Article

Prefrontal AMPA receptors are involved in the effect of methylphenidate on response inhibition in rats

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Abstract

Response inhibition is a critical executive control function in many species. Deficits in response inhibition have been observed in many disorders, *eg*, attention deficit/hyperactivity disorder (ADHD). The stop-signal task (SST) is a unique behavior task for evaluating response inhibition via measuring the covert latency of a stop process, and it is widely used in studies of humans, nonhuman primates and rodents. Methylphenidate (MPH; Ritalin®) is a psychostimulant that is widely used for the treatment of ADHD and that effectively improves response inhibition in individuals with ADHD and normal subjects. However, its mechanism of improving response inhibition remains unknown. In this study we adopted a rodent nose-poking version of the SST to examine response inhibition by estimating the stop signal reaction time (SSRT) in rats. Administration of MPH (1 mg/kg, sc) 25 min before the SST test exerted a baseline-dependent effect of MPH on response inhibition, *ie*, it shortened the SSRTs only in the rats with larger baseline SSRTs, thereby improving response inhibition in these rats. The effect of MPH on response inhibition remained 3 h after MPH administration. Co-administration of PP2 (1 mg/kg, sc), a Src-protein tyrosine kinase (Src-PTKs) inhibitor that inhibited the upregulation of glutamate receptor expression on the plasma membrane of the prefrontal cortex (PFC), abolished the MPH-caused improvement in response inhibition. Furthermore, intra-PFC infusion of a selective AMPAR antagonist. NASPM (0.3 mmol/L, per side) via stainless guide cannulas implanted earlier abolished the effect of MPH on SSRT. These results suggest that AMPA receptors in the PFC are involved in the effect of MPH on response inhibition in rats.

Keywords: response inhibition; stop-signal task; prefrontal cortex; AMPA receptors; methylphenidate; SSRT; PP2; NASPM

Introduction

Response inhibition, an important adaptive capability, instructs subjects to stop inappropriate behaviors under a sudden change of environment[1]. Deficits in response inhibition have been reported in many disorders, such as drug abuse, obsessive-compulsive disorder, schizophrenia, and especially attention deficit/hyperactivity disorder (ADHD)[2-5].

Methylphenidate (MPH; Ritalin®) is a psychostimulant widely used for the treatment of ADHD[6, 7]. A therapeutic dose of MPH improves inhibitory control in individuals with ADHD[8-11] as well as in normal human subjects and animals[9, 10, 12, 13]. As a transporter inhibitor, MPH blocks the dopamine transporter (DAT) and norepinephrine transporter (NET) and preferentially elevates the concentrations of dopamine and norepinephrine at synapses in the prefrontal cortex (PFC)[14-16]; however, the mechanisms by which a therapeutic dose of MPH acutely improves response inhibition are unclear.

The PFC is a key brain region mediating cognitive and executive functions, including working memory, sustained attention, cognitive flexibility, and inhibitory control[17-20]. Malfunctions in the PFC have been related to deteriorated response inhibition[21-25]. Imaging studies have shown that MPH can change the neuronal activity of the cortex during the stop-signal task[26-28]. The effect of MPH on cognitive function is dependent on glutamate receptors in the PFC[29]. Response inhibition requires coordinated activities between the PFC and subcortical brain regions, such as the striatum, global pallidus and subthalamic nucleus[30-33]. Top-down control of the PFC depends on the output neurons within it. Glutamatergic neurotransmissions participate in many brain functions[34] and are key to the output neurons in the PFC; however, it is unknown whether glutamate receptors in the PFC play a role in the effect of MPH on response inhibition.

In the present study, we used a rodent nose-poking stop-signal task (SST) to estimate the stop signal reaction time (SSRT), which reflects the capacity of response inhibition control[21, 35]. We examined the effect of MPH on response inhibition and the contribution of glutamate receptors in the rat PFC to this

process.

Materials and methods
Animals
Male Sprague-Dawley rats (160–180 g) were purchased from SLACC (Shanghai, China). All rats were group-housed under a 12:12 light/dark cycle (light on at 8:00 am). Food and water were available *ad libitum.* The rats were weighed daily to ensure maintenance of ~95% of their original body weights. All of the experimental procedures were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23, 1996) and were approved and monitored by the Ethical Committee of Animal Experiments at the Institutes of Brain Science, Fudan University (Shanghai, China).

The stop-signal task
Chamber
The chamber had 3 nose-poke ports of 30 mm in diameter, which were positioned 50 mm above the chamber floor and were arranged horizontally 50 mm apart. The port in the middle served as a reward port, delivering a drop of water for each correct trial. Nose entries into any of the three ports were monitored with infrared detectors. The light above the center port (reward light) signaled reinforcement delivery, whereas the lights located above the other two ports signaled the availability of these ports for nose-poking. A separated tone generator was placed in the chamber. A microcontroller (Arduino) was used to control the training box, and the behavior data were acquired in customized software written in Python.

Training procedure
The stop-signal task (SST) for rats has been previously described[21]. On the first day, the rats were allowed to explore freely in the chamber for 1 h with all of the ports closed and the lights off. Then, the middle reward port was opened. When the reward light was on, a drop of water reward was delivered if the rats broke the infrared light beam in the reward port. The inter-trial interval (ITI) was 5 s. When the rats were able to finish 100 trials in 30 min, one of the two side ports (action port) opened, and the light above it (action light) was switched on. If the rats inserted their snouts into the action port, the action light turned off, and the reward light turned on. Collection of the water reward resulted in the action light coming back on. The action light remained on until the rats inserted their snouts into the action port to start a new trial. After the animals were able to complete a one-day session of 200 trials within 30 min, the other side port (initial port) was introduced. The rats were trained to insert their snouts into the initial port to start a trial, then to insert their snouts into the action port (Go Response) within a limit hold (LH) of 30 s. If the rats failed to insert their snouts into the action port at the end of the LH, they would receive a timeout punishment (5 s of darkness and no reward). The LH was progressively shortened. The time elapsed between leaving the initial port and nose-poking into the action port was defined as the go trial reaction time (Go RT). When the rats were able to perform two consecutive daily sessions of 300 trials in 30 min with an LH of 3 s, the stop signal was introduced. The stop signal was an auditory stimulus (4000 Hz, ~60-dB tone) that lasted 100 ms during the period of LH and was pseudo-randomly presented in approximately 20% of the total trials. The stop trial was initiated in the same fashion as the go trial, but the stop signal was presented after the rats left the initial port. If the rats refrained from inserting their snouts into the action port during the LH, the water reward was delivered. Otherwise, they experienced a timeout. During the training, the stop signal was presented immediately at the start of the LH (Zero Delay, ZD). When stable performance of the task was achieved (the performances of the go trial and stop trial were over 90% in a 320-trial session), behavioral testing was carried out.

Testing procedure
The testing session was composed of one adaptive block of 20 trials and three testing blocks of 100 trials each. During testing, the stop signal was delivered at variable delays (stop signal delay, SSD). We used a dynamic tracking procedure to achieve a 50% correction of the total stop trials. The initial SSD was set to be the median value of the Go RT in the adaptive block minus 200 ms. In the following testing blocks, 20 stop trials were randomly interleaved in each block, and the SSD was constantly adjusted after every stop trial depending on the outcome: when the stop trial was successful, the SSD was increased by 50 ms for the next stop trial; otherwise, the SSD was decreased by 50 ms. This tracking method resulted in approximately 50% accuracies for the stop trials.

SSRT estimation
The stop signal reaction time (SSRT) was estimated according to the independent-race model, whereby performance in the stop-signal task is modeled as a race between two independent internal processes[35]. The SSRT was calculated for each block separately and then averaged to yield a final estimate for each rat in one testing session. To ensure the accuracy of the SSRT estimation, we used QQ-plot to evaluate the normality of the Go RT (Figure 1C), excluding those with heavy tails.

Surgery
The rats were anesthetized with isoflurane and fixed in a stereotaxic apparatus (Stoelting, USA). Stainless guide cannulas (23-gauge) were implanted bilaterally into the location above the prelimbic (PL) area of the PFC (AP 3.3 mm, ML 0.7 mm, and DV 1.5 mm to the skull surface). Dummy cannulae were inserted into the guide cannula to prevent clotting and decrease the risk of infection. The rats were allowed a minimum recovery of 5 d before behavioral training.

Drug administration
Intra-PFC infusions were performed using 30-gauge infusion cannulas. The length of the infusion cannulas was 2 mm longer than the guide cannulas, thus yielding a total distance of
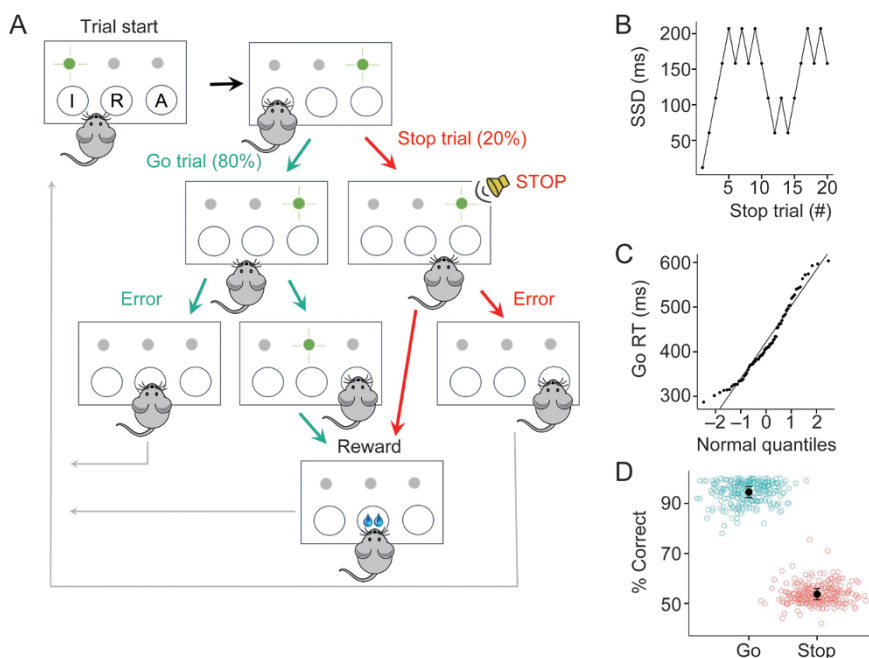
Figure 1. Stop-signal task setup and performance of rats in the study. (A) Schematic illustration of the testing procedure in the stop-signal task. In 80% of the trials (Go trials), rats nose-poked from port I to port A and received a water reward at port R. In a subset of 20% (Stop trials), a stop tone was presented at a variable delay after leaving port I, which indicated that the rats should suppress nose-poking into port A. (B) Change in stop signal delay (SSD) in one exemplary testing block. The SSD was changed dynamically according to the result of the previous stop trial and reached a plateau after several trials. (C) Go reaction time (Go RT) in the same exemplary testing block as shown in (B). The distribution of the Go RT was approximately normal. (D) Overall performance of go trials and stop trials for all the rats involved in the present study. Each point represents the performance of one rat in one session. The dots in the center are the means±SEMs.

3.5 mm from the skull surface. All infusions were performed using a Hamilton syringe at a rate of 0.2 µL/min. The total volume of drug delivered was 0.5 µL per side. The infusion cannulas were left in place for an additional 2 min for drug diffusion.

Histology

After the behavior testing, the rats received trans-cardial perfusion with 4% paraformaldehyde (PFA). The brains were then removed and placed into 30% sucrose for dehydration. Coronal sections (30 µm) were cut using a cryostat (Leica). The guide cannulas and infusion sites were examined using a fluorescence microscope (Olympus, Japan).

Data analysis

The data are expressed as the mean±SEM, with $P<0.05$ indicating significance. Statistical analysis of the drug-induced difference was tested by the paired Wilcoxon rank sum test. When the SSRTs were normalized to range [0, 1], the difference was statistically analyzed using the non-parametric permutation test.

Results

Effect of MPH on response inhibition in rats

We adopted a nose-poking version of the stop-signal task (SST) to evaluate the stop signal reaction time (SSRT) of the rats (Figure 1A). For 20% of the trials, a stop signal was deliv-

ered between the rat leaving the initial port (I) and arriving at an action port (A), thus indicating that the rat should withhold the current action and not insert its snout into port A. Figure 1B and C shows an example testing block from the same rat. The stop signal delays (SSDs) were changed dynamically and reached a plateau value after a few stop trials (Figure 1B), thereby achieving an overall 50% stop accuracy (Figure 1D). The distribution of go reaction time (Go RT) was approximately normal during one testing block (Figure 1C), thus indicating that the rat responded instantly after the trial began and did not change strategies during the task (Figure 1C). The behavior accuracies for all the rats enrolled in the present study were approximately 90% and 50% for the go trial and stop trial, respectively (Figure 1D).

To assess the effect of MPH on response inhibition in rats, we first measured rat SSRTs one day before drug testing to obtain the baseline SSRT for each rat. The following day, the SSRTs were measured 25 min after MPH (1.0 mg/kg) was administered subcutaneously (Figure 2A). To evaluate MPH-induced changes in SSRTs, we calculated the differences in the SSRTs before and after MPH treatment. We found that the MPH-induced change in the SSRTs was correlated with the baseline SSRTs (Figure 2B, $P<0.001$). As shown in Figure 2B, the rats with longer baseline SSRTs (*eg*, longer than the median value of all rat SSRTs) exhibited lower SSRTs after MPH infusion, whereas the rats with baselines shorter than the median had a tendency to exhibit increased SSRTs. Then, the rats were
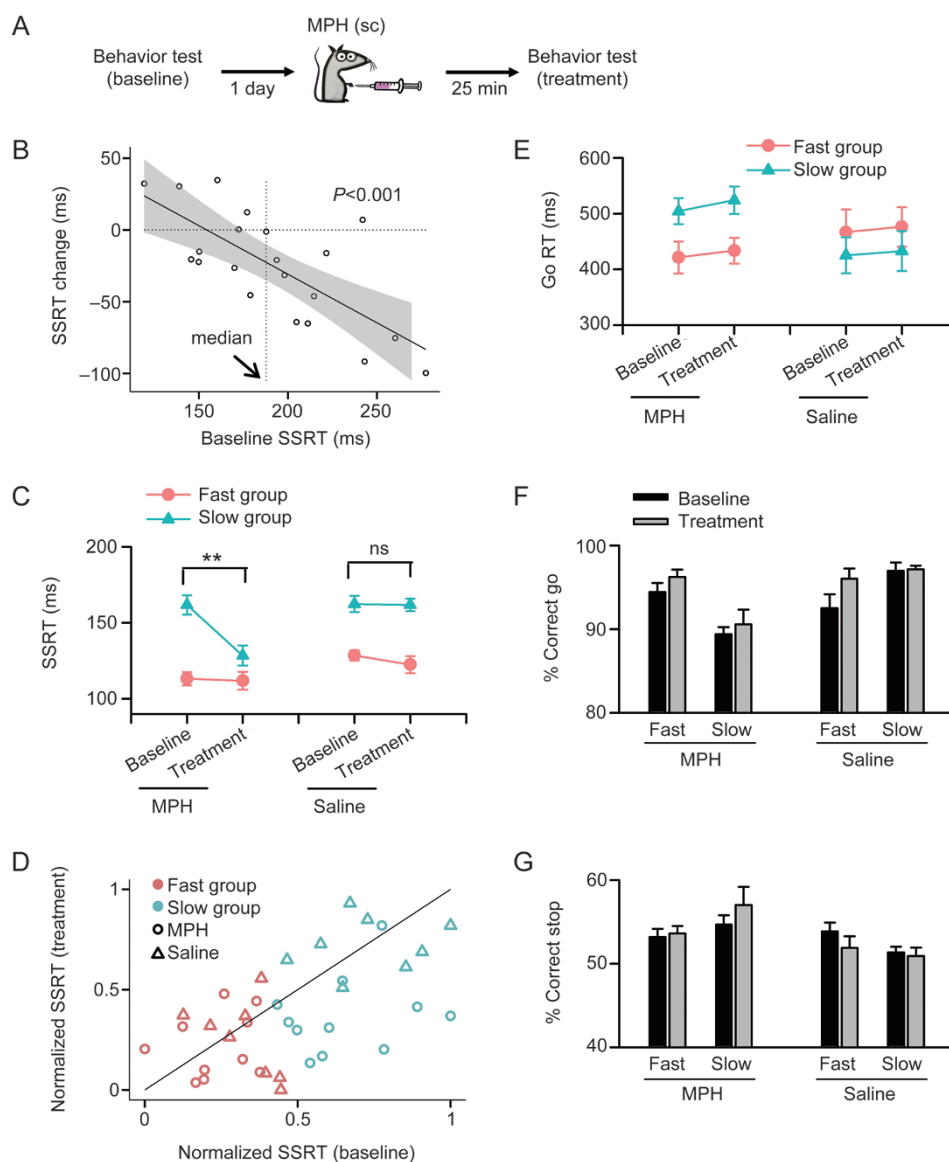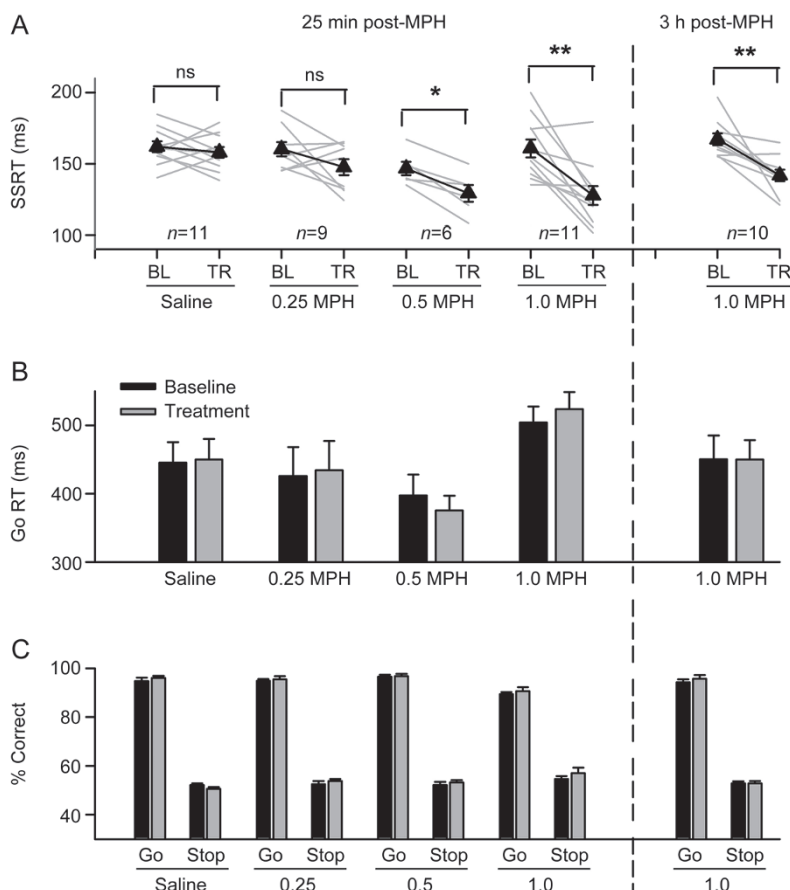
Figure 2. Effects of MPH on response inhibition in rats. (A) Scheme of the experimental procedure. (B) Linear regression of the stop signal reaction time (SSRT) before MPH infusion (baseline SSRT) with the SSRT change induced by MPH. The SSRT change was the difference in the SSRT before and after MPH infusion (1.0 mg/kg). The arrow indicates the median value of the baseline SSRTs. The shaded area represents the 95% CI. Each dot represents one rat (n=21). P<0.001, linear regression. (C) Effects of MPH on response inhibition in rats with different baseline SSRTs. The Fast group (baseline SSRT<median) and the Slow group (baseline SSRT>median) were grouped according to the median of the baseline SSRTs. The MPH dataset is the same as that in (A). n=10–11. **P<0.01, paired Wilcoxon test. (D) Plot of normalized SSRT before (baseline) versus after MPH or saline infusion (treatment) for each rat. P<0.01 for the Slow group with MPH treatment (green circles), permutation test. (E-G) Go reaction time (Go RT) (E), go accuracy (F), and stop accuracy (G) were kept intact in both the Fast group and the Slow group after MPH or saline infusion.

divided into two groups for subsequent analysis. We defined rats with longer baseline SSRTs (>median) as the Slow group and rats with shorter baseline SSRTs (<median) as the Fast group. Figure 2C shows that MPH significantly shortened the SSRTs of the Slow group (P<0.01, n=11) and did not affect the SSRTs of the Fast group (P=0.67, n=10). The SSRTs of both the Slow group (n=8) and the Fast group (n=8) were unchanged after saline infusion (Figure 2C). The MPH-induced changes in the SSRTs were also demonstrated using normalized SSRTs before versus after MPH treatment. As shown in Figure 3D,

the MPH-treated, Slow group was mainly distributed below the diagonal (P<0.01), whereas others were evenly distributed along the diagonal (P>0.05). No changes in the Go RT (Figure 2E), go accuracy (Figure 2F), or stop accuracy (Figure 2G) were observed after MPH versus saline administration in either group (P>0.05), thus indicating that MPH had no effect on the action response and behavior strategy of the rats during the task.

These results demonstrated that MPH exerted a baseline-dependent effect on response inhibition in rats and improved the response inhibition of only rats with greater SSRTs (Slow

Figure 3. Effects of different doses of MPH on response inhibition. Effects of MPH at 0.25, 0.5, and 1.0 mg/kg on the SSRTs of rats with longer SSRTs (Slow group) at 25 min or 3 h after MPH infusion. The data for 25 min after infusion with 1 mg/kg MPH are presented here. Each gray line represents one rat. *$P<0.05$, **$P<0.01$, paired Wilcoxon test. BL, baseline; TR, treatment. (B and C) Go reaction time (Go RT) (B) and trial accuracies (C) were not altered after MPH infusion.

group), in agreement with findings from a previous report[13]. Thus, we focused on the Slow SSRT group in the subsequent analyses.

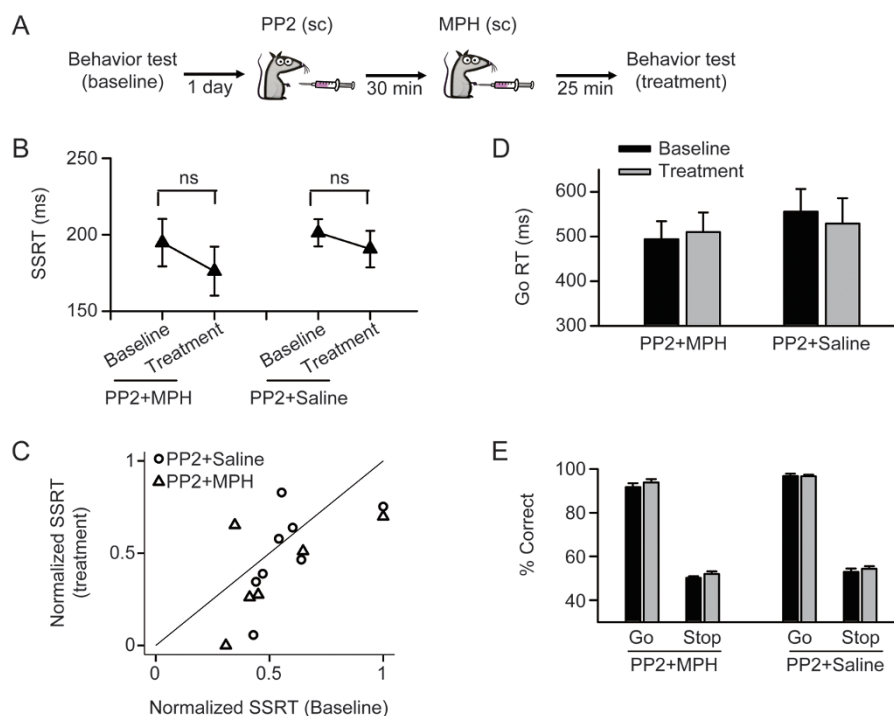### Dose-effects of MPH on response inhibition

To test the effects of different doses of MPH on response inhibition, we assessed the SSRTs of rats with longer SSRTs (Slow group) at 25 min after MPH (0.25, 0.5, or 1.0 mg/kg) infusion. As shown on the left of Figure 3, the SSRTs of the Slow group were significantly decreased by 0.5 mg/kg ($P<0.05$, $n=6$) and 1.0 mg/kg MPH ($P<0.01$, $n=11$) but not 0.25 mg/kg MPH ($P>0.05$, $n=9$). When behavioral testing was extended to 3 h after MPH infusion (1.0 mg/kg), the SSRTs of the Slow group were still dramatically decreased ($P<0.01$, $n=10$; Figure 3A, right), thus suggesting that the effect of MPH lasted more than 3 h. Similarly, the Go RT (Figure 3B) and behavior accuracy (Figure 3C) of the Slow group were unaffected by these conditions ($P>0.05$).

PP2 abolishes the MPH-induced improvement in response inhibition

MPH has been proposed to potentiate glutamate receptor expression and function, thereby enhancing PFC-mediated cognition functions[29]. To determine whether the effect of MPH on response inhibition depends on this mechanism, we used PP2 to block the MPH-induced potentiation of glutamate receptors and then examined the effect of MPH on the SSRTs of rats with longer SSRTs (Slow group) (Figure 4A). PP2 is a Src-protein tyrosine kinase (Src-PTKs) inhibitor that can occlude glutamate receptor transport from the cytoplasm to the cell surface or accelerate glutamate receptor endocytosis by inhibiting tyrosine residue phosphorylation[36, 37]. As shown in Figure 4, PP2 (1.0 mg/kg) alone had no effect on the SSRTs of the Slow group ($P>0.05$, $n=8$; Figure 4B); however, when MPH (1.0 mg/kg) was co-infused with PP2 (1.0 mg/kg), the effect of MPH on the SSRTs of the Slow group was abolished ($P>0.05$, $n=6$; Figure 4B). Normalized SSRTs measured before MPH infusion compared with those measured after MPH infusion in rats pre-treated with PP2 showed no significant change ($P>0.05$; Figure 4C). Similarly, the Go RT (Figure 4D) and behavior accuracy (Figure 4E) of the Slow group were not changed by these treatments ($P>0.05$).

These results suggested that the effect of MPH on response inhibition may also involve the potentiation of glutamate

Figure 4. PP2 abolished the effect of MPH on response inhibition. (A) Scheme of the experimental procedure. (B)Effects of MPH (1.0 mg/kg) and saline on the SSRTs of the longer-SSRT rats (Slow group) pretreated with PP2, a Src-protein tyrosine kinase (Src-PTKs) inhibitor (n=6–8). (C) Plot of the normalized SSRT before versus after MPH or saline treatment for each rat pretreated with PP2. ^{ns}P>0.05 for PP2+MPH and PP2+saline, permutation test. (D) and (E) Go reaction time (D) and trial accuracies (E) were not significantly changed after the treatment.

receptor function in the PFC.

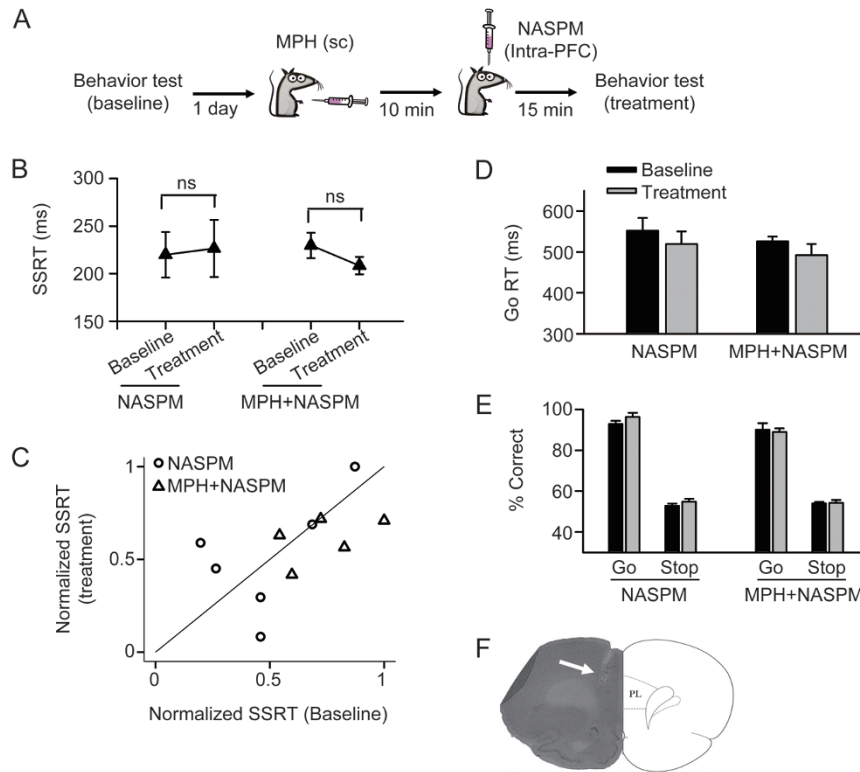### Intra-PFC inhibition of AMPAR abolishes the effect of MPH on response inhibition

Next, we aimed to determine the contribution of glutamate receptors to the effect of MPH on response inhibition. Synaptic transmissions mediated by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and *N*-methyl-*D*-aspartic acid receptor (NMDAR) are key to the output of cortical neurons. Considering that the effect of MPH on response inhibition remained after 3 h when the enhancement of NMDAR-mediated transmission by MPH did not exist, we speculated that AMPARs within the PFC are implicated in the effect of MPH on response inhibition. As shown in Figure 5, the intra-PFC infusion of NASPM (0.3 mmol/L, 0.5 µL per side), a selective Ca^{2+}-permeable AMPAR antagonist, had no effect on the SSRTs of the Slow group (P>0.05, n=6); however, when NASPM was administered after the *in vivo* infusion of MPH (1.0 mg/kg), the suppression effect of MPH on the SSRTs disappeared (P>0.05, n=5) (Figure 5B). Normalized SSRTs with or without intra-PFC infusion of NASPM after *in vivo* MPH infusion showed an even distribution along the diagonal (P>0.05; Figure 5C). Similarly, the Go RT (Figure 5D) and behavior accuracy (Figure 5E) of the Slow group were not changed by these treatments (P>0.05). NASPM was infused into the prelimbic area of the PFC, as shown in Figure 5F.

These results suggested that the prefrontal AMPARs were involved in the effect of MPH on response inhibition in rats.

Discussion

Although imaging studies have revealed that MPH enhances the neural activities of the cortex (including the PFC) during response inhibition tasks, the mechanism underlying its actions is unknown. In the present study, we used a rodent nose-poking stop-signal task (SST) to examine the effect of MPH on response inhibition. The stop signal reaction time (SSRT), which reflects the capacity of response inhibition control, is the covert latency to stop a pre-potent action. We determined that MPH (0.5–1.0 mg/kg) specifically improved response inhibition in rats with longer SSRTs (Slow group) but not with shorter SSRTs (Fast group). We also determined that the effects of MPH on the response inhibition of the Slow group were abolished by the pre-inhibition of glutamate receptor trafficking or intra-PFC inhibition of AMPA receptors. These results suggested that prefrontal AMPARs are involved in the effect of MPH on response inhibition in rats.

Our data showed a baseline-dependent effect of MPH on response inhibition by which the MPH-induced improvement in response inhibition was observed only in rats with longer SSRTs (Slow group). This result was consistent with findings from a previous report[13]; however, we did not find a MPH-induced deficit in rats with shorter SSRTs (Fast group). This discrepancy may have been due to the different strains of rats and the different behavior setups used in these two studies. Different strains of rats may have different sensitivities to the changes in dopamine and norepinephrine levels in response to MPH in the brain[38]. In addition, the nose-poking action can

Figure 5. NASPM abolished the effect of MPH on response inhibition. (A) Scheme of the experimental procedure. (B) Intra-PFC infusion of NASPM, a selective Ca^{2+}-permeable AMPAR antagonist, abolished the effect of MPH on the SSRTs of rats with longer SSRTs (Slow group). ($n=5-6$). (C) Normalized SSRTs in both groups were evenly distributed along the diagonal. $^{ns}P>0.05$ for MPH+NASPM, permutation test. (D, E) Go reaction time (Go RT) (D) and trial accuracies (E) were not significantly changed after the treatments. (F) An example section shows the infusion site of NASPM in the PFC, as indicated by the arrow. PL, prelimbic area.

be performed much faster than lever pressing, thus decreasing the action delay of rats and potentially leading to a more accurate SSRT estimation.

Despite the widespread use of MPH in the treatment of ADHD, approximately 30% of individuals with ADHD are not responsive to MPH[39, 40]. The Fast group, which had shorter SSRTs in our study, may resemble those patients. Several studies suggested that fewer dopamine transporters are expressed in non-responsive patients[41], and individual differences, especially genetic factors, may also partially explain this unexpected outcome[42, 43]. More work is necessary to identify the different features of these two populations, *eg*, the amount or function of AMPA receptors in the PFC.

The dose effects of MPH on cognitive function have been well characterized in rats. At the dose of 0.25 mg/kg, MPH has been proposed to improve working memory[16]; however, our results showed that 0.25 mg/kg MPH had no effect on response inhibition in rats. Moreover, the MPH-induced improvement in response inhibition still persisted at 3 h after treatment, whereas the improvement of working memory by 1.0 mg/kg MPH disappeared (unpublished data). These discrepancies suggested that distinct mechanisms underlie the MPH-induced improvements in working memory and response inhibition.

The behavioral effects of the therapeutic dose of MPH have been linked to MPH-potentiated glutamate receptor expression and function in PFC neurons[29]. A previous report has shown that response inhibition training increases the contribution of AMPAR at excitatory synapses in the prefrontal cortex[44]. In the present study, we used PP2 to prevent the MPH-induced upregulation of glutamate receptor expression. PP2 is a Src-family tyrosine kinase inhibitor used to block glutamate receptor trafficking[36, 37, 45]. Co-infusion of MPH with PP2 diminished the increase in the expression and function of glutamate receptors in PFC neurons (data not shown), and the effect of MPH on response inhibition disappeared in rats that were pre-treated with PP2. AMPARs and NMDARs are major glutamate receptors in the cortex. The present study provides evidence that AMPARs within the PFC mediate the effect of MPH on response inhibition. We locally administered a sub-effective dose of a selective AMPAR antagonist, NASPM, into the PFC of saline-treated rats, and this treatment did not affect response inhibition; however, when NASPM was administered to the MPH-treated rats, the improvement effect of MPH was abolished. These results indicated an important role of AMPA receptors in response inhibition. Consistent with this finding, a recent study has also reported a decrease in the expression and function of AMPAR in the PFC in an ADHD rat model[46]. We speculated that the therapeutic effect of MPH on response inhibition enhances the expression of AMPAR

on the cell surface in the PFC. However, further studies are needed to confirm the underlying mechanism of enhanced AMPAR expression by MPH.

The PFC has extensive interconnections with subcortical regions, especially the basal ganglia structures such as the striatum, global pallidus, and subthalamic nucleus[1, 47-49]. It is well known that the basal ganglia, as a behavior switch, is indispensable in response inhibition[30, 50-52]. The potentiation of AMPAR function in PFC neurons by MPH may enhance the top-down control of the PFC over the basal ganglia, thereby promoting response inhibition[53, 54].

No significant effects of MPH on the Go RT or behavior accuracies were observed, thus suggesting that the doses of MPH used in the present study did not interfere with the correct execution of the stop-signal task. The Go RT represents the speed of response and requires the integrity of movement control. Our data suggested that MPH did not affect head movements, and the motivations of the rats performing the task were intact. Behavior accuracies remained unaffected, thus indicating that the task rules were also actively maintained.

In summary, this study demonstrated that AMPARs in the PFC are involved in the effect of MPH on response inhibition. This advancement in understanding of the complex actions of MPH may aid in the development of potential treatments for impulsivity-related diseases.

Acknowledgements

Author contribution

Xue-han ZHANG and Yu-qiu ZHANG designed research; Dong-dong ZHANG performed research and analyzed data; Dong-dong ZHANG and Xue-han ZHANG wrote the paper.

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