IMMEDIATE COMMUNICATION

Methamphetamine abuse impairs motor cortical plasticity and function

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Exposure to addictive drugs triggers synaptic plasticity in reward-related brain regions, such as the midbrain, nucleus accumbens and the prefrontal cortex. Effects of chronic drug exposure on other brain areas have not been fully investigated. Here, we characterize synaptic plasticity in motor cortex after methamphetamine self-administration in rats. We show that this causes a loss of corticostriatal plasticity in rat brain slices and impaired motor learning in the rotarod task. These findings are paralleled by the observation of a lack of transcranial magnetic stimulation-induced potentiation or depression of motor evoked potentials in human patients with addiction, along with poor performance in rotary pursuit task. Taken together, our results suggest that chronic methamphetamine use can affect behavioral performance via drug-evoked synaptic plasticity occluding physiological motor learning.

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INTRODUCTION

Drug-evoked synaptic plasticity has been proposed as a neural substrate of adaptive behavior.1,2 Initial exposure to an addictive drug leads to insertion of calcium-permeable AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors and calcium-impermeable N-methyl-D-aspartate (NMDA) receptors in dopamine (DA) neurons of the ventral tegmental area;3,4 chronic drug exposure also alters synaptic transmission in medium spiny neurons of the nucleus accumbens synapses and, in some cases, also at cortical synapses.5,6

Most of these studies focused on drug-evoked synaptic plasticity in subcortical regions (for example, ventral striatum, amygdala, ventral tegmental area) and prefrontal cortex,7,8 all of which receive projections from midbrain DA neurons. Sensory and motor areas receive only sparse DA inputs and have not been extensively studied.9 However, evidence for drug-adaptive function also exists for these cortical regions. For instance, brain imaging studies in humans with cocaine or nicotine reveal a cue-induced activation of the sensory association cortex and motor cortex that reflects craving status and predicts relapse of the addicted patients.10–13 Chronic exposure to methamphetamine causes structural deficits and altered DA receptor function in the cortical-striatal projections in humans.14 Animal studies further reported a cocaine-altered expression in genes of the dorsal striatum associated with motor learning.15 Finally, drug abuse accompanies compulsive behavior and drug seeking that could result from altered motor-striatal plasticity and functioning.

In the present study we characterized synaptic plasticity at the motor cortex to the dorsal striatum in rats self-administrated methamphetamine. We then combined transcranial magnetic stimulation (TMS) to monitor plasticity of the motor evoked potential (MEP) in humans to probe a potential plasticity deficit in methamphetamine abusers.

MATERIALS AND METHODS

Animal subjects

A total of 23 male Sprague–Dawley rats (260–300 g, Beijing University Animal Center, Beijing, China) were subjected for methamphetamine self-administration (SA) training as previously described4,13 and 16 male rats were employed as the control (random assignment, animal sample size not preestimated). All animal experimental procedures have been approved by the ethic committee of animal research at Nanjing Normal University, Shanghai Jiaotong University and Beijing University. For self-administration, the training chambers (AniLab Software & Instruments, Ningbo, Zhejiang, China) were equipped with two nose-poke detectors (AniLab Software & Instruments) located 5 cm above the floor of the chambers. Nose pokes in one (active) opening led to methamphetamine infusions that were accompanied by a 5 s tone–light cue. Nose pokes in the other (inactive) opening led to saline infusions (placebo).

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were also recorded but had no consequence. In the present study, all animals were included for analyses (not in blind manner).

Human subjects
A total of 56 male addicts (methamphetamine only (METH) group, treatment seeking) (26–55 years old, right handed) were recruited for the present study and 35 healthy male subjects as controls (24–54 years old, right handed). There were no differences in age, smoking status or alcohol intake history between the two groups. All subjects reported no use of drugs in the 2 weeks before the investigation (abstinence from drug use ranged from 2 weeks to 3 months) and this was verified by urine sample examination; all subjects reported intact sleep before the experiment.

All the subjects recruited for the study participated voluntarily, and signed the written informed consent forms. Subjects reported no prior history of head trauma, epilepsy, heart diseases or metal implants in the body. The study has been approved by the ethics committee of Shanghai Mental Health Center and Nanjing Normal University, and all experimental procedures followed the guidelines of human medical research (Declaration of Helsinki). The clinical trial registration was ChiCTR-IOR-16008060 (Cortical plasticity of addicts) at http://www.chictr.org.cn.

Criteria for METH abuse
The abuse of METH was defined by the following criteria: (1) only METH use (not used with other drugs, for example, heroin) for at least 2 years; (2) METH intake of minimum 3 times per week, for a period at least a month (many METH users change their intake frequency and those with occasional drug use were not included); (3) dosage of >0.3 g per day (range 0.3–2 g); and (4) did not receive additional drug therapy to quit addiction.

Brain slice electrophysiology
For brain slice preparation, rats were deeply anesthetized with isoflurane and decapitated. Brains were quickly removed and submerged in cutting solution (in mM as follows: 119 NaCl, 2.5 KCl, 6 kynurenic acid, 1 NaH2PO4, 13.5 glucose, 77.9 NaHCO3, 3.5 CaCl2 and 7.3 MgCl2). Coronal sections (250 μm) containing motor cortex, dorsal lateral striatum and dorsal medial striatum were cut using a vibratome (VT1200S; Leica Microsystems, Wetzlar, Germany) in ice-cold cutting solutions. Brain slices were submerged in artificial cerebrospinal fluid (ACSF) (in mM as follows: 119 NaCl; 2.5 KCl, 1 NaH2PO4, 11 glucose, 26.2 NaHCO3, 2.5 CaCl2 and 1.3 MgCl2) at 27 °C for 30 min, and equilibrated with 95% O2 and 5% CO2. Slices were then individually transferred to the recording chamber and superfused continuously with 32 °C ACSF containing 50 μM picrotoxin.

For the recording of field population spikes, electrodes (3–5 MΩ) were filled with ACSF, and a stimulation intensity of 30% maximum response is employed. For whole-cell patch-clamp recording, the internal solution contained (in mM): 135 KMeSO4, 30% maximum response is employed. For whole-cell patch-clamp (3 CaCl2 and 1.3 MgCl2) at 27 °C for 30 min, and equilibrated with estimated at 50 ms after the peak of mixed currents at +40 mV.

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Figure 1. Impaired cortical-striatal plasticity and motor skill learning in self-administrated (SA) rats. (a) Nose-poke data of methamphetamine (METH) SA rats (n = 12). (b) Motor cortical–cortical long-term potentiation (LTP)-like plasticity was impaired in SA rats (n = 5 for control, n = 9 for METH, P < 0.05). (c) Motor cortical–cortical long-term depression (LTD)-like plasticity was impaired in SA rats (n = 6 for control, n = 10 for METH, P < 0.05). (d) Motor-dorsal lateral striatum plasticity was impaired in SA rats (n = 5 for control, n = 6 for METH, P < 0.05). (e) Motor-dorsal medial striatum plasticity remains intact in SA rats (n = 7 for the control group, n = 9 for METH, P > 0.05). Scale bar for all field excitatory postsynaptic potential (fEPSP) example traces in (c–f): 0.2 mV, 50 ms. From left to right: recoding site, example trace (gray for after the protocol), group data. Black filled circle: control group; red filled circle: METH group. (f) Motor skill learning was impaired in METH SA rats. Motor skill learning curve was constructed by measuring the latency to fall from the rotating rod (n = 10; METH vs control, P < 0.01, *P < 0.05 and **P < 0.01).
Figure 1. For caption see page on 1275.
hypo-osmotically and centrifuged at 25 000 g for 30 min at 4 °C to generate the synaptosomal membrane fraction (LP1) and supernatant (LS1). Then, the synaptosomal membrane fraction was solubilized and denatured in Tris-buffered saline containing 0.2% SDS (70 °C, 10 min) diluted in 1% Triton X-100 and 5% glycerol and maintained in protease inhibitor cocktail (50 μM MG132 and 10 μM β-lac).

The 4 × loading buffer (16% glycerol, 20% mercaptoethanol, 2% SDS and 0.05% bromophenol blue) was added to each sample (3:1 sample/loading buffer) before boiling for 3 min. After cooling down, the samples were subjected to SDS–polyacrylamide gel electrophoresis (10% acrylamide/0.27% N,N'-methylenebisacrylamide resolving gel) for ~40 min at 80 V in stacking gel and ~1 h at 130 V in resolving gel. The

Figure 2. Altered functioning in cortical-striatal synapses. Synaptic transmission parameters (paired-pulse ratio (PPR) (a–c), AMPA/NMDA (A/N) ratio (d–f), rectification index (RI) (g–h), input–output curve (i–k)) for Motor cortex (MC), dorsolateral (DL) and dorsomedial (DM) pathway synapses. *P < 0.05. There were no significant changes in DM and MC synapses, whereas DL pathway revealed decreased PPR value (enhanced presynaptic release) and increased A/N ratio (enhanced postsynaptic functions). Scale bars for (a–c): 100 pA, 10 ms. Scale bars for (d–h): 100 pA, 50 ms. Dashed line in (d–f) indicates the estimated NMDA receptor (NMDAR) peak at +40 mV for AMPA/NMDA ratio calculation. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; MC, motor cortex; NMDA, N-methyl-D-aspartate; RI, rectification index.

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proteins were electrophoretically transferred onto Immobilon-P transfer membranes (Millipore, Bedford, MA, USA) at 0.25 A for 2.5 h.

Primary antibodies included anti-GluA1 antibody (1:1000; Abcam, Cambridge, MA, USA, ab109450), anti-GluA2 antibody (1:1000; Abcam; ab52932), anti-GluA3 antibody (1:1000; Abcam, ab40845), anti-GluN2A antibody (1:1000; CST, 4205), anti-GluN2B antibody (1:1000; CST, 4207), anti-GluN3A antibody (1:1000; Santa Cruz, Dallas, TX, USA, sc-51160) or anti-Na-K ATPase antibody (1:1000; Abcam, ab7671). Following overnight incubation at 4 °C, the membranes were incubated for 45 min at room temperature on a shaker with horseradish peroxidase-conjugated secondary antibody (goat anti-rabbit IgG, ZSGB-BIO, ZB-2301; goat anti-mouse IgG, ZSGB-BIO, ZB-2301) diluted 1:5000 in blocking buffer. The blots were then screened using the chemiDoc MP system (Bio-Rad, Hercules, CA, USA) for 5–60 s. The level of protein expression was normalized to Na-K ATPase and analyzed with Quantity One software (version 4.4.0; Bio-Rad).

Statistics
Mean and s.e.m. represented data. Intergroup differences were compared by using independent sample t-test with Origin software (Northampton, MA, USA). P < 0.05 was considered as statistically significant.

RESULTS
Impaired cortical-striatal plasticity and motor learning after METH SA in rats
Rats were trained to SA METH for 10 days (Figure 1a).

After 3–9 days of withdrawal, we recorded field potentials in slices of the motor cortex (M1) and the dorsal medial striatum evoked by electrically stimulation as described in a previous study.23 We used TBS combined with transient GABA_\text{A} receptor blockade to induce long-term potentiation and 50 Hz stimulation to elicit long-term depression in motor cortex;24 we used 100 and 50 Hz stimulation to induce long-term depression in dorsolateral (DL) striatum and dorsomedial striatum,25 respectively. We found that these stimulation protocols failed to induce synaptic plasticity in METH SA group (Figures 1b–d) in both the motor cortex and DL striatum, whereas there was no difference in the dorsomedial striatum. This points to a METH effect in the DL, the preferential target of M1 in habit-related drug seeking.25 Given the established role of DL striatum in motor learning, we tested the rats for motor skills on a rotarod task. We found that the learning curve of animals in the METH SA group plateaued after the second block (Figure 1f).

Altered synaptic transmission in cortical-striatal synapses
To investigate the expression mechanisms of METH evoked synaptic plasticity, we established the input–output function, AMPA/NMDA ratio, and the paired-pulse ratio. We found no change in these parameters in the motor cortex M1 (Figures 2a, d and i). In the striatum, neurons of the DL (Figures 2b, e and j) showed a decreased paired-pulse ratio, an increased AMPA/NMDA ratio and steeper input–output function, reflecting enhanced synaptic transmission via increased presynaptic release and upregulated postsynaptic sensitivity.

To examine the subunit composition of AMPA and NMDA receptors, we performed western blot analyses of synaptoosomal proteins on both motor cortex and dorsal striatum. Interestingly, we detected increased amount of GluN2A/2B/3A expression in both the motor cortex and the dorsal striatum, suggesting the insertion of the heterotrimeric GluN3A-containing (calcium-impermeable) NMDA receptors (Figures 3a and b). On the other hand, GluA2 protein levels were unaltered, in line with the linear I–V curve after drug exposure, indicating the presence of Glu2A-containing AMPARs (Figures 2g and h).

RESULTS
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Figure 3. Molecular changes of synaptic glutamate receptors at cortical-striatal synapses. (a) Effects of methamphetamine self-administration (METH SA) on synaptic proteins in the motor cortex. (b) Effects of METH SA on synaptic proteins in dorsal striatum. *P < 0.05 (n = 6; METH vs control).
**Figure 4.** Diminished cortical plasticity in addicts. (a) The design of transcranial magnetic stimulation (TMS) and motor evoked potential (MEP) recordings. Single TMS pulse was administrated on the left motor cortex, and the MEP signal was recorded from abductor pollicis brevis (APB) muscle on right hand. Modified from Shen et al.\(^{20}\) with permission. (b) The 10 Hz repetitive TMS (rTMS) stimulation protocol results in potentiation of MEPs in control but not methamphetamine (METH) group (\(n = 11\) for control and \(n = 18\) for METH); (c) continuous theta burst stimulation (cTBS) protocol results in depression of MEPs in control but not METH group (\(n = 9\) for control and \(n = 11\) for METH); (d, e) control group MEPs exhibit more variance after 10 Hz cTBS protocol. Black open circle: control group; red filled circle: METH group. *\(P < 0.05\).
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DISCUSSION

We report that METH abuse can affect plasticity of the motor cortex in both drug-exposed rats and human addicts. The reduced cortical plasticity in addicts argues for an involvement of motor system in advanced stages of the disease, in line with the hypothesis that with the progression of addiction, the dorsal striatum becomes involved. Moreover, the poor learning ability could reflect a reduced flexibility that contributes to maintenance of the compulsive behavior and inhibits recovery.

One potential molecular correlate of a reduced synaptic plasticity is the insertion of calcium-impermeable (GluN3A-containing) NMDA receptors that were detected on midbrain DA neuron at an early stage of drug exposure, as well as in striatal neurons in degenerative diseases. NMDA receptors in the cortex are also essential for many forms of plasticity, and the presence of calcium-impermeable NMDA receptors alters the rules for plasticity induction. Here we confirm the insertion of GluN3A by western blot, supporting the notion that a failed induction mechanism underlies the impaired bidirectional plasticity.

Another mechanism underlying the diminished cortical plasticity may be the loss of dopaminergic signaling. For instance, human METH addicts exhibit decreased DA transmission in the brain that may manifest as drug-induced parkinsonism. In the present study we found a delayed motor learning ability in addicted patients. Future studies will be required to understand whether other types of motor learning than the pursuit task tested here are also impaired after drug abuse.

We also provide evidence for a decreased intrinsic excitability of neurons in cortical-striatal circuits after repeated METH exposure. The reduced response to TMS protocols could be partly explained by the failure to reach the firing threshold in neurons that are less excitable.

One limitation of the present study is that with electrical stimulation, the exact synaptic pathways in the motor-striatal circuit cannot be reliably identified. Employing optogenetic tools that allow further dissection will be helpful to identify the circuits affected by these changes. On the human study side, the TMS-induced cortical plasticity can be explained by either synaptic plasticity or changes of intrinsic excitability. To refine stimulation protocols that could restore normal plasticity, it will be important to examine which of the two potential mechanisms applies.

In summary, the present study demonstrates an unexpected change in motor cortical plasticity after METH abuse. Clinical studies are needed to explore the relationships between altered motor cortical plasticity and addiction symptoms (for example, craving, relapse). This will enable translation to the clinic of rational therapy for drug addiction, a disease with a tremendous burden for society.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

XH, Y-YC, OA-C, Y-XX, HS and T-FY analyzed the results and wrote the paper together; all authors have read and approved the final version of the manuscript.

Figure 5. Impaired motor learning correlates with the decreased plasticity. (a) In rotary pursuit motor learning task, the subjects were asked to trace a point on the rotating plate with a probe. Each block lasts for 60 s (interval at 10 min) and the success of time with probe targeting the point was recorded. Modified from Zhou et al. with permission. (b) The methamphetamine (METH) group exhibits worse performance during rotary pursuit learning task (n = 7 for control and n = 15 for METH), P < 0.05 for second and third tests. (c) The motor learning performance at block two was correlated to the plasticity induction changes at the same time point (Pearson’s r = 0.705, P = 0.004). Black open circle: control group; red filled circle: METH group.

used distinct TMS protocols to potentiate (10 Hz, 10 min) or depress (cTBS, 48 s) MEPs (Figure 4a). In the control group, 10 Hz repetitive TMS stimulation aimed at the motor cortex potentiated MEPs for at least 30 min. In contrast, this potentiation was not observed in the group of METH addicts (METH group) (Figure 4b). Similarly, cTBS protocol failed to induce a depression of MEPs in the METH group that was robustly observed in the control group (Figure 4c). Notably, with both stimulation protocols, the control group exhibited more individual variability compared with the METH group (Figures 4d and e). Last but not least, the craving score in the METH addict, measured by subjective responses to a probe. Each block lasts for 60 s (interval at 10 min) and the success of time with probe targeting the point was recorded. Modified from Zhou et al. with permission.
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