



# Repeated methamphetamine exposure decreases plasma brain-derived neurotrophic factor levels in rhesus monkeys

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## ABSTRACT

**Background** Brain-derived neurotrophic factor (BDNF) is known to prevent methamphetamine (METH)-induced neurotoxicity and plays a role in various stages of METH addiction. However, there is a lack of research with longitudinal design on changes in plasma BDNF levels in active METH-dependent individuals.

**Aims** The aim of the study was to investigate changes in BDNF levels during METH self-administration in monkeys.

**Methods** This study measured plasma BDNF levels in three male rhesus monkeys with continuous METH exposure and four male control rhesus monkeys without METH exposure. Changes in plasma BDNF levels were then assessed longitudinally during 40 sessions of METH self-administration in the three monkeys.

**Results** Repeated METH exposure decreased plasma BDNF levels. Additionally, plasma BDNF decreased with long-term rather than short-term accumulation of METH during METH self-administration.

**Conclusions** These findings may indicate that the changes in peripheral BDNF may reflect the quantity of accumulative METH intake during a frequent drug use period.

## INTRODUCTION

The prevalence of and mortality associated with methamphetamine (METH) use have increased markedly in the past 10 years.<sup>1 2</sup> METH use disorder can lead to serious consequences, such as neurotoxicity and even permanent brain injury.<sup>3 4</sup> Current diagnostic criteria are qualitative and lack objective measures to quantify drug intake or brain injury.<sup>5 6</sup>

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family,<sup>7</sup> has neuroprotective effects on neurons influenced by the neurotoxic effects of METH, such as blocking METH-induced neuronal death *in vitro* and attenuating dopaminergic and serotonergic deficits in rodent models.<sup>8 9</sup> Similar to findings in preclinical studies, METH-dependent individuals during drug withdrawal have been found to exhibit high basal levels of BDNF,<sup>10</sup> indicating a neuroadaptive process in the brain.<sup>11</sup> However, other studies have found decreased basal levels of BDNF during METH withdrawal.<sup>11 12</sup> The

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous clinical studies have primarily examined plasma brain-derived neurotrophic factor (BDNF) levels during methamphetamine (METH) withdrawal, but there is currently a lack of data on BDNF levels during drug exposure.

## WHAT THIS STUDY ADDS

⇒ This study evaluated changes in plasma BDNF levels in rhesus monkeys during METH exposure through cross-sectional and longitudinal assessments.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings may contribute to the development of composite markers for quantifying cumulative METH intake.

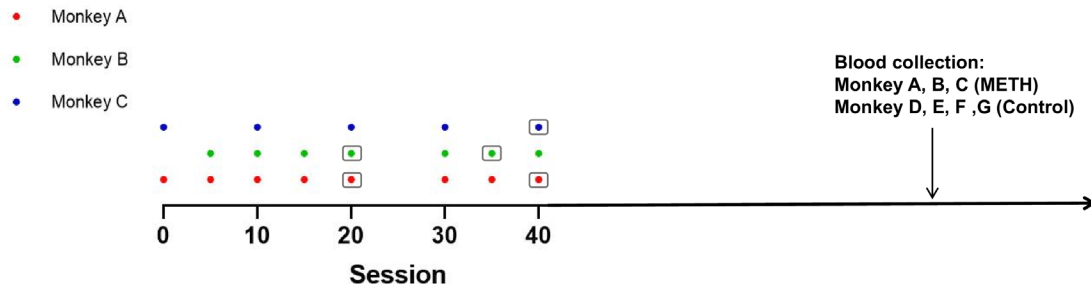
variations may be attributed to differences in the points of BDNF measurements after METH exposure, as BDNF levels in early drug withdrawal likely reflect the neurotoxic effects of repetitive METH exposure.<sup>11</sup> However, no data on plasma BDNF levels in active METH-dependent individuals are currently available.

Non-human primates with neurochemical and pharmacokinetic similarities to humans are well-suited for conducting longitudinal studies to identify critical changes in peripheral and central molecules during the progression of addiction.<sup>13–15</sup> Thus, this study aimed to assess plasma BDNF levels in rhesus monkeys with self-administered METH. Furthermore, we also evaluated the correlation between plasma BDNF and accumulative METH intake. Our findings may indicate that peripheral BDNF could be a potential candidate for a composite biomarker of the quantity of accumulative METH intake.<sup>6</sup>

## MATERIALS AND METHODS

### Subjects

All experimental procedures were carried out in accordance with the guidelines and regulations



**Figure 1** Experimental timeline. Plasma BDNF was measured in three monkeys with continuous METH exposure and four without METH exposure. Changes in plasma and CSF BDNF also were assessed in the three monkeys during the initial 40 sessions of METH self-administration. The circles of various colours represent the blood collection times of the different monkeys, and the grey boxes represent the CSF collection times. BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; METH, methamphetamine.

of the Animal Care Committee of the Institute of Neuroscience and Centre for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences. Animal care protocols aligned with the US National Institutes of Health Guide for the Care and Use of Laboratory Animals. We utilised a sample of seven adult male rhesus monkeys for the study. The monkeys were trained to sit in a primate chair (Suzhou Monkey Animal Experimental Equipment Technology Co, Jiangsu) and weighed between 8.5 and 12 kg during the experiment. They were provided with sufficient monkey chow in the morning and afternoon to maintain a healthy body weight. Fruit was given at noon unless otherwise noted, and water was continuously available throughout the day. The monkeys were individually housed in stainless steel cages with visual, auditory and olfactory contact with other monkeys. Toys were also provided in their cages, and videos were played once or twice a week in the animal housing

rooms to provide additional environmental enrichment. The monkeys were maintained under a 12-hour light–dark cycle (lights on from 07:00 am to 19:00 pm). Online supplemental table 1 provides detailed information about the monkeys' training.

### Apparatus

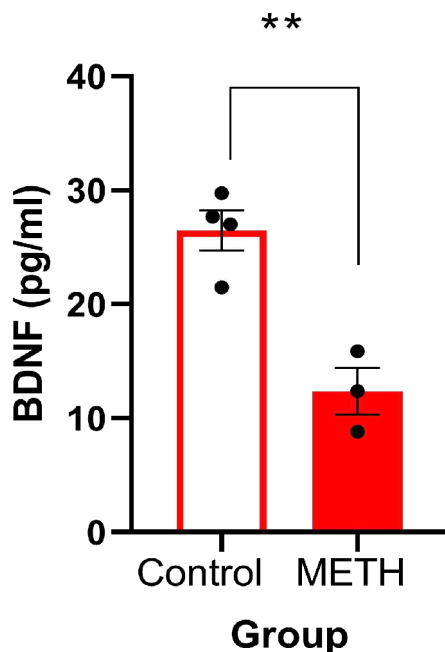
All behavioural studies were conducted in ventilated, sound-attenuating rooms that were equipped with an operant panel (AniLab Scientific Instruments Co, Ningbo, Zhejiang). Monkeys were restrained in a primate chair facing an operant panel with two levers and three lights: a red light above the right lever, a green light above the left lever and a white light on top of the panel. An external syringe pump was used to deliver precise volumes of 10% concentration fruit juice to a metallic straw positioned in front of the monkeys. A second external syringe pump was used to deliver intravenous METH dissolved in saline (1.28 mg/mL) during drug self-administration sessions.

### Training procedures

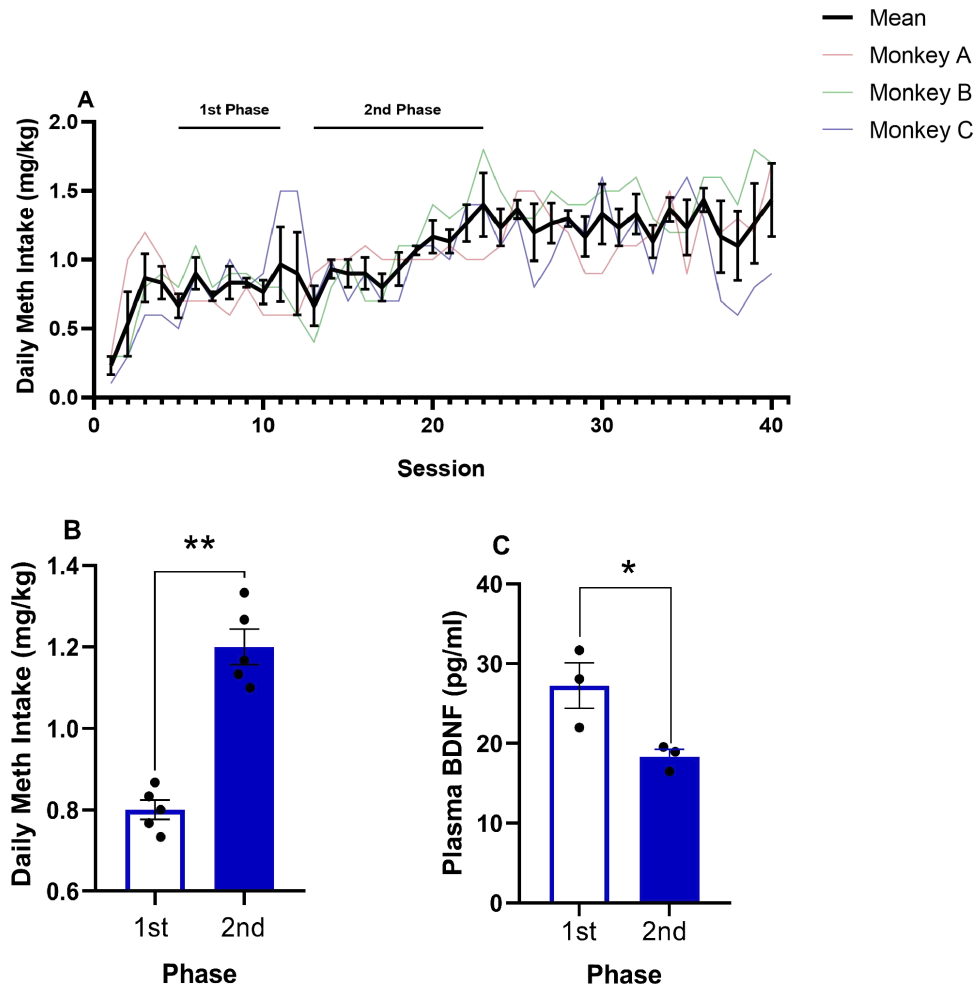
At the beginning of the training stage, the monkeys were provided limited access to fresh fruit (~50 g) and water (25 mL/kg/day) every weekday. Monkeys were trained to self-administer juice during daily 2-hour sessions.

The white light signalled the beginning of a trial. Lever pressing resulted in the delivery of one juice reinforcer (2 mL) paired with the termination of the white light and simultaneous onset of the cue light (a green or red light) stimulus above the lever and a tone stimulus (10 s) corresponding to the lever. Daily sessions were limited to 100 juice reinforcements. Although either lever press completion resulted in juice reinforcer delivery, the monkeys consistently chose the same lever (set as the juice-associated lever) based on their hand preference. Lever pressing behaviour was trained to reach the terminal at a fixed ratio (FR) 30 schedule for juice reinforcements. Following the delivery of each reinforcer, there was a 60 s timeout (TO) period during which all lights remained off and responding had no scheduled consequences.

When the monkey's behaviour stabilised, they were provided more access to water (40 mL/kg/day) after the training session every day. Stable behaviour was defined



**Figure 2** Differences in plasma BDNF levels between the control group and the METH group. The data are presented as the mean (SE). Independent two-sample t-test was used (\*\* $p < 0.01$ ). BDNF, brain-derived neurotrophic factor; METH, methamphetamine; SE, standard error.



**Figure 3** Daily METH intake and differences in drug intake and BDNF levels between the first and the second phases. (A) Data shown are the mean (SE) of three monkeys. The first phase refers to the first time the dose remained stable for 5 consecutive days. The second phase refers to the time when the dose increased and then stabilised again for 5 consecutive days (see Methods section). (B and C) The data are presented as the mean (SE). Paired t-test was used (\* $p < 0.05$ ; \*\* $p < 0.01$ ). BDNF, brain-derived neurotrophic factor; METH, methamphetamine; SE, standard error.

by a stable number of reinforcers over at least five consecutive sessions ( $\pm 20\%$ ).

### Surgery

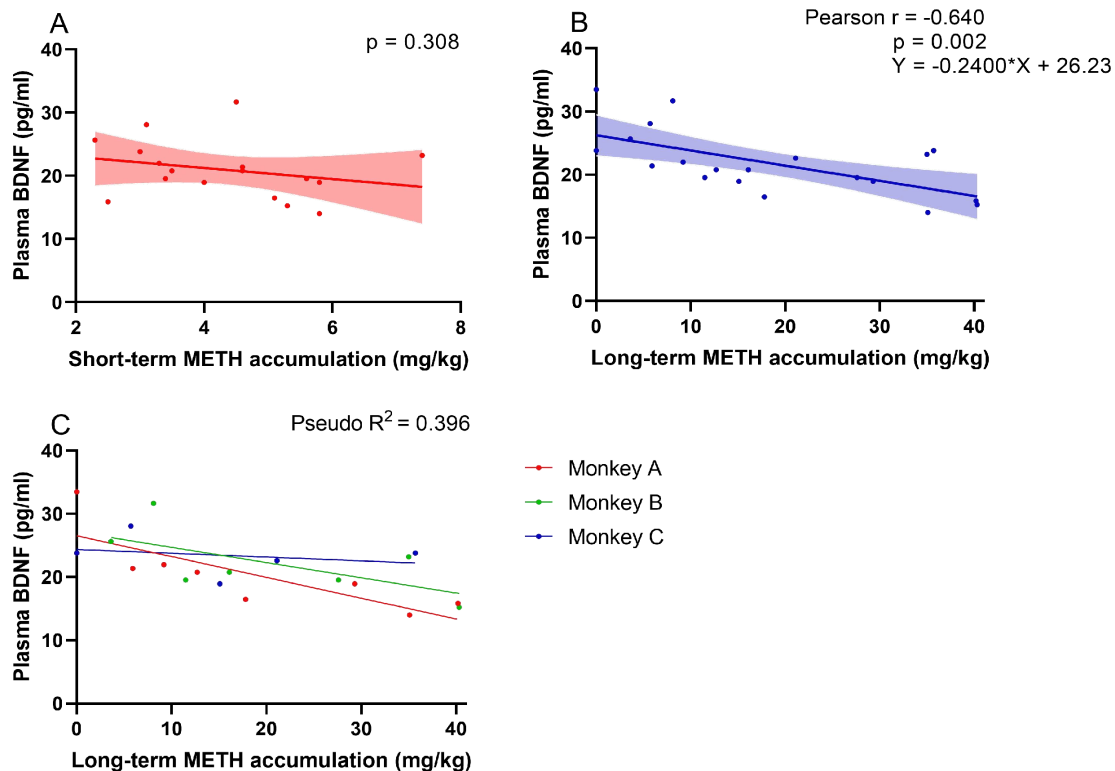
The monkeys were anaesthetised using a combination of Telazol and isoflurane. All animals underwent the placement of a vascular access port (Perouse Medical) located in the back region, with a catheter extending subcutaneously to connect with an internal jugular or femoral vein. This vascular access port facilitates non-stressful percutaneous access to the vasculature for METH self-administration, minimising the risk of infection since there are no external components beyond the skin. We injected ceftriaxone sodium after surgery to decrease infection. Two weeks were given to the monkeys for recovery after their surgery. We flushed the catheters with 1.0 mL of heparinised (250 U/mL) saline once a week to maintain patency.

### Juice-METH choice

The juice-associated lever was determined by the monkeys based on their hand preference (as mentioned earlier). When commencing the Juice-METH choice experiment,

the lever on the non-preferred hand side was set as the METH-associated lever. Both the juice lever and the METH lever were available during the Juice-METH choice session. The white light signalled the beginning of a trial. Monkeys typically would self-administer METH during five sessions/week (Monday to Friday; session duration of 2 hours).

The response requirement of the progressive ratio (PR) schedule was increased according to the Fibonacci sequence (1, 3, 5, 8, 13, 21, 34), and each requirement was repeated three times. The METH-maintained response was initially shaped by occasional lever pressing or passive intravenous administration (1 mg/kg). Completion of a PR requirement on the METH-associated lever resulted in the delivery of a METH injection (0.1 mg/kg/injection) paired with the termination of the white light and simultaneous onset of the cue light stimulus above the METH-associated lever and the tone stimulus (10 s) corresponding to the lever. Similarly, each infusion was followed by a 60 s time-out period. Completing an FR30 requirement on the juice-associated lever resulted in the delivery of one juice reinforcer (2 mL)



**Figure 4** The correlations of plasma brain-derived neurotrophic factor (BDNF) and accumulative methamphetamine (METH) intake. (A) Short-term METH accumulation was calculated as the total drug intake in five consecutive sessions before blood sampling. Short-term accumulation of METH is not significantly correlated with plasma BDNF levels. (B and C) Long-term METH accumulation was calculated as the cumulative amount of drug intake from session 1 to each successive session. Long-term accumulation of METH is negatively correlated with plasma BDNF levels. The red and blue lines are the regression curve, and the red and blue shadow represent the 95% CI of the monkeys' plasma BDNF concentration. The chromatic lines are the regression curves of different individuals.

paired with the termination of the white light and simultaneous onset of the cue light stimulus above the juice-associated lever and a tone stimulus (10 s) corresponding to the lever. Each session ended when 30 total METH reinforcers had been earned, or 2 hours had elapsed, whichever came first. During the Juice-METH choice sessions, monkeys exhibited a rapid reversal of their preference for juice within approximately 10 sessions and, after that, consistently self-administered METH.

Stable behaviour was defined by a stable number of reinforcers ( $\pm 20\%$  of the mean number of injections, with no trends) over five consecutive sessions, and these sessions were defined as the first stable phase. After a period of self-administration, we observed a gradual increase in drug intake. To compare this difference, those sessions at which the METH intake was restabilised were defined as the second stable phase.

### Drugs

The METH (> 99%) was provided by the Center for Excellence in Brain Science and Intelligence Technology. METH was dissolved in a 0.9% saline solution. Drug solutions were passed through a sterile 0.22  $\mu\text{m}$  filter before intravenous administration.

### Sample collection

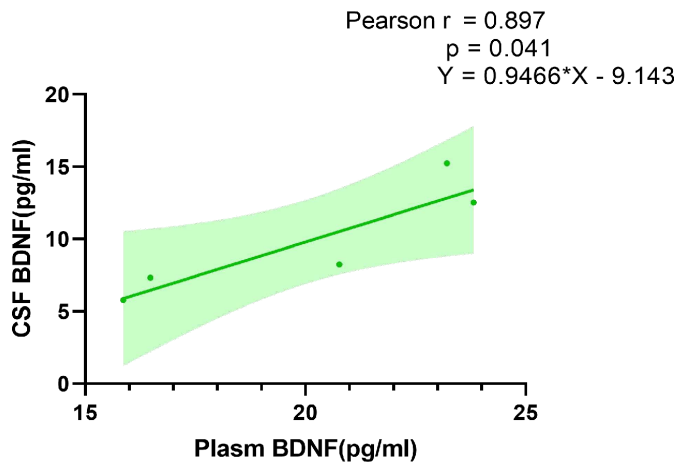
Plasma samples were obtained before the training session on Mondays, while cerebrospinal fluid (CSF) samples were collected on Saturdays, which was 2 days before the plasma collection (figure 1).

Blood samples were collected from conscious monkeys in their home cages via venipuncture by two experienced veterinarians. To minimise the impact of circadian rhythms and acute stress, samples were taken within a 5 min window between 08:00 and 09:00 AM. Chilled EDT tubes were used to collect the samples, which were then centrifuged at 800g for 15 min at 4 °C. The plasma fraction was transferred to 1.5 mL centrifuge tubes and stored at  $-80$  °C until assayed.

For CSF collection, the monkeys were anaesthetised with Telazol, and CSF was obtained via a lumbar puncture using a 22-gauge needle by an experienced technician. Samples were collected between 01:00 pm and 02:00 pm to minimise the potential impact of circadian rhythm variance. CSF samples were transferred to a 1.5 mL centrifuge tube, frozen on dry ice, and stored at  $-80$  °C until assayed.

### Assays

Plasma and CSF BDNF (Arigo Biolaboratories, Hsinchu City, Taiwan), and plasma orexin A



**Figure 5** The correlation of plasma brain-derived neurotrophic factor (BDNF) and cerebrospinal fluid (CSF) brain-derived neurotrophic factor (BDNF). The green shadow represents 95% CI of the monkeys' CSF BDNF concentration.

(MyBioSource, Southern California, San Diego, USA), Cortisol (Arigo Biolaboratories), epidermal growth factor (EGF) (MyBioSource), ghrelin (MyBioSource), Troponin T (TnT) (MyBioSource), interleukin-6 (IL-6) (Arigo Biolaboratories) and interleukin-12 (IL-12) (Arigo Biolaboratories) were measured using sandwich enzyme-linked immunosorbent assays according to the manufacturer protocols. The commercially available Lipid Peroxidation Assay Kit (Abcam, Cambridge, Cambridgeshire, UK) was used to assess plasma malondialdehyde (MDA). Assay sensitivities were 7.8 pg/mL for BDNF, 30.3 pg/mL for cortisol, 9.38 pg/mL for EGF, 1 pg/mL for orexin A, 1 pg/mL for ghrelin, 18.75 pg/mL for TnT, 7.8 pg/mL for IL-6 and 7.8 pg/mL for IL-12. Intra-assay and interassay coefficients of variation, respectively, are 5% and 9% for BDNF, 8.8% and 8.13% for cortisol, <10% and <10% for EGF, <10% and <10% for orexin A, <10% and <10% for ghrelin, <10% and <10% for TnT, <10% and <10% for IL-6 and <10% and <10% for IL-12. Peripheral and central samples were measured in duplicate by commercial assay services (Yanjiang-Bio, Shanghai, China).

### Data analysis

Statistical analyses were performed using IBM SPSS software (V.16.0). An independent two-sample t-test was used to analyse differences in plasma BDNF levels between the control and the METH groups while accounting for age in months as a covariate. A paired t-test was used to analyse the differences in drug intake and BDNF levels between the first and the second phases. Pearson correlation analysis was used to examine the relationships between plasma BDNF levels and other variables. To perform the Pearson correlation, both variables were required to be distributed normally.

We fitted a linear mixed model by lmerTest R package to evaluate whether molecule expression level depended on

drug use and cumulative dosage duration. The regression model was fitted by the lmer function with the following formula: molecules~time (dosage) + (1 | monkey ID). We further applied a generalised linear mixed model implemented in the MuMIn R package to calculate the pseudo-R-square of BDNF.

## RESULTS

### Repeated METH exposure decreases plasma BDNF levels

We measured plasma BDNF levels in three monkeys with continuous METH exposure and four control monkeys without METH exposure (figure 1). Plasma BDNF levels were lower in the METH-exposed monkeys than in the controls ( $t=4.816$ ,  $df=5$ ,  $p=0.009$ ) (figure 2). Moreover, we also measured plasma BDNF levels after 3 months of withdrawal in the three monkeys. Although there was a trend of increased BDNF levels after withdrawal, statistical significance was not observed (online supplemental figure S1).

### Long-term METH accumulation negatively correlates with plasma BDNF levels

To further investigate the effect of METH exposure on plasma BDNF levels, we measured plasma BDNF levels at multiple time points in the three monkeys during METH self-administration. We analysed the daily METH intake during the self-administration period and found that the daily intake of the three monkeys reached the first stable phase at sessions 9, 11 and 10, respectively, and the second stable phase at sessions 17, 28 and 23, respectively (figure 3A). The average daily METH intake in the second phase was higher than in the first phase (paired  $t=6.708$ ,  $df=4$ ,  $p=0.003$ ) (figure 3B), with a 40% increase in daily intake from the first to the second phase (figure 3A). Plasma BDNF levels were lower in the second phase than in the first phase (paired  $t=4.658$ ,  $df=2$ ,  $p=0.043$ ) (figure 3C). These results suggest that METH accumulation may be associated with changes in plasma BDNF levels.

We then separately compared the effects of plasma BDNF levels with short-term and long-term METH accumulation on plasma BDNF levels. Short-term METH accumulation was calculated as the total amount of drug intake in five consecutive sessions before blood sampling. In contrast, long-term METH accumulation was calculated as the cumulative amount of drug intake from session 1 to each successive session. Pearson correlation analysis showed a correlation between plasma BDNF and long-term METH accumulation ( $p=0.002$ ,  $r=-0.640$ ) (figure 4B) but not short-term METH accumulation ( $p=0.308$ ) (figure 4A). The mixed-effects model confirmed this finding (coefficient= $-0.047$ ,  $SE=0.013$ ,  $p=0.002$ , pseudo  $R^2=0.396$ ) (figure 4C). There were no significant correlations between other molecules in plasma and METH intake (see online supplemental table 2).

To elucidate the correlation between BDNF in the peripheral and central nervous systems, we collected five CSF samples during self-administration in three monkeys. There was a positive correlation between plasma and CSF BDNF levels ( $p=0.041$ , Pearson  $r=0.897$ ) (figure 5).

## DISCUSSION

### Main findings

Our research showed that repeated exposure to METH decreased plasma BDNF levels, and plasma BDNF decreased as long-term rather than short-term accumulation of METH increased during METH self-administration. To our knowledge, this is the first study showing the association between altered BDNF levels and METH self-administration in monkeys.

The decrease in plasma BDNF levels in rhesus monkeys during self-administration is consistent with preclinical studies in rodents in which BDNF is reduced in several brain regions, such as the occipital cortex, hypothalamus, striatal and hippocampal, after repeated amphetamine or METH administration.<sup>16–18</sup> In contrast, several preclinical studies in rodents discovered that METH could increase BDNF levels in the nucleus accumbens, striatum, hippocampal, and so on.<sup>19–21</sup> These differential effects of METH on BDNF levels suggest that the neurobiological response to METH may be influenced by the duration of drug exposure,<sup>17–20</sup> which is supported by our findings that plasma BDNF decreased with long-term rather than short-term accumulation of increased METH. In addition, the results of blood BDNF levels during METH withdrawal are inconsistent, possibly due to differences in detection time points. Some clinical studies have found that the baseline levels of BDNF are lower in the early stages of METH withdrawal,<sup>11–12</sup> which may be due to the impact of drug accumulation on BDNF levels, and our data during the drug use period supports this view. Other clinical studies have found that the baseline levels of BDNF are higher after a period of METH withdrawal,<sup>10–22</sup> potentially due to a diminishing impact of drug accumulation on plasma BDNF; our data from the withdrawal period also supports this view. Overall, our results suggest that chronic METH exposure decreases the level of plasma BDNF during the drug use period.

Currently, biomarkers of METH use disorder are used to detect a drug and its metabolite(s), providing only a binary outcome measure of abuse; therefore, developing quantifiable measures contributes to objectively diagnosing addiction.<sup>5–6</sup> The negative association of plasma BDNF and accumulation of METH indicates that peripheral BDNF could be a potential candidate for a composite biomarker of the quantity of accumulative METH intake.<sup>5</sup> In addition, distinguishing the long-term and short-term impacts of METH is crucial since amphetamine-type stimulants are used to treat certain disorders, but their long-term effects are unclear.<sup>23</sup> Our individual analysis results suggest that the long-term accumulation of METH may be more correlated with the decrease in BDNF than the short-term accumulation. Future studies are needed to determine the optimal duration of plasma BDNF response to cumulative methamphetamine exposure.

The connection between central and peripheral BDNF remains incompletely understood, but our results suggest a positive correlation between BDNF levels in the plasma and CSF. Similarly, a clinical study has found a positive correlation between CSF and plasma BDNF levels in

patients with schizophrenia. Moreover, preclinical studies have shown significant positive correlations between serum and brain BDNF levels in rats and between the hippocampus and blood in pigs.<sup>24–26</sup> CSF biomarkers reflecting ongoing biochemical changes in the brain are powerful, but the method of measuring them is invasive.<sup>5,27</sup> Peripheral blood samples are more accessible, less invasive and, thus, more suitable for diagnosing mental illness.<sup>5</sup> Thus, these findings indicate that peripheral BDNF levels could serve as a biomarker for central global changes in BDNF levels. Moreover, the levels of BDNF in the CSF could reflect a central neuroprotective function due to the BDNF in the CNS exerting neuroprotective activity.<sup>28</sup> Therefore, the decreased peripheral BDNF levels may reflect the extent of impaired neuroprotective function of the CNS after repetitive drug exposure.

### Limitations

There are some limitations in this study. First, the control group was not included in a within-subject longitudinal design. However, previous research suggests minimal variation in blood BDNF levels over 1 year.<sup>29</sup> Second, our sample size is relatively small because of the costs of working with macaques. However, a longitudinal design can partially compensate for the limitations of a small sample size because it has greater statistical power than a cross-sectional design for a small number of subjects.<sup>30</sup>

### Implications

The decrease in plasma BDNF and the negative association of plasma BDNF and drug intake indicate that peripheral BDNF could reflect the quantity of accumulative METH intake during a period of frequent drug use and the extent of impaired neuroprotective function after repetitive drug exposure. This study preliminarily investigated the effects of METH on peripheral BDNF. In addition, our unpublished data revealed the time-course patterns of drug preference and drug-seeking behaviours in monkeys. Future research could use our model to explore biomarkers (peripheral indicators or functional magnetic resonance imaging) associated with drug preference and seeking time-course patterns.

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**Contributors** MZ and ZX contributed to conceptualisation; WZ, JZ, ZW, CT and XZ to methodology; WZ and WS to formal analysis; WZ to investigation; WZ to writing—original draft preparation; HS, JZ and KU to writing—review and editing; RZ and HJ to supervision; MZ and ZX to project administration; MZ, RZ and HJ to funding acquisition; all authors have read and agreed to the published version of the manuscript. RZ and HJ are guarantors.

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**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** The study was conducted in accordance with the Declaration of Helsinki and approved by the Animal Care Committee of Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences (Approval Code: ION-2017006).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request.

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