NEUROSCIENCE

Time perception deficits and its dose-dependent effect in methamphetamine dependents with short-term abstinence

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Intake of addictive substances acutely modifies dopaminergic transmission in the striatum and prefrontal cortex, which is the neural substrate underlying time processing. However, the persistent effects of methamphetamine (meth) abuse (e.g., during abstinence) on temporal processing have not been fully elucidated. Here, we recruited different samples in two experiments. We first compared the potential differences in motor timing between healthy controls and meth dependents with varied length of abstinence and then examined the ability of perceptual timing between the healthy subjects and the meth group at short abstinence. We found that motor timing, but not perceptual timing, was altered in meth dependents, which persisted for at least 3 months of abstinence. Dose-dependent effects on time perception were only observed when short-term abstinent meth abusers processed long time intervals. We conclude that time perception alteration in meth dependents is task specific and dose dependent.

INTRODUCTION

Human beings can precisely perceive temporal duration across multiple scales—from milliseconds to minutes (*1*). This ability is fundamental to our daily behavior and survival. Theoretically, time perception is based on an internal clock (*2*): A pacemaker continually emits pulses that are received by an accumulator from the beginning of an event, and individuals compare the accumulative event intervals with the target duration stored in their reference memory to inform temporal decision (e.g., shorter/longer and same/different) (*3*). At the molecular level, dopaminergic projections within the corticostriatal circuits play a crucial role in time perception (*4*). Changes in the dopaminergic system consequently affect time perception and related cognitive functions (e.g., impulsive decision-making) (*5*). Studying the effect of drugs on temporal perception and abnormal temporal processing will help improve the understanding of the psychological, pharmacological, and neurological mechanisms that manipulate time perception, as well as their clinical remediation.

As one of the most widespread illicit psychostimulants, methamphetamine (meth) addiction imposes notable economic, social, and disease burden to society (*6*). Evidence shows that meth primarily disrupts the dopaminergic system in the striatum and prefrontal cortex (PFC). Compared with healthy controls (HCs), long-term exposure to meth increases extracellular dopamine concentrations by reversing dopamine release and decreasing availability of dopamine transporter and D2/D3 receptor (*7*). In addition, meth dependents exhibit abnormal functional connectivity in the corticostriatal circuits. For example, the resting functional connectivity of the midbrain with the hippocampus, striatum, amygdala, insula, and PFC in abstinent meth dependents is stronger than that in HCs (*8*). These aberrations may contribute to impairments in cognitive and behavioral performance observed in meth dependents, including attention, executive function, working memory, risky decision-making, and temporal discounting (*8*, *9*). Although the motor cortex receives relatively few dopaminergic inputs, its impairment has recently been implicated to have a critical role in meth abuse (*10*). For example, Huang *et al.* (*11*) observed the loss of corticostriatal plasticity in rat brain slices and diminished motor learning in a rotarod task. In their study, transcranial magnetic stimulation–induced motor evoked potentials, an index of plasticity, were attenuated in male meth dependents, along with poor performance in a rotary pursuit task. Furthermore, the cue-induced activation of the motor and sensory cortex may reflect craving level and predict relapse of drug addiction (*10*).

The frontostriatal network and motor cortex are defined as the primary neural substrates, underpinning timing and time perception. In addition to the cerebellum, one of the first regions contributing to timing (*12*), other brain areas have been implicated. The role of basal ganglia in time perception has been demonstrated by pharmacological research and investigations of neurodegenerative disorders, including Parkinson's disease (*13*). Recent studies in rats have provided evidence for the value of striatal and midbrain neurons, which constitute a vital component of the dopaminergic system, in predicting duration judgments (*14*, *15*). Neuroimaging studies have documented the activation of the primary motor cortex (M1), supplementary motor area (SMA), and dorsolateral PFC during the performance of a timing task (*4*, *16*). Virtual damage to these areas with transcranial magnetic stimulation verifies the effects of their participation on temporal perception (*17*). Overall, meth-induced deficits and changes in the perception of time feature overlap in their underlying neurochemical and neuroanatomical correlates.

Previous research in rats has investigated the impact of meth on timing and time perception. A meth-induced leftward shift in rats' proportional timing functions has been typically reported, indicating temporal overestimation (*18*). Maricq *et al.* (*19*) pioneered to find that acute meth injection decreased the peak time and point of indifference

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by approximately 10% (i.e., leftward shift); this finding has been validated by subsequent research (*20*). Other investigations have also suggested that acute meth use increases the speed of the internal clock during a temporal bisection task, which may be associated with the changes in the dopamine levels in corticostriatal circuits induced by the meth-mediated release of several catecholamines, including dopamine (*21*). Other factors modulated this finding: Meth administration shifted psychometric function to the left at 100 to 180 min after injection, not in the early window (20 to 100 min) (*22*); while low to moderate doses of meth (0.5 to 2.0 mg/kg) caused this typical leftward shift in timing functions, high doses of meth (3.0 mg/kg) induced neurotoxicity and decreased temporal sensitivity (i.e., flat curve) without affecting the horizontal position (*23*, *24*). These findings may indicate an inverted U-shaped association between the internal clock speed and dopaminergic level.

The acute and chronic effects of meth use on humans' time perception have received relatively scant attention in the literature. Mohs *et al.* (*25*) revealed relatively shortened production (30, 60, and 120 s) following acute meth injection after 1, 2, and 3 hours, respectively, reflecting a continuous acceleration of cognitive processes. Wittmann *et al.* (*26*) employed 15 abstinent stimulant-dependent individuals (meth and/or cocaine) and instructed them to complete perceptual timing tasks (duration discrimination and time estimation), motor timing tasks (temporal reproduction, synchronization, and continuation tapping), prefrontal cortical function (attention and working memory), and the Barratt Impulsiveness Scale (BIS). The set of temporal tasks ranged from 0.1 to 53 s. The study demonstrated that stimulant-dependent subjects exhibited deficits in perceptual and motor timing in short temporal intervals (1 to 2 s). Conversely, only the 53-s estimation was mediated by no-planning impulsiveness, and other parameters were not significant. Briefly, evidence from rats and humans suggests that meth increases the dopamine level and the speed of the internal clock, finally leading to temporal overestimation that can be modulated by factors such as dosage.

Despite the significant progress achieved by the studies above, much remains unclear. First, while prior research has clarified dose-dependent effects of meth on the alteration of time perception in rats (*24*), whether this profile applies to humans has yet to be determined. Second, other critical indices in humans (i.e., abstinence duration) were unexplored. In the study by Wittmann *et al.* (*26*), stimulant-dependent subjects had been abstinent from 20 to 40 days. Meth dependents are not deficient in all aspects of the dopaminergic system or cognitive tasks (*9*). With sustained abstinence, dopamine transporter binding partially recovers, and some cognitive functions may return to normal (e.g., executive function) (*27*). However, how factors such as abstinence affect meth-induced alterations of time perception remains unclear.

Moreover, the few studies of meth abuse and dysfunctional temporal perception that involved humans were marred by small sample sizes, and drug use was not pure, which may limit the generalizability of the results. Many drugs, including cocaine and meth, cause long-term changes in dopaminergic function. These alterations may further be linked to enduring deficits in time perception commonly observed in laboratory animals repeatedly exposed to these drugs. However, meth may have an impact on cognitive function different from that of cocaine. For instance, a meta-analysis has found that meth dependents have significantly reduced striatal dopamine transporter availability relative to cocaine consumers (*28*). Individuals addicted to meth may also exhibit impairments of perceptual speed and manipulation of information; this pattern is not observed in cocaine groups (*29*). Larger sample sizes composed only of meth dependents should be recruited to clarify the true impact of meth on time perception.

The present study aimed to elucidate whether meth impairs time perception in humans across different durations of abstinence and whether these effects might be dose dependent. Tasks used to study time perception have various categories. The first to consider is motor or perceptual timing. The former defines temporal duration as a motor response, in which individuals need to build a stopwatch-like fashion in their memory when a target duration begins and ends, but the latter requires participants to make temporal judgments (e.g., shorter/longer). In experiment 1, two meth groups [short-term abstinence (MS) versus long-term abstinence (ML)] and age- and education-matched HCs (Table 1) completed a temporal reproduction task (Fig. 1A), one of the most common paradigms in motor timing. The results of this task often

Table 1. Demographic characteristics of the HC, MS, and ML groups in experiment 1 (mean ± SD). BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; PSQI, Pittsburgh Sleep Quality Index; BIS, Barratt Impulsivity Scale; NA, not applicable.

	HC (n = 54)	MS (n = 53)	ML (n = 50)	Statistics (F or t)	P	Effect size (η_p^2 or Cohen's d)	Post hoc test*
Age (years)	36.02 ± 11.93	37.34 ± 7.17	36.40 ± 8.67	0.274	0.760	0.004	NA
Education (years)	9.80 ± 2.45	9.05 ± 3.66	8.68 ± 2.91	1.829	0.164	0.023	NA
BAI	26.19 ± 7.25	29.06 ± 10.54	26.94 ± 7.43	1.610	0.203	0.020	NA
BDI	7.81 ± 6.99	16.34 ± 10.92	14.00 ± 9.22	12.329	<0.001	0.138	MS > HC, ML > HC
PSQI	4.15 ± 2.55	6.98 ± 3.97	6.76 ± 3.79	10.884	<0.001	0.124	MS > HC, ML > HC
BIS-11	69.85 ± 19.27	83.47 ± 19.29	83.54 ± 18.22	9.197	<0.001	0.107	MS > HC, ML > HC
Duration of current abstinence (months)	NA	3.00 ± 1.86	16.30 ± 6.28	−14.384	<0.001	2.872	NA
Years of meth use before abstinence	NA	8.41 ± 4.79	7.95 ± 4.52	0.496	0.621	0.099	NA
Dosage of meth use before abstinence (g/month)	NA	13.40 ± 14.96	19.46 ± 13.52	−2.155	0.034	0.425	NA

*The greater than symbol indicates direction of the significant results.

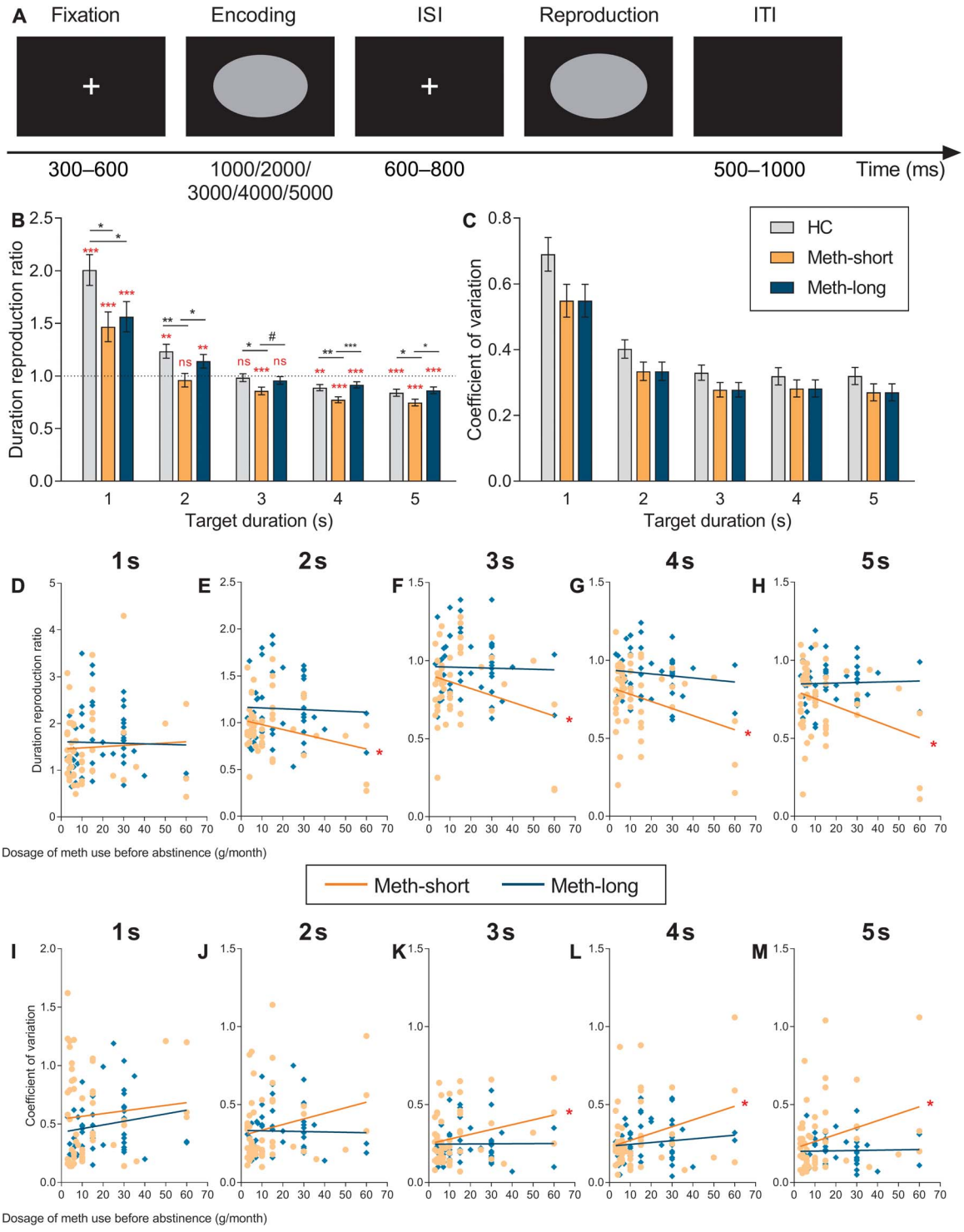

Fig. 1. Temporal reproduction task and findings of experiment 1. (**A**) All participants needed to complete a temporal reproduction task where the duration of the gray oval (1 to 5 s) in the encoding phase should be remembered in people's mind. Then, when the duration of the gray oval displayed in the reproduction phase matched the encoding one, participants were asked to press the space bar. ISI, interstimulus interval; ITI, intertrial interval. (**B**) For the meth-long group and HCs, the duration reproduction ratio (DRR) was higher than 1 at durations of 1 and 2 s, lower than 1 at durations of 4 and 5 s, but not different from 1 at duration of 3 s. For the meth-short group, the indifferent time point dropped at 2 s. The dotted line indicates accurate reproduction. ns, not significant, $^{\#}P = 0.051$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. Error bars represent SEM. (**C**) HCs showed a higher coefficient of variation (CV) than the two meth groups across all target durations. Error bars represent SEM. (**D** to **H**) When the target duration was longer than 1 s, there was a significant negative correlation between the DRR and dosage of meth use before abstinence in the meth-short group. This pattern did not exhibit in the meth-long group. $^{*}P < 0.05$. (**I** to **M**) When the target duration was longer than 2 s, there was a significant positive correlation between the CV and dosage of meth use before abstinence in the meth-short group. This pattern did not exhibit in the meth-long group. $^{*}P < 0.05$.

reflect Vierordt's law. Specifically, short durations tend to be judged as longer, and long durations as shorter, with an "indifference point" in between the two duration lengths (*30*). We hypothesized that the results obtained from the MS group would feature an aberrant relationship with Vierordt's law relative to those corresponding to the ML and HC groups. According to prior studies, poor adherence to Vierordt's law may indicate an accelerated or decelerated internal clock speed. In addition, the coefficient of variation (CV) of temporal reproductions, an index of temporal variability, was investigated in all groups. In experiment 2, participants in the MS and HC groups (Tables 2 and 3) performed a temporal discrimination task within the subsecond (Fig. 2A) and suprasecond (Fig. 3A) scales to investigate the effects of short-term abstinence on temporal timing. Note that these two experiments were conducted in different samples. According to prior studies, subsecond durations are processed relatively automatically, while suprasecond durations require more cognitive control (*16*). Thus, we predicted that dose-dependent meth-induced impairments of suprasecond processing would be clearer than those of subsecond processing. Behavioral performance was based on the function fitting of responses, in which the point of subjective equality (PSE) and the slope of the curve could indicate temporal overestimation and sensitivity, respectively.

RESULTS

An advanced Vierordt's law in the MS group

The demographics and clinical data of all participants in experiment 1 are reported in Table 1. The univariate analysis of variance (ANOVA) revealed no group differences among HC (matched HCs), MS (who were abstinent for more than 1 month and less than 8 months, with an average of 3 months), and ML (who were abstinent for over 9 months, with an average of 16 months) in age ($P = 0.760$), level of education (years) ($P = 0.164$), and the Beck Anxiety Inventory (BAI) score

Table 2. Demographic characteristics of the HC and MS groups in experiment 2a (mean ± SD).

	HC (n = 43)	MS (n = 35)	t	P	Effect size (Cohen's d)
Age (years)	34.60 ± 8.97	35.34 ± 7.36	−0.391	0.697	0.090
Education (years)	9.67 ± 1.57	8.69 ± 3.22	1.661	0.103	0.387
BAI	26.70 ± 7.05	28.79 ± 7.73	−1.241	0.218	0.283
BDI	12.00 ± 9.64	16.26 ± 8.27	−2.050	0.044	0.474
PSQI	5.65 ± 3.22	6.40 ± 3.16	−1.029	0.307	0.235
BIS-11	76.35 ± 18.56	87.76 ± 18.25	−2.706	0.009	0.620
Duration of current abstinence (days)	NA	69.74 ± 35.95	NA	NA	NA
Years of meth use before abstinence	NA	7.69 ± 3.78	NA	NA	NA
Dosage of meth use before abstinence (g/month)	NA	14.04 ± 13.47	NA	NA	NA

Table 3. Demographic characteristics of the HC and MS groups in experiment 2b (mean ± SD).

	HC (n = 37)	MS (n = 30)	t	P	Effect size (Cohen's d)
Age (years)	33.19 ± 6.39	34.90 ± 7.06	−1.040	0.302	0.254
Education (years)	10.32 ± 1.89	9.53 ± 2.44	1.536	0.129	0.362
BAI	25.81 ± 6.24	27.66 ± 5.61	−1.246	0.217	0.312
BDI	9.24 ± 7.64	16.93 ± 9.08	−3.765	<0.001	0.916
PSQI	5.08 ± 2.44	6.90 ± 3.00	−2.737	0.008	0.666
BIS-11	74.81 ± 21.25	85.76 ± 16.13	−2.302	0.025	0.580
Duration of current abstinence (days)	NA	58.83 ± 17.51*	NA	NA	NA
Years of meth use before abstinence	NA	7.07 ± 4.06	NA	NA	NA
Dosage of meth use before abstinence (g/month)	NA	15.24 ± 11.48	NA	NA	NA

*Because of the technical fault, only 18 meth abusers were recorded, but the duration of abstinence of others was around 3 months.

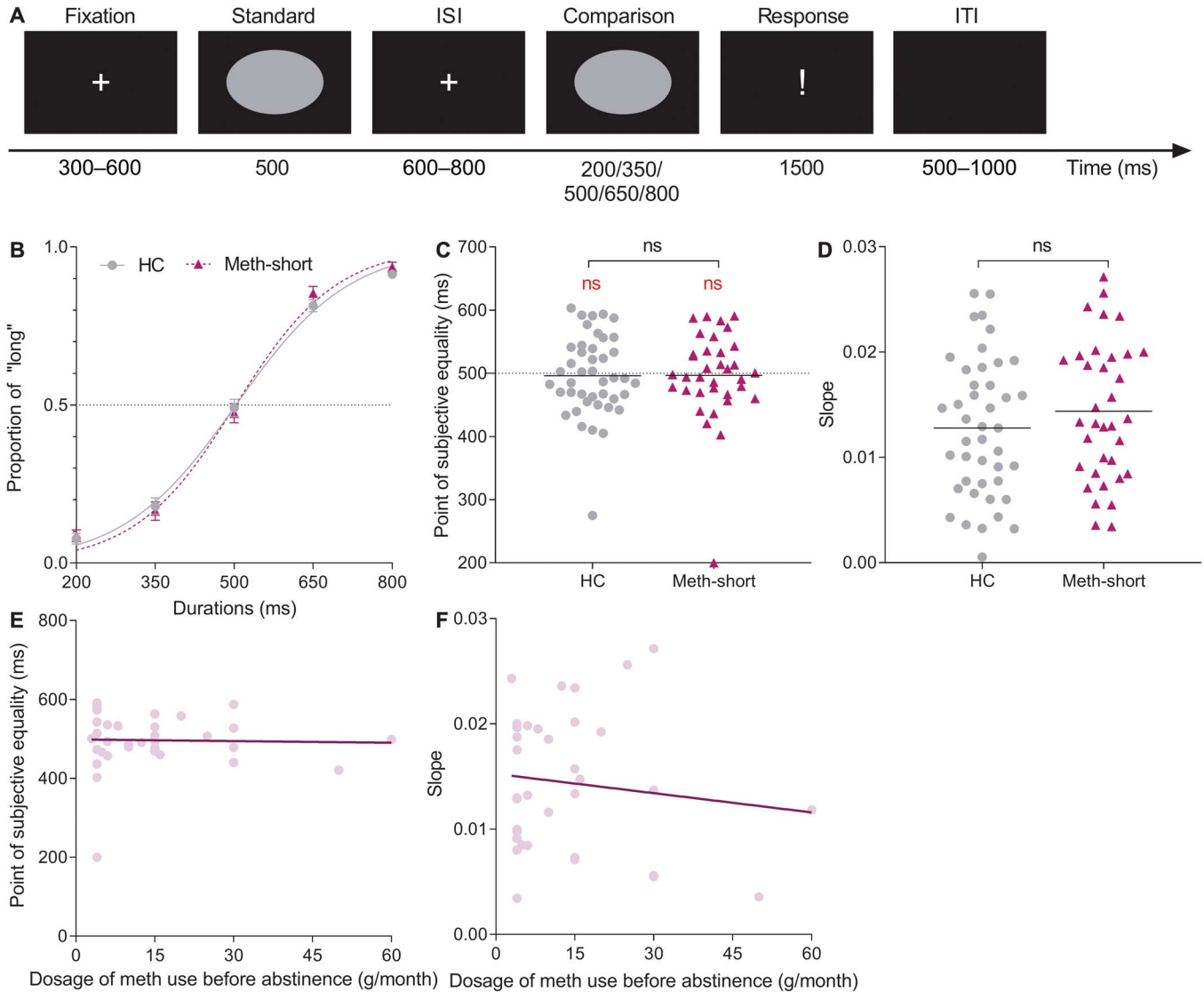

Fig. 2. Temporal discrimination task (subsecond) and findings of experiment 2a. (**A**) In the task, a gray oval with the standard duration (500 ms) appeared first, and then a comparison duration (200, 350, 500, 650, or 800 ms) was shown. Participants indicated whether the comparison was longer or shorter than the standard when an exclamation mark was displayed. (**B**) Mean proportion of "long" responses in each comparison duration was fitted a logistic function for HCs (gray) and the meth-short group (purple), respectively. The dotted line represents 50% of "long" responses. (**C**) Both HCs (gray) and the meth-short group (purple) did not overestimate or underestimate the subsecond duration. The group difference was not significant. The dotted line represents the standard duration (500 ms). (**D**) There was no significant group difference in the slope of the curve. (**E**) The relationship between the dosage of meth use before abstinence and PSE was not significant (r = −0.026, P = 0.881). (**F**) The relationship between the dosage of meth use before abstinence and slope was not significant (r = −0.125, P = 0.475).

(P = 0.203). However, both the MS and ML groups scored higher in the Beck Depression Inventory (BDI) (Ps < 0.001), Pittsburgh Sleep Quality Index (PSQI) (Ps < 0.001), and BIS (Ps < 0.001) compared with HCs. Thus, these three variables were considered as covariates in the following repeated-measures analysis of covariance (ANCOVA). In addition, while the MS and ML groups showed no significant difference in years of meth use (t_{101} = 0.496, P = 0.621, Cohen's d = 0.099), they differed in abstinence duration (t_{101} = −14.384, P < 0.001, Cohen's d = 2.872) and dosage of meth use before abstinence (t_{101} = −2.155, P = 0.034, Cohen's d = 0.425).

The duration reproduction ratio (DRR) was considered an indicator of temporal accuracy. The 3 (group: MS/ML/HC) × 5 (target duration: 1/2/3/4/5 s) repeated-measures ANCOVA for DRR demonstrated a main effect of group ($F_{2,151}$ = 4.587, P = 0.012, η_p^2 = 0.057), and the group × target duration interaction ($F_{8,604}$ = 3.111, P = 0.038, η_p^2 = 0.040) was significant, but the main effect of target duration ($F_{4,604}$ < 1, P = 0.351, η_p^2 = 0.006) was not significant (Fig. 1B). The simple effects analysis revealed the following: When the target duration was 1 s, the DRR in the HC group was higher than those of both meth groups (Ps < 0.036), and when the target duration was longer than 1 s, the MS group had the lowest DRR relative to the other groups (Ps < 0.051). Results from the one-sample t test against 1 in DRR indicated that HCs overestimated 1 s (t_{53} = 5.236, P < 0.001, Cohen's d = 0.713) and 2 s (t_{53} = 2.868, P = 0.010, Cohen's d = 0.365), underestimated 4 s (t_{53} = −3.260, P = 0.002, Cohen's d = 0.444) and 5 s (t_{53} = −3.639, P < 0.001, Cohen's d = 0.495), but correctly estimated

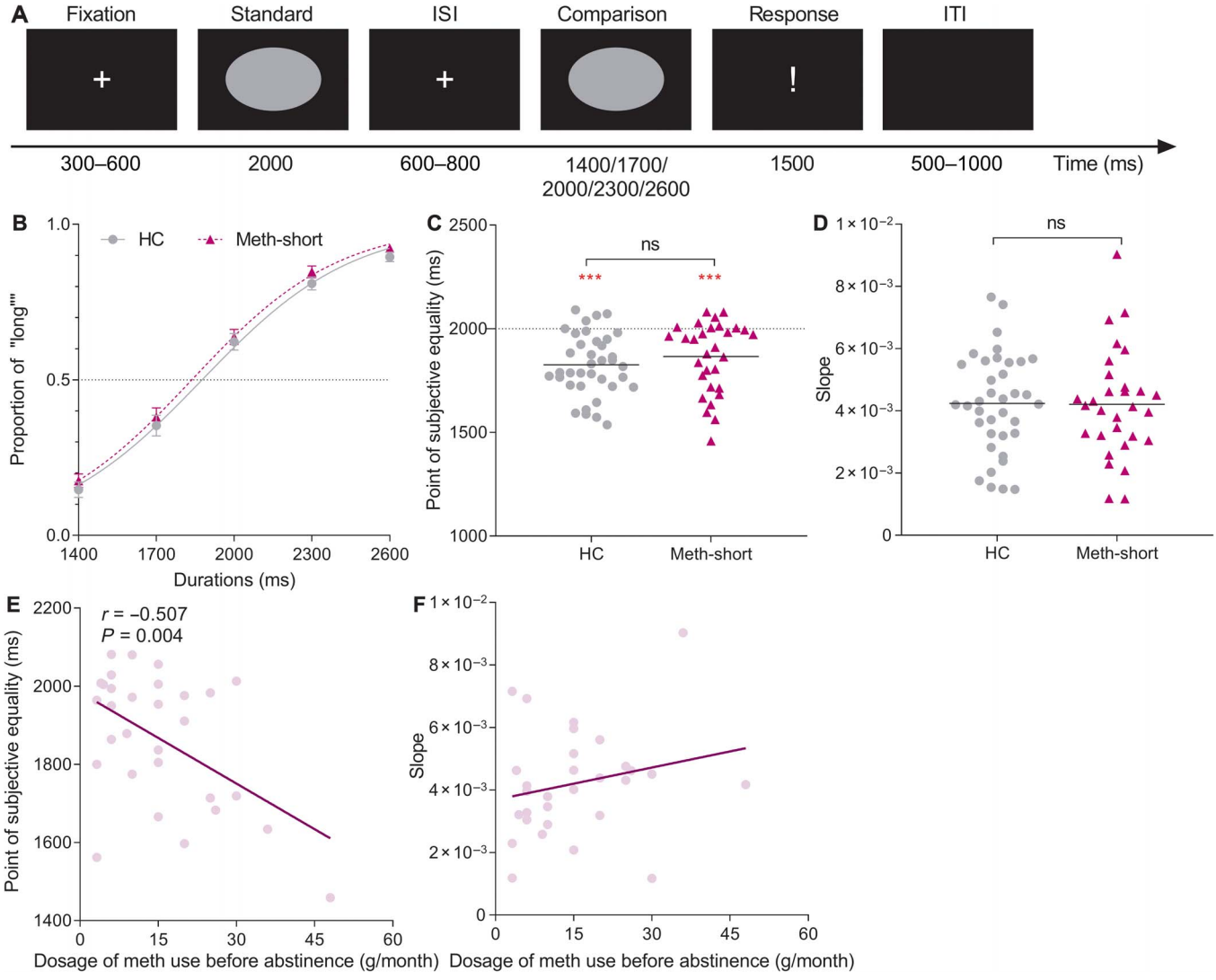

Fig. 3. Temporal discrimination task (suprasecond) and findings of experiment 2b. (**A**) In the task, a gray oval with the standard duration (2000 ms) appeared first, and then a comparison duration (1400, 1700, 2000, 2300, or 2600 ms) was shown. Participants indicated whether the comparison was longer or shorter than the standard when an exclamation mark was displayed. (**B**) Mean proportion of "long" responses in each comparison duration was fitted a logistic function for HCs (gray) and the meth-short group (purple), respectively. The dotted line represents 50% of "long" responses. (**C**) Both HCs (gray) and the meth-short group (purple) overestimated the suprasecond duration, but the group difference was not significant. The dotted line represents the standard duration (2000 ms). ***$P < 0.001$. (**D**) There was no significant group difference for the slope of the curve. (**E**) The negative relationship between the dosage of meth use before abstinence and PSE was significant ($r = -0.507$, $P = 0.004$). (**F**) The relationship between the dosage of meth use before abstinence and slope was not significant ($r = 0.221$, $P = 0.241$).

durations of 3 s ($t_{53} = -0.172$, $P = 0.864$, Cohen's $d = 0.023$). This pattern was also observed in the ML group. However, the one-sample t test against 1 in DRR for various time durations (1/2/3/4/5 s) showed that the MS group overestimated durations of 1 s ($t_{52} = 4.526$, $P < 0.001$, Cohen's $d = 0.622$), underestimated durations of 3 s ($t_{52} = -4.579$, $P < 0.001$, Cohen's $d = 0.629$), 4 s ($t_{52} = -7.995$, $P < 0.001$, Cohen's $d = 1.098$), and 5 s ($t_{52} = -8.557$, $P < 0.001$, Cohen's $d = 1.175$), and only estimated durations of 2 s correctly ($t_{52} = -1.056$, $P = 0.296$, Cohen's $d = 0.145$). These results indicated that the temporal indifference point (the length of time that is neither underestimated nor overestimated) was observed at 3 s both in the long-term abstinence and HC groups and at 2 s in the MS group, indicating a temporally advanced pattern of Vierordt's law.

Lower variability of motor timing in the meth groups relative to the HC group

For the CV of motor timing, which represents temporal variability, the same 3 (group: MS/ML/HC) × 5 (target duration: 1/2/3/4/5 s) repeated-measures ANCOVA revealed neither a significant main effect of target duration ($F_{4,604} = 1.007$, $P = 0.359$, $\eta_p^2 = 0.007$) nor an interaction of group and time duration ($F_{4,604} = 1.608$, $P = 0.180$, $\eta_p^2 = 0.021$) (Fig. 1C). However, we observed a significant main effect of group ($F_{2,151} = 5.831$, $P = 0.004$, $\eta_p^2 = 0.072$): The HC group showed a larger CV (mean ± SE, 0.412 ± 0.024) than the MS (0.343 ± 0.023, $P = 0.045$) and ML groups (0.296 ± 0.023, $P = 0.001$). Further comparison demonstrated that there was no significant difference in CV between the MS and ML groups ($P = 0.148$).

Dose-dependent effects of motor timing in the MS group when reproducing long durations

The MS group exhibited a negative correlation between the DRR and dosage of meth use before abstinence when intervals of longer than 1 s were estimated (Ps < 0.046; Fig. 1, D to H, and table S1). This trend was not observed in the ML group (Ps > 0.412; Fig. 1, D to H, and table S1).

In addition, for the MS group, the dosage of meth use before abstinence was positively associated with CV (Ps < 0.047; Fig. 1, I to M, and table S1) when target durations were longer than 2 s. No significant correlations were observed for any target duration in the ML group (Ps > 0.221; Fig. 1, I to M, and table S1).

No difference in perceptual timing between the MS and HC groups

Experiment 1 revealed meth-induced deficits only in the MS group, relative to HCs. Thus, only the MS group was included in the second experiment on perceptual timing, the other essential aspect of human time perception.

In both the subsecond (Fig. 2A) and suprasecond (Fig. 3A) discrimination task in experiment 2, the behavioral psychometric curves of the MS and HC groups followed similar patterns (Figs. 2B and 3B). Specifically, the one-sample t test against 500 in the PSE of both groups (MS: 496.65 ± 11.99 ms, $t_{34} = -0.279$, $P = 0.782$, Cohen's $d = 0.047$; HC: 496.28 ± 9.74 ms, $t_{42} = -0.382$, $P = 0.704$, Cohen's $d = 0.058$) did not manifest any temporal underestimation or overestimation (Fig. 2C). The PSE between the MS and HC groups was not significantly different ($t_{76} = 0.024$, $P = 0.981$, Cohen's $d = 0.006$; Fig. 2C). The slope, an index of temporal sensitivity, did not reveal any significant differences between the MS and HC groups either (MS: 0.014 ± 0.007 versus HC: 0.013 ± 0.007, $t_{76} = 1.070$, $P = 0.288$, Cohen's $d = 0.244$; Fig. 2D). When participants discriminated a suprasecond duration (i.e., 2000 ms), both the MS and HC groups exhibited an overestimation effect (MS: 1865.80 ± 169.63 ms, $t_{29} = -4.333$, $P < 0.001$, Cohen's $d = 0.781$; HC: 1825.86 ± 148.49 ms, $t_{36} = -7.133$, $P < 0.001$, Cohen's $d = 1.173$; Fig. 3C). However, there were no significant differences in PSE ($t_{65} = 1.027$, $P = 0.308$, Cohen's $d = 0.250$; Fig. 3C) or slope (MS: 0.004 ± 0.002 versus HC: 0.004 ± 0.002, $t_{65} = -0.064$, $P = 0.949$, Cohen's $d = 0.016$; Fig. 3D) between the two groups.

Experiment 2a revealed significant differences in BDI ($t_{75} = -2.050$, $P = 0.044$, Cohen's $d = 0.474$) and BIS ($t_{75} = -2.706$, $P = 0.009$, Cohen's $d = 0.620$) between the two groups (Table 2). Pearson's correlation analyses did not reveal any significant correlation with behavioral outcomes (Ps > 0.077; table S2). In experiment 2b, BDI, PSQI, and BIS differed significantly between the two groups (ts < −2.302, Ps < 0.025, Cohen's ds > 0.580; Table 3). However, the Pearson's correlations between the clinical indices and PSE and slope were not significant (Ps > 0.077; table S3). These findings suggested that the clinical characteristics of either group did not affect the present results. Overall, we observed no perceptual timing deficits in meth dependents with short-term abstinence.

Dose-dependent effects of perceptual timing in suprasecond discrimination

To investigate the relationship between the dosage of meth use before abstinence and perceptual timing, we conducted correlation analyses in both experiments 2a (Fig. 2, E and F) and 2b (Fig. 3, E and F). We found a significantly negative correlation between the dosage of meth use before abstinence (g/month) and PSE in the suprasecond discrimination task ($r = -0.507$, $P = 0.004$; Fig. 3E).

DISCUSSION

This study aimed to investigate the impact of meth-induced impairments on time perception in humans, and thus, examined the role of drug use history (dosage of meth use before abstinence, years of meth use, and abstinence duration) in motor and perceptual timing. We observed that motor timing deficits in meth dependents persisted for at least 3 months and no perceptual timing impairments in the MS group. In addition, individuals in the MS group exhibited a meth dosage–dependent effect when they estimated time intervals longer than 1 or 2 s. To the best of our knowledge, the present study is the first to examine the motor timing from 1 to 5 s and perceptual timing from 500 to 2000 ms involving a large group of individuals addicted to meth and their healthy counterparts.

An advanced pattern of Vierordt's law was found in experiment 1. As described in the Introduction, Vierordt's law refers to the overestimation of short durations, underestimation of long durations, and an indifference point situated between these two ranges at which durations can be correctly estimated. Although the law was proposed nearly 150 years ago, it has recently attracted attention in the literature. Vierordt's law challenges a commonly held assumption that a linear relationship exists between internal subjective time and external objective time (*30*). That is, individuals' reproductions show a central tendency, which depends on the distribution of displayed durations (i.e., temporal context) rather than current visual or auditory stimuli (*31*). During this dynamic process, individuals form internal reference. Described as the internal reference model (*32*), this theory was initially developed to explain performances on a temporal discrimination task that was used to explore perceptual timing. Bausenhart *et al.* (*33*) reported that internal reference also influenced temporal reproduction. When participants were required to reproduce a series of comparison stimuli followed by standard stimuli, reproductions were strongly biased toward the latter items (i.e., the mean of the comparison distribution). This finding indicated that the internal reference, which was based on a prior comparison duration, was continuously variable. Otherwise, task performances almost coincided with objective time. In the present study, although there were no comparison and standard durations in the same trial, the central tendency or internal reference of reproductions from 1 to 5 s was biased to shorter durations (i.e., a temporally advanced manifestation of Vierordt's law). Our results accord well with numerous previous studies showing a leftward shift in the acute effect of meth on interval timing, indicating that meth dependents may exhibit accelerated internal clock in the early period of abstinence.

The current study only observed this pattern in the MS group, which suggests that the aberrant clock speed of motor timing in meth dependents persists for at least 3 months after the cessation of drug intake. When the duration of abstinence reaches an approximate 16 months, partial motor timing function recovers to levels exhibited by the HCs. The capacity of prolonged abstinence to recover from the meth-induced impairments of the dopaminergic system and cognitive function has received increasing support in the literature (*34*). Longitudinal positron emission tomography studies have documented the recovery of striatal dopaminergic transporter loss in meth dependents within 12 to 17 months of abstinence (*35*) and normalized thalamic metabolism within a mean of 14 months of abstinence; neither of these improvements were observed across short-term abstinence (mean

of 3 months) (*36*). Frontal gray matter changes also follow a similar pattern (*37*). These changes may be linked to improvements in cognitive functions (e.g., cognitive control) (*38*). Here, our study also demonstrated that the MS group achieved worse performance than did the ML and HC groups. Future investigations with a greater range of abstinence durations and longitudinal neural imaging studies are needed to elucidate the critical period at which motor timing impairments in abstinent meth dependents may reverse.

Although we observed behavioral differences between meth dependents and HCs across all target durations, our results conflict with those of some previous investigations. Wittmann *et al.* (*26*) employed 15 stimulant-dependent subjects (meth and/or cocaine) with abstinence durations of 20 to 40 days and only observed group differences in reproducing durations of 2 s. While the discrepancy in results may be attributable to a lack of power, rendering dynamic changes over several months undeletable, they may also be attributed to differences in experimental settings (e.g., instruction and materials).

The CVs of the meth groups were significantly lower than that of HCs for all target durations. The lower CV represented lower temporal variability, reflecting the fact that repeated responses were centralized from the target duration within each condition. This finding was seemingly inconsistent with the observation of Wittmann *et al.* (*26*) that the CV of the stimulant-dependent group was significantly higher than that of HCs at a duration of 1 s. The periods of abstinence assessed in the present study may partly account for this difference.

Concerning motor timing, when the target duration was longer than 1 or 2 s, we observed a negative relationship between the dosage of meth use before abstinence and DRR and a positive relationship between the dosage of meth use before abstinence and CV. These patterns were shown only in the MS group. That is, in the early stage of abstinence, meth dependents who consumed higher doses prior to cessation would exhibit lower temporal accuracy and higher temporal variability (i.e., worse stability) than those who took lower doses of meth before abstinence. However, this dose-dependent effect disappeared as abstinence progressed. Regarding perceptual timing, the dose-dependent effects were only reported in the PSE of the suprasecond task. This finding suggests that the impacts of meth dose on motor timing could last for at least 3 months. The influence of meth dose on timing and time perception has only been investigated in rats. For example, low-dose meth (0.5 mg/kg) induced a leftward shift in temporal bisection, and high-dose meth (3.0 mg/kg) yielded a less steep temporal curve (*23*). However, the present study indicates that meth-induced aberrations in motor timing may be more complex. We observed that the dose of meth affected temporal accuracy and variability along with abstinence duration. While the dopaminergic system gradually recovers from the cessation of meth intake, it does not reach normal levels required for healthy functioning in the initial stages of abstinence (*34*).

It is notable that the dose-dependent effects were not observed in motor responses to 1 or 2 s but existed for suprasecond discrimination; this finding may be related to the differences in the processing of various ranges of time. Meta-analyses have indicated that the bilateral SMA and right inferior frontal gyrus are key brain regions for time processing across all time tasks and scales. However, subsecond timing is more likely to activate subcortical structures, such as the cerebellum, whereas suprasecond timing shows a stronger association with cortical areas, such as the SMA and PFC (*4*, *16*). Transcranial magnetic stimulation studies have also provided direct causal evidence (*17*). In the present study, the relatively automatic reproduction of short durations was not affected by meth dose, while the reproduction of long durations that require more cognitive components was affected by meth dose. Nevertheless, longitudinal experiments should be performed to clarify the causal influence of meth dose on timing and time perception across all periods of abstinence.

This study is subject to several limitations. First, we only included male meth dependents. Given the robust gender differences in time processing (*39*), women should be recruited in future research to verify our results. Second, in experiment 1, PSQI, BDI, and BIS scores in the meth groups were significantly higher than those in the HC group. While we defined these factors as covariates in the ANCOVA, they may confound the present results and lead to the overcorrection of the data. Both depression and impulsivity could potentially have been increased by the monoaminergic deficit associated with meth abstinence. Previous studies have also revealed the influence of depression (*40*) and impulsivity (*5*) on time perception. The sleep-wake cycle based on circadian timing also relates to time perception (*1*). Thus, future research may be warranted to explore the comprehensive effect of these variables in meth addiction. Third, experiment 1 had fewer trials than did experiment 2. We considered the length of the present study and followed prior research investigating the effect of drug (e.g., stimulant, depressant, or hallucinogen) on motor timing (*26*, *41*, *42*), where they used the same temporal reproduction task and provided similar trials to participants. Hence, most researchers in this field may consider the number of trials in the reproduction paradigm appropriate. However, few trials might confound the results because we conducted a 3 SD cutoff to remove the extreme values (see section on Behavioral tasks). In addition, while few data were excluded from the analysis of experiment 1, it may have induced a disproportionate effect considering the few overall trials conducted. Future investigations should consider increasing the number of trials appropriately.

In summary, the present results suggest that motor timing deficits persist for at least 3 months after the cessation of meth intake; the dose-dependent effects on motor and perceptual timing for long durations tend to appear in short-term abstinence subjects. These findings open a question for more neural mechanisms underlying these changes, potentially the dopaminergic signaling in the striatum.

MATERIALS AND METHODS

Participants

All patients in experiments 1 and 2 were required to meet the following inclusion criteria prior to enrollment: Met the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* criteria in a structured interview; had been using purely meth for at least 1 year; intake of drug at least three times per week, lasting for at least a month for one period (occasional drug use was not included); dosage of more than 0.1 g/day; and willingness to participate in the study. All participants, including HCs, were right-handed and had normal or corrected-to-normal vision. Exclusion criteria were current major or neurological diseases. Participants in the MS group remained abstinent between 1 and 8 months (with an average of 3 months); the ML group was abstinent for over 9 months (with an average of 16 months).

In experiment 1, 194 men were assessed for eligibility (57 HCs, 73 meth-short subjects, and 64 meth-long subjects; fig. S1). Some participants failed to meet the inclusion criteria (3 HCs, 19 meth-short dependents, and 13 meth-long dependents). Moreover, one patient in the MS group and one patient in the ML group were removed because of poor data (see section on Behavioral tasks). Last, 54 healthy men (age

range, 19 to 59 years; mean, 36.02 years), 53 in the MS group (age range, 25 to 54 years; mean, 37.34 years), and 50 in the ML group (age range, 23 to 57 years; mean, 36.40 years) were analyzed. In experiment 2a, 150 men were assessed for eligibility (68 HCs and 82 meth-short subjects; fig. S2). One participant in the HC group and 38 participants in the MS group were removed because they did not meet the inclusion criteria. Sixty-seven participants in the HC group and 44 participants in the MS group participated in experiment 2a. However, 2 individuals in the control group and 1 meth-short subject misunderstood the rules of the task, 1 control participant and 1 meth-short subject had poor data (see section on Statistical analyses), and the function parameters for the 21 HCs and 7 meth-short dependents could not be calculated (i.e., fitting failure). In total, 43 HCs (age range, 18 to 55 years; mean, 34.60 years) and 35 meth-short subjects (age range, 22 to 53 years; mean, 35.34 years) were included in the analysis. In experiment 2b, 136 men were evaluated for eligibility (56 HCs and 80 meth-short subjects; fig. S3). Three HCs and 41 meth-short dependents were removed because of not having met the inclusion criteria. Fifty-three HCs and 39 meth-short dependents participated in experiment 2b; however, 2 HCs and 3 meth-short dependents misunderstood the rules of the task, 5 HCs and 1 meth-short dependent had poor data, and the function parameters for 9 HCs and 5 meth-short subjects could not be calculated because of the fitting failure. Last, 37 HCs (age range, 20 to 45 years; mean, 33.19 years) and 30 meth-short dependents (age range, 23 to 51 years; mean, 34.90 years) were included in the analysis.

The study was approved by the Human Research Institutional Review Board of Liaoning Normal University. All participants provided written informed consent in accordance with the Declaration of Helsinki (1991).

Demographics and clinical measures

For the meth groups, the following drug use history and demographic variables were collected using a self-report survey (Tables 1 to 3): age, education level (years), duration of current abstinence (months), years of meth use before abstinence, and dosage of meth use before abstinence (g/month). All participants completed the 19-item PSQI (*43*), 30-item BIS (*44*), 21-item BAI (*45*), and 21-item BDI (*46*). These standardized questionnaires were used to evaluate depression, anxiety, sleep quality, and impulsivity symptomatology.

Behavioral tasks

In experiment 1, the temporal reproduction task was conducted with E-Prime 2.0 (Psychology Software Tools Inc.). Each trial began with a fixation cross (lasting from 300 to 600 ms) at the center of the monitor. Participants were required to remember the duration (1/2/3/4/5 s) of a gray oval (12 × 16 cm) in the encoding phase. After which, a fixation cross was then displayed for 600 to 800 ms. In the reproduction phase, participants were required to press the space bar until they felt the duration of the current oval matches that of the remembered oval. A complete trial ended with the choice. An intertrial interval (ITI) was randomly set to between 500 and 1000 ms. All stimuli were displayed in the center of the screen. To avoid the influence of timing categories, all subjects were told to view the stimuli passively and not to count or beat time at any point during the procedure to prevent distortion of the results (*47*). A total of 50 trials (10 trials × 5 durations) were randomly assigned to two blocks; each time duration (1/2/3/4/5 s) was presented five times per block. Participants were allowed a break between blocks. Each participant performed a training session to fully understand the task (10 trials in total, 2 trials for each time duration) and then performed the two experimental blocks (50 arranged trials, 10 trials for each time duration).

Before statistical analysis, reaction time exceeding the range of the mean ± 3 SD in each condition and each group was removed (HC: 0.52% of total trials, ML: 1.40% of total trials, and MS: 1.09% of total trials). Note that all data for a person whose half trials in most target conditions were cut off would be excluded (i.e., poor data). Two dependent variables (i.e., accuracy and variability) from this behavioral task were analyzed: (i) DRR, an index of temporal accuracy and the ratio of reproduction duration to that of the respective target interval, where values higher and lower than 1 indicate overestimation and underestimation, respectively; and (ii) CV, which was derived by dividing the SD of the scores by the mean value of those scores, where a higher CV indicates greater temporal variability.

In experiment 2, the temporal discrimination task featured the same durations for the fixation cross presentation, interstimulus interval, and ITI as in experiment 1. For the subsecond discrimination, the standard duration was 500 ms, and the comparison durations consisted of 200/350/500/650/800 ms. For the suprasecond discrimination task, the standard duration was 2000 ms, and the comparison durations included 1300/1700/2000/2300/2600 ms. Participants needed to decide whether the duration of the second oval was longer or shorter than that of the first oval by pressing "F" or "J" on the keyboard. Responses with latencies of less than 1500 ms were recorded. The response keys were counterbalanced across participants. There were 100 trials (20 × 5 trials) in each task that were randomly allocated to two blocks. Other experimental settings were equivalent to those in experiment 1.

Statistical analyses

All statistical analyses were performed with SPSS 22.0 (IBM, Armonk, NY). In experiment 1, differences in the demographic and clinical measures among the three groups were analyzed using univariate ANOVA. Post hoc comparisons were investigated using the Bonferroni correction. An independent-samples *t* test was used to assess the difference of meth use characteristics between the MS and ML groups. For the outcomes of the reproduction task (i.e., DRR and CV), we conducted separate repeated-measures ANCOVA with time duration (1/2/3/4/5 s) as the within-subjects factor, group (HC/MS/ML) as the between-subjects factor, and BDI, PSQI, and BIS as the covariates. *P* values were corrected using the Greenhouse-Geisser method. One-sample *t* test against 1 in DRR for each target duration was used to examine temporal overestimation (higher than 1) or underestimation (lower than 1). Pearson's correlations were computed to evaluate the relationships between the dosage of meth use before abstinence (g/month) and behavioral outcomes in both meth groups.

In experiment 2, demographic and clinical measurements between the MS and HC groups were analyzed using an independent-samples *t* test. For the temporal discrimination task, the proportion of "long" for all participants for each comparison duration was fitted with a two-parameter logistic model (function 1) using GraphPad Prism 7 software.

$$f(x) = 1/(1 + \exp(-b \times (x - c))) \quad (1)$$

In function 1, *c* represents the PSE, the value of the stimulus durations for which the *P* (long) = 0.5. PSEs higher than 500 in experiment 2a or higher than 2000 in experiment 2b indicated temporal underestimation and vice versa. *b* indicates the slope of the curve, an index of temporal sensitivity, where a higher slope indicates greater sensitivity

to time. Note that when a PSE exceeded the set limit (200 to 800 ms in experiment 2a and 1400 to 2600 ms in experiment 2b), the data were removed (i.e., poor data). Cases in which the fit does not adequately incorporate the values of all parameters were termed "fitting failure" (*48*). Independent-samples *t* tests were performed to compare the differences in the PSE and slope between the meth-short group and HCs. Pearson's correlations were computed to evaluate the relationships between different clinical measures, meth use before abstinence (g/month), and behavioral outcomes.

All effect sizes of the univariate ANOVA and ANCOVA were reported as η_p^2. Cohen's *d* represented the effect size of the *t* test.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/5/10/eaax6916/DC1

Fig. S1. Consort flow diagram for experiment 1.
Fig. S2. Consort flow diagram for experiment 2a.
Fig. S3. Consort flow diagram for experiment 2b.
Table S1. Pearson's correlations between behavioral indices of experiment 1 and dosage of meth use before abstinence (g/month), *r* (*P* value).
Table S2. Pearson's correlations between behavioral indices of experiment 2a and some demographic characteristics, *r* (*P* value).
Table S3. Pearson's correlations between behavioral indices of experiment 2b and some demographic characteristics, *r* (*P* value).

View/request a protocol for this paper from *Bio-protocol*.

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