lasted about 10 min. The standardized clinical assessment and the task administration were performed to the CocUD patients at baseline and immediately after the conclusion of the first treatment week (Day 5), excluding BDI-II evaluation, whose instructions require the participant to consider the last two weeks preceding the test. To adapt to the timepoints assessment of the CocUD cohort, healthy controls performed the time bisection task twice with a 5-day gap between sessions.

The time perception investigation (for Study 1 and 2), limited to the psychological research protocol, was approved by the Ethical Committee for the Department of general Psychology, University of Padova (Protocol no. 3396), and the study was conducted according to the Helsinki's Declaration. For CocUD patients, at treatment entry, the clinical staff (i.e., a psychiatrist and a psychologist) collected an exhaustive family, physiological, and pathological history, including detailed psychiatric and toxicological aspects. Before such clinical collection, patients signed an informed consent agreeing to the use of their data for research purposes included in the protocol approved by the Ethical Committee at Padua Teaching Hospital (protocol number: 4743/U6/19). All participants were advised that the data collected would be elaborated according to the law on privacy and the Legislative Decree N°. 196 of June 30, 2003, "Personal Data Protection Code", safeguarding anonymity.

2.1.4. *Materials*

2.1.4.1. Time bisection task. We used a time bisection task to test the temporal abilities of our participants. The task is composed of a learning and a testing phase. In the learning phase, the short anchor duration was 480 ms and the long anchor was 1920 ms repeated 10 times. After the learning phase, participants were instructed to estimate whether the probe durations were closer to the "anchor short" or the "anchor long" previously memorised. The probe durations were 480, 720, 960, 1200, 1440, 1680, and 1920 ms. Participants performed three blocks and within each block, each duration was presented 10 times in random order. Participants were asked to respond with their left and right index fingers, and response keys were counterbalanced between participants.

2.1.5. *rTMS procedure*

The rTMS protocol was provided to each patient while seated in a comfortable chair by a trained clinical physiologist. TMS stimuli were delivered via medical device (MagPro R30, MagVenture, Farum, Denmark) targeting the l-DLPFC (MNI coordinates: $x = -50$, $y = 30$, $z = 36$). To best identify the target region, an optical TMS Navigator (LOCALITE, St. Augustin, Germany) and a magnetic resonance image (MRI) template were employed. Resting motor threshold (rMT) was determined using visual observation of muscle twitch (OM-MT), as previously reported [76]. The stimulation protocol parameters, in line with the international standards for safety [69], were: 15 Hz frequency, 100% of rMT, 40 trains, 60 pulses per train, 15 s intertrain interval, and 2400 pulses per session. Patients received 2 sessions per day for the first consecutive 5 days of treatment (10 sessions) with a time interval between daily sessions of 30 min at least. At each session, the possible occurrence of adverse events was also monitored. Moreover, individualized psychological support was supplied day-to-day by an addiction expert clinical psychologist.

2.1.6. *Statistical analyses*

Independent sample *t*-tests were estimated to test differences in age and education between CocUD and healthy control participants. Regarding the analyses of time bisection task, we used two different approaches following Capizzi and colleagues [11]. Both were performed using Mixed-Effects models implemented in the R environment (http://www.R-project.org/) by the means of functions from the *lme4* library. The first approach considered all trials for each subject, modelling the probability of "long" responses through logistic regressions conducted with the *glmer* function (i.e., a generalized linear mixed model, GLMM, with probit-link function). The fixed terms included in the GLMM were: "*Time Interval*" as a continuous variable centred and scaled to improve the interpretation and the fit of the model, "*Session*" as a factor (Pre vs Post), "*Group*" as a factor (Controls vs CocUD patients), and their interactions. Participants were treated as random effects. Data from trials with missing responses were discarded from the analysis. To quantify and evaluate the contribution of *Session* and *Group* in explaining the data two model comparisons were conducted, each one including three models: (i) a simple model with just *Time Interval* as a fixed term; (ii) a model adding in one case *Session* and in the other case *Group* (and their interaction with *Time Interval*); and (iii) the full model including *Time Interval* and both *Session* and *Group* variables. The summary of the best-fitting model will be reported.

Indeed, with the second approach, we calculated for each subject two indices as dependent variables. The first was the Bisection Point (BP), that is, the stimulus duration at which participants responded "short" or "long" with equal frequency. An observed shift of the BP can be understood as a marker of differences in perceived duration [37], with smaller BP values meaning longer perceived durations. The second dependent variable was the Weber ratio (W*R*), a measure of temporal sensitivity, which is based on the just noticeable difference (JND, i.e., the smallest change in the stimulus that produces a change in behaviour) divided by the BP. The JND was defined as the difference between estimated durations yielding 75% and 25% accuracy [37]. Linear mixed models, with a random intercept for each subject, were computed for each primary outcome (BP, W*R*), considering the following variables as fixed effects: *Session*, *Group*, and *Session* × *Group* interaction. To estimate the overall effect of predictors it was performed a type III analysis of variance with Satterthwaite's method for computing the denominator degrees of freedom of each F-test. Post-hoc multiple pairwise comparisons were corrected using the Bonferroni method. Data were expressed as mean ± standard deviation (SD), unless otherwise specified; alpha was set at $< .05$, two-tailed. Referred to CocUD patients, paired sample *t*-tests were estimated to test differences in the self-report scale scores between timepoints.

2.2. Results

2.2.1. Logistic regression

Model comparison showed that the full model, including *Time Interval*, *Session* and *Group* variables, had the best fit. The summary of the model output is presented in Table 2.

Fig. 1 shows the finding of significant interactions between *Time Interval* and *Group*, and between *Session* and *Group*. Specifically, CocUD patients tended to overestimate brief temporal intervals compared to controls independently of the Session (Fig. 1. A). Also, control participants significantly reduced the proportion of "long" responses in the post assessment as revealed by the post-hoc analyses (OR: 1.345, $p = .01$) (Fig. 1. B) (see supplementary materials for analyses and results of RT).

2.2.2. Time perception indices

Concerning the BP, the analysis of variance showed no significant effects (all $p > .13$). Indeed, we found a significantly main effect of *Group* in the prediction of *WR* [$F(1,38) = 16.93$, $p < .001$]: CocUD patients showed a higher *WR* compared to controls (Table 3).

2.2.3. Clinical outcome scores

Paired sample *t*-tests showed a significant improvement in the clinical symptomatology of CocUD patients over time. In particular, at Day 5 it was observed a significant decrease of craving [CCQ: $t(17) = 6.4$, $p < .001$], anxiety [SAS: $t(17) = 8.08$, $p < .001$], and of global severity index [GSI: $t(17) = 6.49$, $p < .001$], and an improvement in subjective quality of sleep [PSQI: $t(17) = 3.08$, $p = .001$].

3. Discussion

Regarding the clinical symptomatology of CocUD patients, we observed a significant reduction of core symptoms (e.g., craving, anxiety, self-perceived quality of sleep) after the first week of treatment with rTMS. Clearly, it is not possible to exclude a placebo effect and patients should be observed for longer time periods. However, previous studies showed how this same pattern of improvement observed after 5 days of treatment was maintained overtime [12,22,13]. It is out of the purpose of the present study to assess the clinical efficacy of rTMS in the treatment of cocaine dependence and future studies using a standardized approach are necessary to provide more clarity.

Table 2
Summary of the best fitting model output in Study 1.

Fixed Effects	Odds Ratios	CI	*p*
(Intercept)	1.64	1.11 – 2.40	**.012**
Time Interval	22.29	17.65 – 28.15	**< .001**
Session	0.74	0.62 – 0.90	**.002**
Group	1.28	0.73 – 2.23	.388
Time Interval × Session	1.04	0.76 – 1.42	.823
Time Interval × Group	0.62	0.45 – 0.84	**.002**
Session × Group	1.37	1.05 – 1.78	**.020**
Time Interval × Session × Group	0.77	0.51 – 1.17	.220
N_{ID}	38		
Observations	9055		
Marginal R^2 / Conditional R^2	0.637 / 0.699		

Regarding time processing, we did observe a shift in the psychometric function consistent with temporal overestimation in CocUD patients compared with controls. CocUD patients tended to respond more time "long" when brief temporal intervals were presented. Considering the lack of evidence for a systematic over- or underestimation bias in the BP task but a flatter psychometric function for brief intervals we can hypothesise that CocUD patients had a noisier memory representation of short standard durations [11] rather than a specific dysfunction at the level of the internal clock. This is also in line with the lower temporal sensitivity observed in CocUD patients. It is worth mentioning that we did not find a clear temporal impairment in CocUD patients at baseline compared to controls, the interaction between Session and Group indicated that at retest controls tended to press less time "long" probably an index of learning effect.

The lack of clear temporal impairment at baseline was surprising considering that previous studies have found lower temporal abilities in CocUD patients relative to controls. It is important to note that previous studies have used longer temporal intervals compared to the present study: Mohs et al.'s [60] study participants were asked to produce intervals of 30, 60, and 120 s; Wittmann et al. [88] showed temporal impairment in patients around 1–2 s and Zhang et al. [90] used temporal intervals between 1 and 5 s for the time reproduction task and sub-second (between 200 and 800 ms) and supra-second (between 1300 and 2600 ms) intervals for the time discrimination task. Only Mioni and colleagues [58] used brief temporal intervals and similarly to the present study, did not observe temporal impairment in substance user patients. The authors claimed that the lack of group difference was due to patients' clinical characteristics (very long time of abstinence). For the second study, we decided to use longer intervals considering that previous studies reported temporal disfunction in CocUD patients in particular when tested with longer temporal intervals [88,90].

It is well known that not only the temporal range but also the type of task used affects temporal performance. Previous studies showed that temporal impairment in methamphetamine users is more pronounces using motor timing tasks rather than using perceptual timing tasks [88,90]. In perceptual tasks (i.e., time bisection task) participants typically judge relative durations, i.e., for time bisection task if the presented interval is more similar -in duration- to the standard short or to the standard long. In motor timing tasks, participants are asked to produce a motor action i.e., in the time reproduction task participants are asked to keep pressed the space bar as long as the duration of the temporal interval previously presented [17]. Therefore, in Study 2 we add a second timing task, the time reproduction task to test also the motor timing component.

Taken together, we predict lower temporal abilities in CocUD patients compared to control in particular when tested with the motor timing task (time reproduction) compared to the perceptual timing task (time bisection task). Moreover, we predict attenuated temporal dysfunction and reduced temporal variability in patients compared to controls after rTMS stimulation.

4. Study 2 – time bisection and time reproduction tasks with long temporal intervals range

4.1. Materials and methods

4.1.1. Participants and procedure

A new sample of 22 right-handed CocUD participants (18 males and 4 females) and twenty-three right-handed healthy control participants (18 males and 5 females) matched for age [$t(43) = -1.31$, $p = .19$] and education years [$t(43) = -1.04$, $p = .3$] were studied. The recruitment procedure, the CocUD diagnostic modality, and the sample exclusion criteria were the same as those described in Study 1. The full baseline demographic and clinical features of the participants are shown in Table 4. CocUD patients reported being addicted to cocaine for more than 5 years on average (5.32 ± 4.94). The self-reported days of cocaine

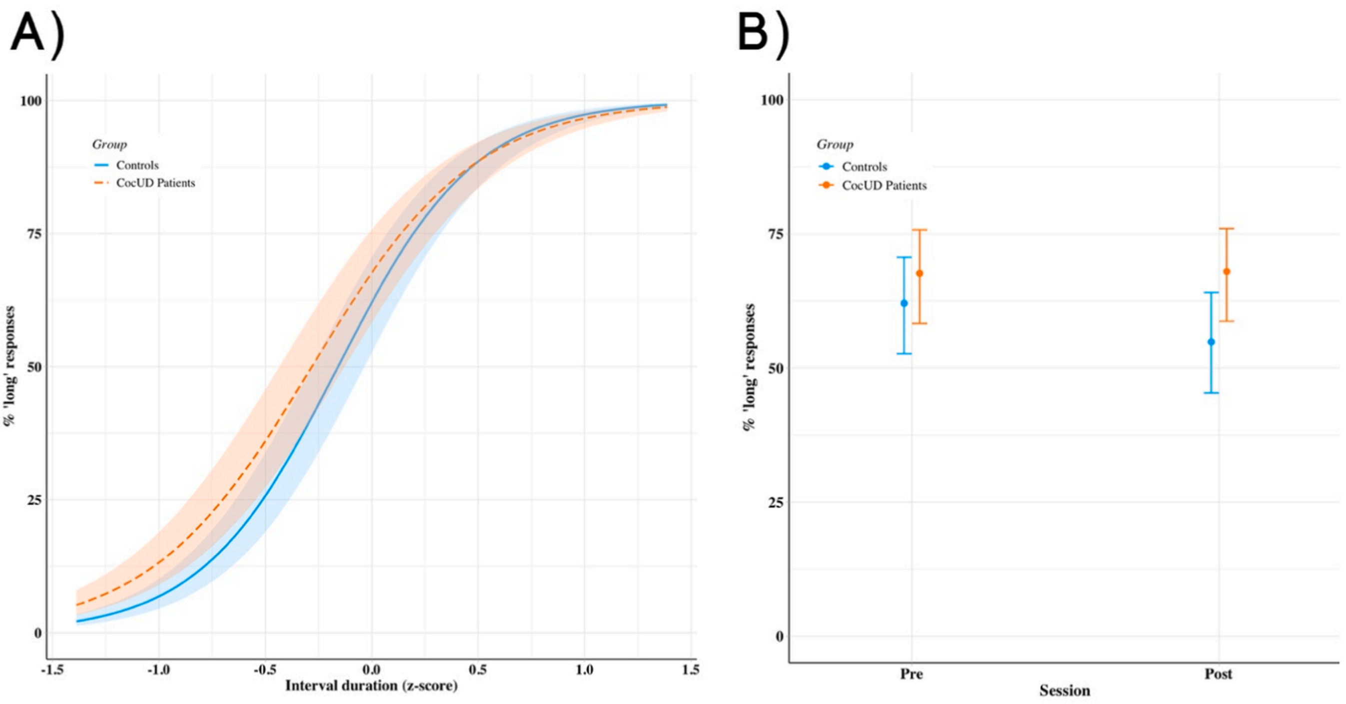

Fig. 1. Significant interaction effects of the full model for Study 1. Panel A depicts the interaction between *Time Interval* and *Group*. Panel B depicts the interaction between *Session* and *Group*. Shaded error areas and error bars show 95% confidence intervals.

Table 3
Bisection Point (BP) and Weber Ratio (*WR*) indices observed in Study 1 and Study 2 grouped by *Group* and *Session.*

			CocUD Patients	Controls
			M (SD)	M (SD)
Study 1	**BP**	Baseline	1085.63 (173.81)	1124.98 (137.54)
		Day 5	1052.52 (226.89)	1169.32 (191.01)
	WR	Baseline	0.35 (0.08)	0.26 (0.07)
		Day 5	0.33 (0.12)	0.23 (0.06)
Study 2	**BP**	Baseline	1887.43 (196.28)	1898.42 (146.85)
		Day 5	1932.23 (234.25)	1897.73 (133.65)
	WR	Baseline	0.23 (0.09)	0.16 (0.03)
		Day 5	0.17 (0.07)	0.15 (0.04)

assumption during the 30 days prior to admission was high (18.73 ± 10.87). No significant differences were found between groups in age and education (p's > 0.19). Participants underwent identical experimental protocol and rTMS procedures as described in Study 1.

4.1.2. *Materials*

4.1.2.1. Time bisection task. We used the same temporal task used in Experiment 1 but with longer temporal intervals. In the learning phase, the short anchor duration was 1200 ms and the long anchor was 2640 ms repeated 10 times. After the learning phase, participants were instructed to estimate whether the probe durations were closer to the "anchor short" or the "anchor long" previously memorised. The probe durations were 1200, 1440, 1680, 1920, 2140, 2400, and 2640 ms. Participants were asked to refrain from counting [67].

4.1.2.2. Time reproduction task. Participants were instructed to reproduce the duration of a previously viewed stimulus. The stimulus was a blue circle that appeared at the centre of the computer screen; after a 1-s inter-stimulus interval, a question mark was presented, and participants had to press the spacebar for the same duration the stimulus was on the screen. Participants were asked to refrain from counting [67]. The stimuli used lasted 1200, 1680, 2160, and 2640 ms, each interval was repeated 12 times. A practice phase was introduced to familiarise the task.

Table 4
Demographic and clinical characterization of Experiment 2 sample.

Variables	Controls	CocUD Patients (test)	CocUD Patients (retest)
n	23	22	
Gender (Female / Male)	5/18	4/18	
Age (years)	34.48 (7.77)	37.27 (6.40)	
Education (years)	12.39 (3.62)	13.4 (2.82)	
Age of first exposure		21.36 (4.77)	
Addiction years		5.32 (4.94)	
Duration of current abstinence (days)		12.30 (10.15)	
CCQ score		25.1 (12.06)	6.43 (8.27)
BDI-II score*		19.45 (10.73)	-
SAS score		48.5 (9.92)	38.95 (9.68)
PSQI score		9.14 (4.43)	6.95 (3.75)
GSI score		70.16 (16.80)	51.14 (14.98)

Data are presented as mean (standard deviation), unless otherwise specified. *BDI-II* Beck Depression Inventory-II; *CCQ* Cocaine Craving Questionnaire; *GSI* Global Severity Index of the Symptoms checklist 90 - Revised; *PSQI* Pittsburgh Sleep Quality Index; *SAS* Self-rating Anxiety Scale; * The instructions of BDI-II require the participant to consider the last 2 weeks preceding the test; thus, it was not included in the retest at Day 5.

4.1.3. *Statistical analyses*

Similarly, the same analyses conducted in Study 1 were followed here for the time bisection task. For the time reproduction task, the data were analysed in terms of the estimated-to-target-duration ratio (RATIO) and the coefficient of variation (CV). The RATIO was obtained by dividing each participant's time performance by the time duration of the interval presented for that trial [RATIO=Rd/Td]. This also provided an index of the direction of errors, with coefficients above and below 1.0

being indicative of over-reproduction and under-reproduction, respectively. The CV was computed by dividing the standard deviation by the mean judgment [CV=SD/M]. The CV index represented the variability in temporal judgments for each participant and evaluated the consistency of time performance for the same target duration [56]. Linear mixed models, with a random intercept for each subject, were computed for both RATIO and CV coefficients, considering as fixed effects *Session*, *Group*, *Time Interval,* and *Session* × *Group* × *Time Interval* interaction.

4.2. Results

4.2.1. Time bisection task

4.2.1.1. Logistic regression. Model comparison showed that the best fitting model was the full one, which included *Time Interval* duration, *Session* and *Group* variables. The summary of the model output is presented in Table 5.

Fig. 2 shows the finding of significant interactions between *Time Interval* and *Group*, and between *Session* and *Group*. Specifically, the shape of the psychometric curve is significantly flattered in CocUD patients compared to controls (Fig. 2. A). With regard to the significant effect of the interaction between *Session* and *Group*, post-hoc analyses showed a reduction in the proportion of “long” responses in the post-assessment, only in the CocUD patients (OR: 1.260, $p = .04$; Fig. 2. B). The *Time Interval* × *Session* × *Group* three-way interaction was not significant (see supplementary materials for analyses and results of RT).

4.2.1.2. Time perception indices. Regarding the BP indicator data, no predictor had a significant effect (all $p > .4$. Instead, when the data were analysed in terms of *WR* index, significant effects emerged for variable *Session* [$F(1,45)= 13.869$, $p < .001$], *Group* [$F(1,45)= 5.389$, $p = .02$], and their interaction [$F(1,45)= 7.406$, $p = .009$] (Fig. 3) (Table 6). Pairwise comparisons of *WR* scores showed a significant difference between groups at baseline [$t(73.7) = -3.277, p < .01$] but not at Day 5 [$t(73.7) = -0.689$, $p = 1$] due to a significant difference between timepoints (i.e., baseline and Day 5) in the CocUD group [$t(47.1) = 4.407$, $p < .001$] which was not observed in the healthy control group [$t(47.1) = 0.701$, $p = 1$].

4.2.2. Time reproduction task indices

Due to technical issues data of 8 CocUD patients were broken for this reason we are reporting the analyses on 14 CocUD patients [mean age= 34.2 (5.55) years; level of education= 12.8 (13.0) years] and their matched controls [mean age= 31.5 (5.98) years; level of education= 12.6 (13.0) years]. No differences were observed between groups in terms of age [$t(26) = 1.24$, $p = .224$] or level of education [$t(26) = 0.11$, $p = .916$].

Concerning the RATIO, the analysis of variance showed a significant effect of *Time Interval* [$F(1196)= 17.82$, $p < .001$), indicating that participants tended to under estimate time as duration of temporal interval increased. No other significant effects were found nor interactions (all $ps > .2$). similarly for the analyses conducted on CV we found a significant main effect of *Time Interval* [$F(1196)= 29.15$, $p < .001$] indicating that participants were less variable as the duration of the temporal interval increased. No other significant effects were found nor interactions (all $p > .1$).

Table 5
Summary of the best fitting model output in Study 2.

Fixed Effects	Odds Ratios	CI	*p*
(Intercept)	1.19	0.86 – 1.63	.294
Time Interval	15.06	12.35 – 18.36	**< .001**
Session	1.02	0.86 – 1.22	.816
Group	1.11	0.71 – 1.75	.648
Time Interval × Session	1.25	0.94 – 1.67	.125
Time Interval × Group	0.67	0.52 – 0.87	**.003**
Session × Group	0.78	0.61 – 0.99	**.043**
Time Interval × Session × Group	1.07	0.73 – 1.57	.720
N_{ID}	45		
Observations	9287		
Marginal R^2 / Conditional R^2	0.615 / 0.667		

4.2.3. Clinical outcome scores

Paired sample *t*-tests showed a significant improvement in the clinical symptomatology of CocUD patients over time. Specifically, on Day 5 it was observed a significant decrease in craving [CCQ: $t(19) = 6.08$, $p < .001$], anxiety [SAS: $t(20) = 4.01$, $p < .001$], and global severity index [GSI: $t(19) = 6.81$, $p < .001$], and a significant improvement of subjective quality of sleep [PSQI: $t(20) = 2.41$, $p = .02$].

4.3. Discussion

Concerning the clinical measures, the results of Study 2 draw a similar pattern to those of Study 1, showing a significant CocUD core symptomatology reduction after the first week of treatment. These results are in line not only with what has been reported in other open-label rTMS studies [12,22,13] but also with the outcome of recent sham-controlled, double-blind rTMS trials [20,41], especially in individuals with CocUD and depressive symptomatology [47].

Concerning the time bisection task, results from Study 2 mirror what was observed in Study 1; in spite of the time of assessment, the shape of the psychometric curve was significantly flattered in CocUD patients compared to controls indicating a noisier memory representation of time in patients rather than a specific dysfunction at the level of the internal clock [11]. This is also in line with the higher temporal variability observed in CocUD patients. As for Study 1, CocUD patients were more variable on Day 1 compared to controls, interestingly when tested on Day 5 we observed a reduction in variability in patients compared to controls. No effect of session was observed in controls in terms of variability.

Study 2 also included a time reproduction task to tap motor timing. Participants tended to over-reproduce short intervals and under-reproduce longer intervals consistent with Vierordt’s law [39] also called the migration effect [43]. Vierordt’s law describes an individual’s reproduction central tendency, which depends on the distribution of displayed durations (i.e., temporal context) rather than current stimuli [27]. The effect cannot be explained in terms of decreased internal timekeeper speed. Based on the finding that the effect does not occur when only one-time duration is included in a single session, the shift of reproduced temporal duration has been ascribed to dysfunctional short-term memory [43], more specifically, “temporal memory averaging,” when two or more temporal representations have to be stored in memory [5]. Differently from Wittman et al. [88] and Zhang et al. [90] we did not observe lower temporal ability or higher variability in CocUD patients compared to controls on Day 1. Both studies used a time reproduction task with temporal intervals between 1 and 5 s. Wittmann et al., [88] showed temporal underestimation at 2 s and higher temporal variability at 1 s in patients compared to controls; Zhang et al. [90] showed higher temporal underestimation for durations longer than 2 s but unexpectedly patients were less variable than controls.

5. General discussion

The present study was conducted to further investigate temporal misperception in stimulant-dependent users. We included two temporal intervals: short range (480 – 1920 ms) and long range (1200 – 2640 ms) and two timing tasks tapping perceptual (time bisection task) and motor (time reproduction task) temporal abilities.

The strongest evidence of an effect of stimulant on timing comes from studies with rats [14,15]. They reported that stimulant induced leftward shift, suggesting an accelerated speed of the internal clock and temporal overestimation [16]. The underlying mechanism of this effect

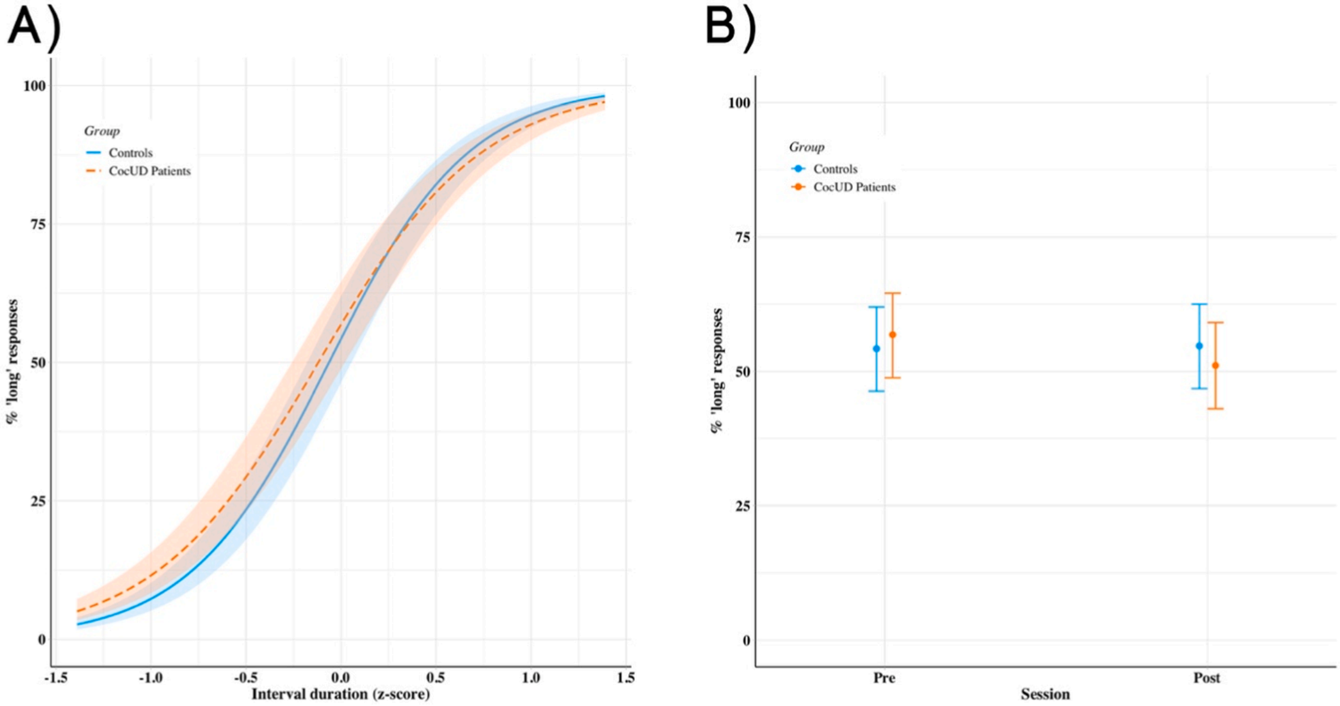

Fig. 2. Significant interaction effects of the full model for Experiment 2. Panel A depicts the interaction between *Time Interval* and *Group*. Panel B depicts the interaction between *Session* and *Group*. Shaded error areas and error bars show 95% confidence intervals.

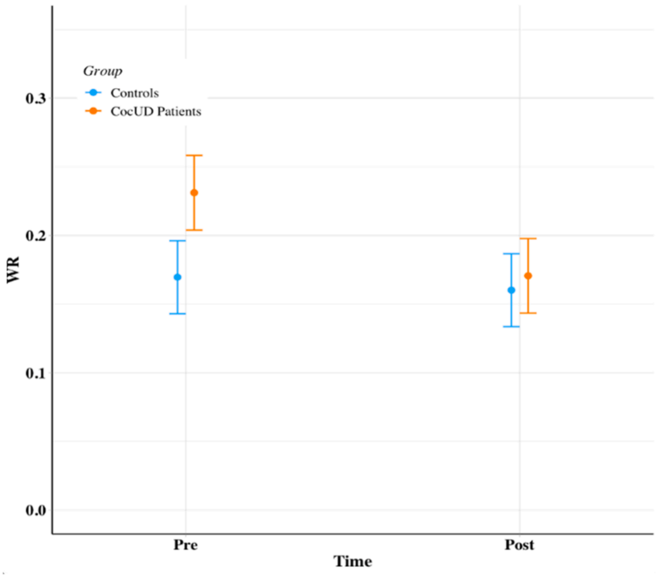

Fig. 3. Significant interaction effect in the linear mixed model predicting *WR* in Study 2. Error bars show 95% confidence intervals.

mainly relates to the effect of stimulant to the dopaminergic system in the striatum and prefrontal cortex [23,63]. In other words, the dopamine mechanism of time perception overlaps with stimulant-affected brain regions (e.g., prefrontal-striatum network, motor cortex). Studies conducted with humans seem to point in the direction of temporal impairment in stimulant dependent patients but a closer look at the results indicate a mixed patter of results. Indeed, temporal misperception depends on the temporal task used, the temporal range under investigation, and the length of abstinence [60,88,90,58].

Our results limit our ability to draw strong conclusions regarding the causal effect of stimulant dependence on time processing. They suggest that temporal processing abnormalities in CocUD patients result from dysfunctions in fronto-striatal areas of the brain that increased temporal variability rather than time perception. Higher variability has been observed in patients and interpreted as a marker of lower cognitive abilities. Overall, the prefrontal cortex is strongly involved in executive functions such as attention regulation, the control of behaviour and thoughts, and planning for future actions [46,61,72,84,82,83]. These complex cognitive functions are intimately related to impulse control and are impaired in substance abusing individuals [36].

Previous studies showed a specific role of the right DLPFC in explicit time processing in the range of seconds [17,57,87]. Koch and colleagues (2004) showed an improvement in time processing (accuracy) in patients with PD when rTMS (5 rTMS trains of 50 stimuli at 5-Hz frequency) was applied over the right DLPFC. The authors suggested that

Table 6
Mean and standard deviation for RATIO and CV of time reproduction task in Study 2 grouped by *Group, Time Interval* and *Session.*

		Time Intervals							
		1200 ms		1680 ms		2160 ms		2640 ms	
		Baseline M(SD)	*Day 5* M(SD)	*Baseline* M(SD)	*Day 5* M(SD)	*Baseline* M(SD)	*Day 5* M(SD)	*Baseline* M(SD)	*Day 5* M(SD)
Ratio	*CocUD Patients*	0.98 (0.23)	1.09 (0.21)	0.98 (0.19)	0.99 (0.18)	1.02 (0.31)	0.97 (0.10)	0.89 (0.2)	0.92 (0.13)
	Controls	1.01 (0.18)	1.07 (0.20)	1.02 (0.12)	1.05 (0.12)	1.00 (0.14)	0.99 (0.10)	0.93 (0.10)	0.97 (0.14)
CV	*CocUD Patients*	0.29 (0.15)	0.22 (0.11)	0.25 (0.09)	0.19 (0.10)	0.24 (0.27)	0.12 (0.06)	0.16 (0.11)	0.14 (0.08)
	Controls	0.20 (0.09)	0.20 (0.08)	0.17 (0.05)	0.18 (0.06)	0.14 (0.05)	0.12 (0.04)	0.14 (0.06)	0.11 (0.04)

rTMS over the right DLPFC may improve time perception in PD patients by enhancing directly the DLPFC activity, which is decreased because of reduced input from the basal ganglia. Here we target the left DLPFC because of strong evidence that stimulation of this region modulates the activity of the meso-cortico-limbic circuitry via the anterior cingulate cortex (ACC) [77], which is a crucial area for craving states emergence [32], but the ACC-DLPFC interplay is also thought to be determinant in the adjustment to other cognitive processes [44]. Therefore, we expected a similar beneficial effect of rTMS on CocUD patients as the one observed in PD patients [34]. We observed a reduction in temporal variability rather than a modulation of perceived time. Accuracy and variability are two distinct indices, with accuracy reflecting how close timing responses are to their target, and variability reflecting how repeated responses are spread from their target [28]. Previous studies speculated on right/left hemispheric differences for temporal accuracy and variability, respectively. It is important to note that previous studies targeted different brain areas but is still worth mentioning that they showed reduced temporal variability when electric stimulation was applied over the left hemisphere. Vicario et al., [80] targeted the right and left posterior parietal cortex (PPC) with anodal/cathodal transcranial direct current stimulation (tDCS). Results showed that cathodal tDCS applied over the right PPC produced temporal over-estimation (modulates accuracy), instead, when cathodal tDCS was applied to the left PPC reduced temporal variability. Further support to a possible role of the left hemisphere in monitoring timing variability originates from a study on individuals with a left-sided stroke, who were asked to perform a tapping task; a higher variability of the inter-tap interval was observed in stroke patients compared to control individuals (Kwon et al., 2007).

However, when it comes to interpreting our results, several limitations need to be considered. First, the naturalistic clinical setting in which our cohort of CocUD patients underwent the rTMS treatment did not allow to manipulate the brain stimulation protocols and therefore, to better control whether the effects were due to differential practice effects or not. Future time perception research on CocUD participants undergoing rTMS should address this issue by inserting sham or vertex stimulation as control groups. Second, male participants were overrepresented in our study sample. Since important gender differences in the cocaine dependence symptomatology and neurobiology, including arousal and stress reactivity process, which are mostly increased cocaine-dependent women compared with men [51], and that are known to produce time distortion effects [79], more pronounced time misperception findings than that of the present study would be expected from forthcoming timing CocUD studies with samples better distributed by gender. Taken together we showed a temporal overestimation of CocUD patients compared to controls independently of the day of testing; rTMS modulated temporal variability in Study 2 indicating reduced variability in patients at Day 5. Moreover, our results confirmed previous evidence of a clinical improvement in CocUD patients after rTMS treatment.

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CRediT authorship contribution statement

Mioni Giovanna: Conceptualization, Data curation, Methodology, Software, Supervision, Writing – original draft. **Gómez Pérez Luis J.:** Data curation, Formal analysis, Methodology, Writing – review & editing. **Cardullo Stefano:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **Gallimberti Luigi:** Project administration, Supervision, Writing – review & editing. **Terraneo Alberto:** Supervision, Writing – review & editing.

Conflict of interest statement

No conflict declared.

Data Availability

Data will be made available on request.

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Contributors

All authors contribute to the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2023.114816.

References

[1] M.J. Allman, W.H. Meck, Pathophysiological distortions in time perception and timed performance, Brain 135 (3) (2012) 656–677.

[2] M.J. Allman, A. Vatakis, in: A. Allman, J. Melissa, Vatakis (Eds.), Time distortions in mind: temporal processing in clinical populations, Brill, 2015.

[3] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition. DSM-5, American Psychiatric Publishing, 2013, https://doi.org/10.1176/appi.books.9780890425596.744053.

[4] A. Barrós-Loscertales, V. Costumero, P. Rosell-Negre, P. Fuentes-Claramonte, J. Llopis-Llacer, J.C. Bustamante, Motivational factors modulate left frontoparietal network during cognitive control in cocaine addiction, Addict. Biol. 25 (4) (2020), e12820.

[5] K.M. Bausenhart, O. Dyjas, R. Ulrich, Temporal reproductions are influenced by an internal reference: Explaining the Vierordt effect, Acta psychologica 147 (2014) 60–67.

[6] A., Beck, R., Steer, & G., Brown, (1996). Beck Depression Inventory-II (BDI-II). In Beck Depression Inventory-II.

[7] K.C. Berridge, T.E. Robinson, What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? Brain Res. Rev. 28 (3) (1998) 309–369, https://doi.org/10.1016/S0165-0173(98)00019-8.

[8] J.-C. Bizot, Effects of psychoactive drugs on temporal discrimination in rats, Behav. Pharmacol. 8 (4) (1997) 293–308.

[9] C.V. Buhusi, W.H. Meck, What makes us tick? Functional and neural mechanisms of interval timing, Nat. Rev. Neurosci. 6 (10) (2005) 755–765.

[10] D.J. Buysse, C.F. Reynolds III, T.H. Monk, S.R. Berman, D.J. Kupfer, The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research, Psychiatry research 28 (2) (1989) 193–213.

[11] M. Capizzi, A. Visalli, A. Faralli, G. Mioni, Explicit and implicit timing in older adults: Dissociable associations with age and cognitive decline, Plos one 17 (3) (2022), e0264999.

[12] S. Cardullo, L.J. Gómez Pérez, D. Cuppone, M. Sarlo, N. Cellini, A. Terraneo, L. Gallimberti, G. Madeo, A retrospective comparative study in patients with cocaine use disorder comorbid with attention deficit hyperactivity disorder undergoing an rTMS protocol treatment, Front. Psychiatry 12 (March) (2021) 1–9, https://doi.org/10.3389/fpsyt.2021.659527.

[13] S. Cardullo, L.J. Gómez Pérez, D. Cuppone, M. Sarlo, N. Cellini, A. Terraneo, L. Gallimberti, G. Madeo, A retrospective comparative study in patients with cocaine use disorder comorbid with attention deficit hyperactivity disorder undergoing an rTMS protocol treatment, Front. Psychiatry 12 (2021), 659527, https://doi.org/10.3389/fpsyt.2021.659527.

[14] R.K. Cheng, C.J. MacDonald, W.H. Meck, Differential effects of cocaine and ketamine on time estimation: implications for neurobiological models of interval timing, Pharmacology Biochemistry and Behavior, 85 (1) (2006) 114–122.

[15] R.K. Cheng, Y.M. Ali, W.H. Meck, Ketamine "unlocks" the reduced clock-speed effects of cocaine following extended training: evidence for dopamine–glutamate interactions in timing and time perception, Neurobiology of learning and memory 88 (2) (2007) 149–159.

[16] R.-K. Cheng, J. Tipples, N.S. Narayanan, W.H. Meck, Clock speed as a window into dopaminergic control of emotion and time perception, Time. Time Perception 4 (1) (2016) 99–122.

[17] J.T. Coull, A.C. Nobre, Dissociating explicit timing from temporal expectation with fMRI, Current opinion in neurobiology 18 (2) (2008) 137–144.

[18] Derogatis, L . (1994). SCL-90-R: Administration, scoring, and procedures manual. Minneapolis , MN : Nationa l Compute r Systems.

[19] B.J. Everitt, T.W. Robbins, Neural systems of reinforcement for drug addiction: from actions to habits to compulsion, Nat. Neurosci. 8 (11) (2005) 1481–1489, https://doi.org/10.1038/nn1579.

[20] E.A. Garza-Villarreal, R. Alcala-Lozano, S. Fernandez-Lozano, E. Morelos-Santana, A. Dávalos, V. Villicaña, S. Alcauter, F.X. Castellanos, J.J. Gonzalez-Olvera, Clinical and functional connectivity outcomes of 5-Hz repetitive transcranial magnetic stimulation as an add-on treatment in cocaine use disorder: a double-blind randomized controlled trial, Biol. Psychiatry.: Cogn. Neurosci. Neuroimaging 6 (7) (2021) 745–757.

[21] R.Z. Goldstein, N.D. Volkow, Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications, Nature reviews neuroscience 12 (11) (2011) 652–669.

[22] L.J. Gómez Pérez, S. Cardullo, N. Cellini, M. Sarlo, T. Monteanni, A. Bonci, A. Terraneo, L. Gallimberti, G. Madeo, Sleep quality improves during treatment with repetitive transcranial magnetic stimulation (rTMS) in patients with cocaine use disorder: a retrospective observational study, BMC Psychiatry 20 (1) (2020), 153, https://doi.org/10.1186/s12888-020-02568-2.

[23] T.S. Gouvêa, T. Monteiro, A. Motiwala, S. Soares, C. Machens, J.J. Paton, Striatal dynamics explain duration judgments, Elife 4 (2015), e11386.

[24] R. Hester, H. Garavan, Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity, J. Neurosci. 24 (49) (2004) 11017–11022.

[25] L.L. Howell, K.A. Cunningham, Serotonin 5-HT2 receptor interactions with dopamine function: implications for therapeutics in cocaine use disorder, Pharmacol. Rev. 67 (1) (2015) 176–197.

[26] M. Jahanshahi, C.R.G. Jones, G. Dirnberger, C.D. Frith, The substantia nigra pars compacta and temporal processing, J. Neurosci. 26 (47) (2006) 12266–12273.

[27] M. Jazayeri, M.N. Shadlen, Temporal context calibrates interval timing, Nature neuroscience 13 (8) (2010) 1020–1026.

[28] C.R. Jones, D.O. Claassen, M. Yu, J.R. Spies, T. Malone, G. Dirnberger, M. Kubovy, Modeling accuracy and variability of motor timing in treated and untreated Parkinson's disease and healthy controls, Frontiers in Integrative Neuroscience 5 (2011), 81.

[29] C.R.G. Jones, M. Jahanshahi, Motor and perceptual timing in Parkinson's disease. Neurobiology of Interval Timing, Springer,, 2014, pp. 265–290, https://doi.org/10.1007/978-1-4939-1782-2_14.

[30] C.R.G. Jones, M. Jahanshahi, Striatal and Frontal Pathology: Parkinson's Disease and Patients with Lesions of the Basal Ganglia and Frontal Cortex. In *Time distortions in mind: temporal processing in clinical populations*, Brill, 2015, pp. 250–280.

[31] D. Jovanovski, S. Erb, K.K. Zakzanis, Neurocognitive deficits in cocaine users: a quantitative review of the evidence, J. Clin. Exp. Neuropsychol. 27 (2) (2005) 189–204, https://doi.org/10.1080/13803390490515694.

[32] H. Kober, C.M. Lacadie, B.E. Wexler, R.T. Malison, R. Sinha, M.N. Potenza, Brain activity during cocaine craving and gambling urges: an fMRI study, Neuropsychopharmacology 41 (2) (2016) 628–637.

[33] G. Koch, L. Brusa, M. Oliveri, P. Stanzione, C. Caltagirone, Memory for time intervals is impaired in left hemi-Parkinson patients, Neuropsychologia 43 (8) (2005) 1163–1167.

[34] G. Koch, L. Brusa, C. Caltagirone, M. Oliveri, A. Peppe, P. Tiraboschi, P. Stanzione, Subthalamic deep brain stimulation improves time perception in Parkinson's disease, Neuroreport 15 (6) (2004) 1071–1073.

[35] G. Koch, A. Costa, L. Brusa, A. Peppe, I. Gatto, S. Torriero, E. Gerfo, Lo, S. Salerno, M. Oliveri, G.A. Carlesimo, Impaired reproduction of second but not millisecond time intervals in Parkinson's disease, Neuropsychologia 46 (5) (2008) 1305–1313.

[36] G.F. Koob, N.D. Volkow, Neurobiology of addiction: a neurocircuitry analysis, Lancet Psychiatry 3 (8) (2016) 760–773, https://doi.org/10.1016/S2215-0366(16)00104-8.

[37] C.D. Kopec, C.D. Brody, Human performance on the temporal bisection task, Brain and cognition 74 (3) (2010) 262–272.

[38] K.W. Lange, O. Tucha, A. Steup, W. Gsell, M. Naumann, Subjective time estimation in Parkinson's disease, J. Neural Transm. Suppl. 46 (1995) 433–438.

[39] H. Lejeune, J.H. Wearden, Vierordt's The Experimental Study of the Time Sense (1868) and its legacy, European Journal of Cognitive Psychology 21 (6) (2009) 941–960.

[40] F. Lolli, M. Salimova, M. Scarpino, G. Lanzo, C. Cossu, M. Bastianelli, B. Occupati, F. Gori, A. Del Vecchio, A. Ercolini, A randomised, double-blind, sham-controlled study of left prefrontal cortex 15 Hz repetitive transcranial magnetic stimulation in cocaine consumption and craving, PloS One 16 (11) (2021), e0259860.

[41] F. Lolli, M. Salimova, M. Scarpino, G. Lanzo, C. Cossu, M. Bastianelli, B. Occupati, F. Gori, A. Del Vecchio, A. Ercolini, K.C. Berridge, T.E. Robinson, A randomised, double-blind, sham-controlled study of left prefrontal cortex 15 Hz repetitive transcranial magnetic stimulation in cocaine consumption and craving, PloS One 16 (11) (2021), e0259860, https://doi.org/10.1016/S0165-0173(98)00019-8.

[42] G. Madeo, A. Terraneo, S. Cardullo, L.J. Gómez Pérez, N. Cellini, M. Sarlo, A. Bonci, L. Gallimberti, Long-term outcome of repetitive transcranial magnetic stimulation in a large cohort of patients with cocaine-use disorder: an observational study, Front. Psychiatry 11 (2020), 158, https://doi.org/10.3389/fpsyt.2020.00158.

[43] C. Malapani, B. Deweer, J. Gibbon, Separating storage from retrieval dysfunction of temporal memory in Parkinson's disease, Journal of cognitive neuroscience 14 (2) (2002) 311–322.

[44] F.A. Mansouri, K. Tanaka, M.J. Buckley, Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex, Nat. Rev. Neurosci. 10 (2) (2009) 141–152.

[45] V. Marinho, T. Oliveira, K. Rocha, J. Ribeiro, F. Magalhães, T. Bento, G.R. Pinto, B. Velasques, P. Ribeiro, L. Di Giorgio, The dopaminergic system dynamic in the time perception: a review of the evidence, Int. J. Neurosci. 128 (3) (2018) 262–282.

[46] D. Martinez, R. Narendran, R.W. Foltin, M. Slifstein, D.-R. Hwang, A. Broft, Y. Huang, T.B. Cooper, M.W. Fischman, H.D. Kleber, Amphetamine-induced dopamine release: markedly blunted in cocaine dependence and predictive of the choice to self-administer cocaine, Am. J. Psychiatry 164 (4) (2007) 622–629.

[47] G. Martinotti, M. Pettorruso, C. Montemitro, P.A. Spagnolo, C.A. Martellucci, F. Di Carlo, F. Fanella, M. di Giannantonio, B.S. Group, Repetitive transcranial magnetic stimulation in treatment-seeking subjects with cocaine use disorder: a randomized, double-blind, sham-controlled trial, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 116 (2022), 110513.

[48] M.S. Matell, W.H. Meck, Neuropsychological mechanisms of interval timing behavior, Bioessays 22 (1) (2000) 94–103.

[49] M.S. Matell, W.H. Meck, Cortico-striatal circuits and interval timing: coincidence detection of oscillatory processes, Cogn. Brain Res. 21 (2) (2004) 139–170.

[50] Y. Mateo, E.A., Budygin,C.E. John, & S.R., Jones, (2004). Role of serotonin in cocaine effects in mice with reduced dopamine transporter function. *Proceedings of the National Academy of Sciences*, 101(1), 372–377.

[51] A.L. McRae-Clark, A.M. Cason, A.S. Kohtz, M. Moran Santa-Maria, G. Aston-Jones, K.T. Brady, Impact of gender on corticotropin-releasing factor and noradrenergic sensitivity in cocaine use disorder, J. Neurosci. Res. 95 (1–2) (2017) 320–327.

[52] W.H. Meck, Neuropharmacology of timing and time perception, Cogn. Brain Res. 3 (3–4) (1996) 227–242.

[53] W.H. Meck, Frontal cortex lesions eliminate the clock speed effect of dopaminergic drugs on interval timing, Brain Res. 1108 (1) (2006) 157–167.

[54] W.H. Meck, T.B. Penney, V. Pouthas, Cortico-striatal representation of time in animals and humans, Curr. Opin. Neurobiol. 18 (2) (2008) 145–152.

[55] H. Merchant, M. Luciana, C. Hooper, S. Majestic, P. Tuite, Interval timing and Parkinson's disease: heterogeneity in temporal performance, Exp. Brain Res. 184 (2) (2008) 233–248.

[56] G. Mioni, F. Stablum, S.M. McClintock, S. Grondin, Different methods for reproducing time, different results, Attention, Perception, & Psychophysics 76 (2014) 675–681.

[57] G. Mioni, S. Grondin, L. Bardi, F. Stablum, Understanding time perception through non-invasive brain stimulation techniques: A review of studies, Behavioural brain research 377 (2020), 112232.

[58] G. Mioni, N. Sanguin, G. Madeo, S. Cardullo, Time perception in cocaine-dependent patients, Brain Sciences 12 (6) (2022), 745.

[59] S.J. Moeller, M.I. Froböse, A.B. Konova, M. Misyrlis, M.A. Parvaz, R.Z. Goldstein, N. Alia-Klein, Common and distinct neural correlates of inhibitory dysregulation: stroop fMRI study of cocaine addiction and intermittent explosive disorder, J. Psychiatr. Res. 58 (2014) 55–62.

[60] R.C. Mohs, J.R. Tinklenberg, W.T. Roth, B.S. Kopell, Sensitivity of some human cognitive functions to effects of methamphetamine and secobarbital, Drug Alcohol Depend. 5 (2) (1980) 145–150.

[61] K.P. Morie, De Sanctis, P. Garavan, H, J.J. Foxe, Executive dysfunction and reward dysregulation: a high-density electrical mapping study in cocaine abusers, Neuropharmacology 85 (2014) 397–407.

[62] M.A. Pastor, J. Artieda, M. Jahanshahi, J.A. Obeso, Time estimation and reproduction is abnormal in Parkinson's disease, Brain 115 (1) (1992) 211–225.

[63] J.J. Paton, D.V. Buonomano, The neural basis of timing: distributed mechanisms for diverse functions, Neuron 98 (4) (2018) 687–705.

[64] J. Peirce, J.R. Gray, S. Simpson, M. MacAskill, R. Höchenberger, H. Sogo, E. Kastman, J.K. Lindeløv, PsychoPy2: Experiments in behavior made easy, Behav. Res. Methods 51 (1) (2019) 195–203.

[65] S. Perbal, B. Deweer, B. Pillon, M. Vidailhet, B. Dubois, V. Pouthas, Effects of internal clock and memory disorders on duration reproductions and duration productions in patients with Parkinson's disease, Brain Cogn. 58 (1) (2005) 35–48.

[66] T.H. Rammsayer, Neuropharmacological evidence for different timing mechanisms in humans, *Q. J. Exp. Psychol.: Sect.* B 52 (3) (1999) 273–286.

[67] A.C. Rattat, S. Droit-Volet, What is the best and easiest method of preventing counting in different temporal tasks? Behavior Research Methods 44 (1) (2012) 67–80.

[68] J.M. Riesen, A. Schnider, Time estimation in Parkinson's disease: normal long duration estimation despite impaired short duration discrimination, J. Neurol. 248 (1) (2001) 27–35.

[69] S. Rossi, A. Antal, S. Bestmann, M. Bikson, C. Brewer, J. Brockmöller, L. L. Carpenter, M. Cincotta, R. Chen, J.D. Daskalakis, V. Di Lazzaro, M.D. Fox, M. S. George, D. Gilbert, V.K. Kimiskidis, G. Koch, R.J. Ilmoniemi, J.P. Lefaucheur, L. Leocani, M. Hallett, Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines, *Clin. Neurophysiol.*: Off. J. Int. Fed. Clin. Neurophysiol. 132 (1) (2021) 269–306, https://doi.org/10.1016/j.clinph.2020.10.003.

[70] E.K. Sawyer, J. Mun, J.A. Nye, H.L. Kimmel, R.J. Voll, J.S. Stehouwer, K.C. Rice, M. M. Goodman, L.L. Howell, Neurobiological changes mediating the effects of chronic fluoxetine on cocaine use, Neuropsychopharmacology 37 (8) (2012) 1816–1824.

[71] R. Sinha, D. Catapano, S. O'Malley, Stress-induced craving and stress response in cocaine dependent individuals, Psychopharmacology 142 (4) (1999) 343–351.

[72] R. Sinha, M. Garcia, P. Paliwal, M.J. Kreek, B.J. Rounsaville, Stress-induced cocaine craving and hypothalamic-pituitary-adrenal responses are predictive of cocaine relapse outcomes, Arch. Gen. Psychiatry 63 (3) (2006) 324–331.

[73] R. Sinha, C. Lacadie, P. Skudlarski, R.K. Fulbright, B.J. Rounsaville, T.R. Kosten, B. E. Wexler, Neural activity associated with stress-induced cocaine craving: a

functional magnetic resonance imaging study, Psychopharmacology 183 (2) (2005) 171–180.
[74] D.B. Spronk, J.H.P. van Wel, J.G. Ramaekers, R.J. Verkes, Characterizing the cognitive effects of cocaine: a comprehensive review, Neurosci. Biobehav. Rev. 37 (8) (2013) 1838–1859, https://doi.org/10.1016/j.neubiorev.2013.07.003.
[75] K.M. Taylor, J.C. Horvitz, P.D. Balsam, Amphetamine affects the start of responding in the peak interval timing task, Behav. Process. 74 (2) (2007) 168–175.
[76] A. Terraneo, L. Leggio, M. Saladini, M. Ermani, A. Bonci, L. Gallimberti, Transcranial magnetic stimulation of dorsolateral prefrontal cortex reduces cocaine use: a pilot study, Eur. Neuropsychopharmacol. 26 (1) (2016) 37–44, https://doi.org/10.1016/j.euroneuro.2015.11.011.
[77] M. Tik, A. Hoffmann, R. Sladky, L. Tomova, A. Hummer, L.N. de Lara, H. Bukowski, J. Pripfl, B. Biswal, C. Lamm, Towards understanding rTMS mechanism of action: stimulation of the DLPFC causes network-specific increase in functional connectivity, Neuroimage 162 (2017) 289–296.
[78] D.M.E. Torta, L. Castelli, L. Latini-Corazzini, A. Banche, L. Lopiano, G. Geminiani, Dissociation between time reproduction of actions and of intervals in patients with Parkinson’s disease, J. Neurol. 257 (8) (2010) 1356–1361.
[79] K. Van Hedger, E.A. Necka, A.K. Barakzai, G.J. Norman, The influence of social stress on time perception and psychophysiological reactivity, Psychophysiology 54 (5) (2017) 706–712.
[80] C.M. Vicario, D. Martino, G. Koch, Temporal accuracy and variability in the left and right posterior parietal cortex, Neuroscience 245 (2013) 121–128.
[81] N.D. Volkow, G.F. Koob, A.T. McLellan, Neurobiologic advances from the brain disease model of addiction, N. Engl. J. Med. 374 (4) (2016) 363–371, https://doi.org/10.1056/NEJMra1511480.
[82] N.D. Volkow, J.S. Fowler, G.J. Wang, R. Baler, F. Telang, Imaging dopamine’s role in drug abuse and addiction, Neuropharmacology 56 (2009) 3–8.
[83] N.D. Volkow, G.-J. Wang, F. Telang, J.S. Fowler, J. Logan, A.-R. Childress, M. Jayne, Y. Ma, C. Wong, Dopamine increases in striatum do not elicit craving in cocaine abusers unless they are coupled with cocaine cues, Neuroimage 39 (3) (2008) 1266–1273.
[84] N.D. Volkow, D. Tomasi, G.J. Wang, J. Logan, D.L. Alexoff, M. Jayne, J.S. Fowler, C. Wong, P. Yin, C. Du, Stimulant-induced dopamine increases are markedly blunted in active cocaine abusers, Mol. Psychiatry 19 (9) (2014) 1037–1043.
[85] J.H. Wearden, J.H. Smith-Spark, R. Cousins, N.M.J. Edelstyn, F.W.J. Cody, D. J. O’Boyle, Stimulus timing by people with Parkinson’s disease, Brain Cogn. 67 (3) (2008) 264–279.
[86] R.D. Weiss, M.L. Griffin, C. Hufford, L.R. Muenz, L.M. Najavits, S.B. Jansson, J. Kogan, H.J. Thompson, Early prediction of initiation of abstinence from cocaine, Am. J. Addict. (1997), https://doi.org/10.1111/j.1521-0391.1997.tb00401.x.
[87] M. Wiener, P. Turkeltaub, H.B. Coslett, The image of time: a voxel-wise meta-analysis, Neuroimage 49 (2) (2010) 1728–1740.
[88] M. Wittmann, D.S. Leland, J. Churan, M.P. Paulus, Impaired time perception and motor timing in stimulant-dependent subjects, Drug Alcohol Depend. 90 (2–3) (2007) 183–192.
[89] L. Wojtecki, S. Elben, L. Timmermann, C. Reck, M. Maarouf, S. Joergens, M. Ploner, M. Suedmeyer, S.J. Groiss, V. Sturm, Modulation of human time processing by subthalamic deep brain stimulation, PLoS One 6 (9) (2011), e24589.
[90] M. Zhang, D. Zhao, Z. Zhang, X. Cao, L. Yin, Y. Liu, T.-F. Yuan, W. Luo, Time perception deficits and its dose-dependent effect in methamphetamine dependents with short-term abstinence, Sci. Adv. 5 (10) (2019) eaax6916.
[91] W.W.K. Zung, A rating instrument for anxiety disorders, Psychosomatics (1971), https://doi.org/10.1016/S0033-3182(71)71479-0.