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# Autistic-like social deficits in hippocampal MeCP2 knockdown rat models are rescued by ketamine

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**Autism or autism spectrum disorder (ASD) is a behavioral syndrome characterized by persistent deficits in social interaction, and repetitive patterns of behavior, interests, or activities. The gene encoding Methyl-CpG binding protein 2 (*MeCP2*) is one of a few exceptional genes of established causal effect in ASD. Although genetically engineered mice studies may shed light on how *MeCP2* loss affects synaptic activity patterns across the whole brain, such studies are not considered practical in ASD patients due to the overall level of impairment, and are technically challenging in mice. For the first time, we show that hippocampal *MeCP2* knockdown produces behavioral abnormalities associated with autism-like traits in rats, providing a new strategy to investigate the efficacy of therapeutics in ASD. Ketamine, an N-Methyl-D-aspartate (NMDA) blocker, has been proposed as a possible treatment for autism. Using the *MeCP2* knockdown rats in conjunction with a rat model of valproic acid (VPA)-induced ASD, we examined gene expression and ASD behaviors upon ketamine treatment. We report that the core symptoms of autism in *MeCP2* knockdown rats with social impairment recovered dramatically following a single treatment with ketamine. [BMB Reports 2022; 55(5): 238-243]**

## INTRODUCTION

Autism spectrum disorder (ASD) is a highly prevalent neurodevelopmental disorder that is characterized by impaired social interaction and communication, repetitive behaviors, and restricted interests (1, 2). Early behavioral intervention is recommended for children diagnosed with ASD. Currently, its core symptoms cannot be cured and there is a need to develop pharmacological treatments. In order to develop effective pharmacological treatments that can be started during the early developmental stage, the pathogenesis of ASD needs to be understood. As extensively demonstrated in both humans (3) and rodent models (4), *MeCP2* is one of the few genes known to play a causal role in ASD (5). Using genetically manipulated rodent models, researchers have demonstrated that both loss and gain of *MeCP2* function can alter synaptic transmission and disrupt the overall excitation/inhibition balance in neural circuits (6). Consistent with this, dendritic spines in cortical neurons, which are postsynaptic to excitatory synapses and a proxy for synaptic densities, are affected in people with ASD (7). In fact, multiple ASD-related genes are involved in synaptic function (8).

Evidence for the possibility that loss of *MeCP2* function results in developmental dysregulation of *N*-methyl-D-aspartate receptor (NMDAR) expression has attracted interest to NMDAR as a therapeutic target for rett syndrome (RTT), a neurodevelopmental disease caused by disruption of the *MeCP2* gene (9, 10). One class of molecules that have shown promise in preclinical models of RTT are channel-blocking NMDAR antagonists (10). Kron *et al*. (11) demonstrated that treatment of heterozygous female *MeCP2* mutant mice with a subanesthetic dose of ketamine (8 mg/kg) is highly effective in acutely reversing disease phenotypes, including abnormal patterns of neuronal activation in cortical and subcortical structures as well as sensorimotor dysfunction. Although *MeCP2* gain-of-function and loss-of-function in genetically engineered rodents recapitulates typical phenotypes of patients with autism, it is still not known where ketamine affects the rodent brain, and whether/how it relates to autism pathology due to *MeCP2* mutation. Therefore, the present study investigated the induction of ASD behaviors by knocking down *MeCP2* in the hippocampus, and the effects of ketamine on the behaviors and synaptic molecules in the hippocampus of rats infused with lenti-shMeCP2.

## RESULTS

### Behavioral validation of the neonatal VPA-induced animal models of autistic-like behaviors

VPA rats were generated by intraperitoneally injecting pregnant SD rats on embryonic day 12.5 (E12.5) with a single dose of

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VPA (500 mg/kg) (Fig. 1A). Behavioral assays showed that the VPA rats did not display any difference in locomotor activity compared to saline rats (Fig. 1B: $t_{54}$ = 1.27, P = 0.2095). However, the VPA rats spent less time in the middle zone in the OFT (Fig. 1B: $t_{54}$ = 2.139, P < 0.05), indicating that they had anxiety-like behaviors. Autistic-like behavior is characterized by repetitive behaviors (12). To test if VPA rats displayed this type of behavior, we performed the self-grooming test. The VPA rats spent significantly longer self-grooming than the saline rats (Fig. 1C: $t_{54}$ = 2.247, P < 0.05). Aberrant reciprocal social interaction is a core symptom of autistic-like behaviors (13, 14). We evaluated social interaction with the social approach. In this assay, the VPA rats spent less time sniffing at the social stimulus than the saline rats (Fig. 1D: $t_{18}$ = 3.59, P < 0.01), indicating that they displayed impaired social interaction.

## Ketamine ameliorates autistic-like social deficit features in VPA rats

Next, we used a three-chamber apparatus to assess sociability and social novelty preference for social interaction, which may be relevant to autistic-like behaviors (15, 16). In the three-chamber sociability test, if the test animal spends more time with the empty wire cage (E) than with the wire cage containing the stranger (S), this points to a deficit of sociability (Fig. 1E). In the first session, we assessed sociability by measuring staying time in the compartment with a stranger rat in the wire cage *versus* in the one with the empty wire cage. We found that VPA rats treated with saline demonstrated significantly reduced social interaction compared with saline rats, as indicated by the relative amount of time spent investigating the stranger cage compared with the empty cage (Fig. 1F). This measure-

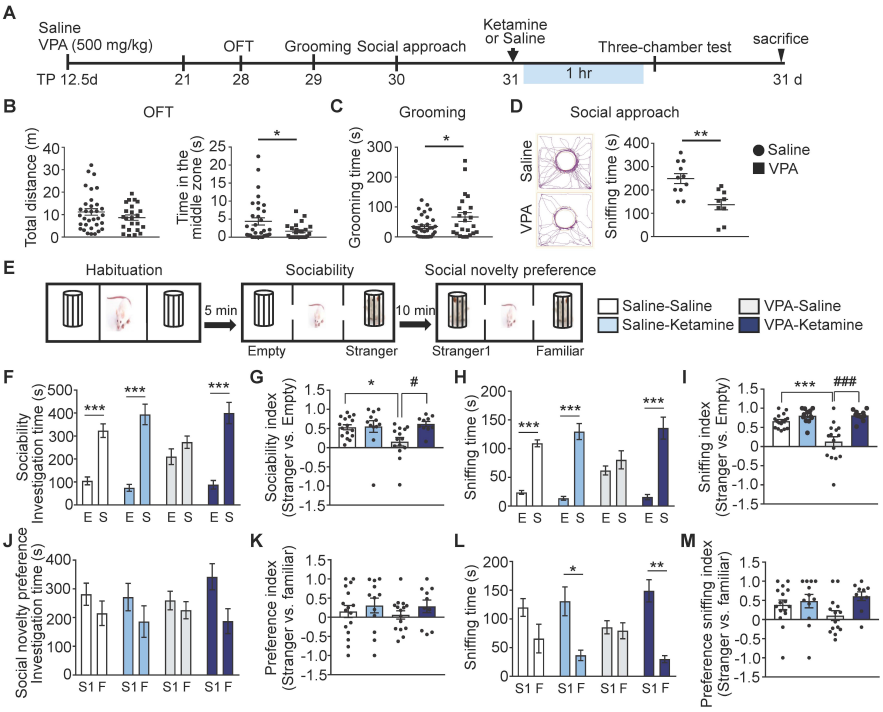


**Fig. 1.** Ketamine recovers autistic-like social deficits in VPA rats. (A) Schematic diagram of drug administration and behaviors. (B) (Left) Plot of total distance moved in the locomotion test. (Right) Plot of time in middle zone in the open field test (OFT). (C) Plot of the time spent on repetitive behaviors in the grooming test (A-C, n = 23-33 per group). (D) (Left) Representative paths illustrating the time spent in different locations of the equipment in the social approach. Locations of social stimuli are labeled with the wire cage. (Right) Plot of sniffing time in social approach (n = 9-11 per group). (E) Schematic diagram of the three-chamber test. (F, G) Plots showing the time spent investigating either the S or E stimulus (F), and the sociability index (G) during sociability testing of saline or VPA rats treated with saline or ketamine (20 mg/kg). (H, I) Plots showing sniffing time in response to either the S or E stimulus (H), and the sniffing index (I) during sociability testing of saline and VPA rats treated with saline or ketamine (20 mg/kg) (F-I, n = 10-16 per group, F: $F_{3,96(interaction)}$ = 7.665, P = 0.0001; G: $F_{1,48(interaction)}$ = 4.324, P = 0.0429; H: $F_{3,96(interaction)}$ = 10.51, P < 0.0001; I: $F_{1,48(interaction)}$ = 15.2, P = 0.0003; *P < 0.05, ***P < 0.001, $^{\#}$P < 0.05, $^{\#\#\#}$P < 0.001, S vs. E, two-way ANOVA). (J, K) Plots showing the time spent investigating either the S1 or F stimulus (J), and the preference index (K) during social novelty preference testing of saline or VPA rats treated with saline or ketamine (20 mg/kg) (n = 10-16 per group, S1 vs. F, two-way ANOVA) (L, M) Plots showing the sniffing time in response to either the S1 or F stimulus (L), and the sniffing index (M) during social novelty preference testing of saline or VPA rats treated with saline or ketamine (20 mg/kg) (J-M, n = 10-16 per group, J: $F_{3,96(interaction)}$ = 0.6436, P = 0.5889; K: $F_{1,48(interaction)}$ = 0.04305, P = 0.8365; L: $F_{3,96(interaction)}$ = 3.613, P = 0.0160; M: $F_{1,48(interaction)}$ = 2.077, P = 0.1560, *P < 0.05, **P < 0.01, S1 vs. F, two-way ANOVA). (B-D) Unpaired two-tailed *t*-test, *P < 0.05, **P < 0.01 compared with saline rats.

ment yields the sociability index (Fig. 1G). To determine whether ketamine ameliorates autistic-like social deficits in the VPA rats, we tested the effect of ketamine treatment on social interaction in the three-chamber test. Administration of ketamine (20 mg/kg) to VPA rats 1 h before the three-chamber test significantly attenuated the reduction in social interaction, restoring this behavior to levels comparable to those in saline rats. In contrast, ketamine treatment of saline rats had no effect on investigation time (Fig. 1F) and sociability index (Fig. 1G). In addition, VPA rats spent significantly less time sniffing around a caged stranger rat when analyzed by sniffing time (Fig. 1H) and sniffing index (Fig. 1I), and both of these measures were recovered by ketamine treatment.

In the second session of the three-chamber test we assessed social interaction by measuring the preference for the stranger1 cage (S1) *versus* the familiar cage (F) (Fig. 1E). A new rat was added to the previously empty compartment and social preference between the familiar rat and novel rat was assessed by measuring the time spent close to the cage with the familiar versus the stranger rat. VPA rats treated with saline displayed a similar social novelty preference to that of saline rats treated with (Fig. 1J, K). Ketamine (20 mg/kg) did not significantly alter the investigation time (Fig. 1J) and preference index (Fig. 1K) both in saline and VPA rats. Similar results were obtained using preference sniffing time as measured by sniffing time (Fig. 1L) and preference sniffing time index (Fig. 1M). Together, these results indicate that prenatal VPA induces autism-like social deficits in social interaction, similar to previous findings (17) and ketamine alleviates the observed social deficits (Fig. 1J-M).

## Ketamine recovers PTEN expression in VPA rats

We first examined whether endogenous MeCP2 levels were decreased in VPA rats and found that *MeCP2* mRNA (Supplementary Fig. 1A: $t_{12} = 3.386$, $P < 0.01$) and protein (Supplementary Fig. 1B: $t_6 = 2.528$, $P < 0.05$) levels were indeed significantly lower in the VPA rats on postnatal day 28 (P28). Given this result, we next examined the effect of ketamine on MeCP2 expression by investigating the changes in expression of various regulators related to synaptic function and MeCP2 target genes. Quantitative real-time PCR analyses indicated that the level of *Pten* mRNA was significantly lower in hippocampal lysates from the VPA rats, while the levels of *Psd95*, *Glur1*, *Synapsin1*, *Rab3d* and *Vamp3* mRNAs were largely unchanged (Supplementary Fig. 1C, D). There are reports that abnormalities in PTEN lead to neurological disorders such as autism, seizures and schizophrenia (18-21). Ketamine treatment significantly increased *Pten* mRNA, while the *Psd95*, *Glur1*, *Synapsin1*, *Rab3d* and *Vamp3* mRNAs were not altered (Supplementary Fig. 1C, D).

## Hippocampal MeCP2 knockdown produces autistic-like behaviors in rats

To test whether hippocampal MeCP2 knockdown generates autistic-like behaviors, we infused lentivirus expressing shRNA targeted against rat MeCP2 (lenti-shMeCP2) into the dentate gyrus (DG), 4 weeks before ketamine injection (Fig. 2A). A recovery period of 4 weeks was chosen because effective knockdown was achieved by infusion of lentivirus-mediated shMeCP2 into rats after 21 days (22). Lenti-shMeCP2 infusions lowered MeCP2 mRNA (Fig. 2B: $t_{14} = 6.169$, $P < 0.001$) and protein (Fig. 2C: $t_8 = 3.072$, $P < 0.05$) levels in the hippocampal DG of rats compared to control lenti-shNC rats. We investigated whether the deficiency in MeCP2 led to autistic-like behaviors, including anxiety and repetitive behaviors. The locomotor activity of the MeCP2 knockdown rats was unchanged (Fig. 2D: $t_{51} = 0.6303$, $P = 0.5313$), but they spent less time in the middle zone than the lenti-shNC rats, indicating that they experienced increased anxiety (Fig. 2D: $t_{51} = 2.129$, $P < 0.05$). They also spent significantly more time self-grooming than the lenti-shNC rats (Fig. 2E: $t_{51} = 2.431$, $P < 0.05$), and less time sniffing in the direct social approach (Fig. 2F: $t_{41} = 4.675$, $P < 0.001$). Taken together, these results indicate that reducing hippocampal MeCP2 levels leads to pronounced autistic-like behaviors such as anxiety, repetitive behavior, and social deficit.

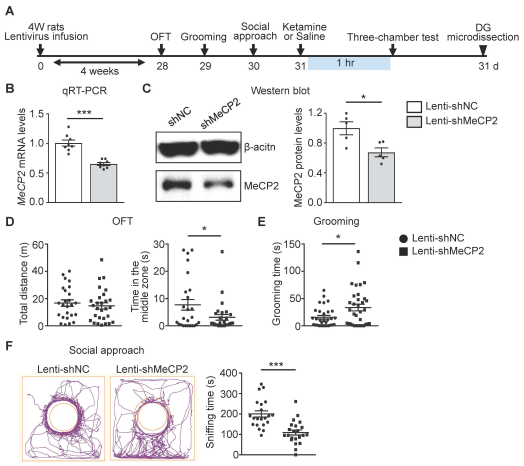


**Fig. 2.** Hippocampal DG-specific *MeCP2* deficiency leads to repetitive and social deficit behaviors. (A) Schematic diagram of drug administration and behaviors. (B) Lentiviral-mediated knockdown of MeCP2 mRNA levels in the DG (n = 8 per group). (C) Representative immunoblots (Left) and quantitative data (Right) for MeCP2 protein levels normalized to the level of β-actin (n = 5 per group). (D) (Left) Plot of total distance moved in the locomotion test of lenti-shNC and lenti-shMeCP2 rats. (Right) Plot of times in middle zone in OFT of lenti-shNC and lenti-shMeCP2 rats (n = 25-28 per group). (E) Plot of times spent on repetitive behaviors in the grooming test by lenti-shNC and lenti-shMeCP2 rats (n = 25-28 per group). (F) (Left) Representative data illustrating the times spent in different locations of the equipment in the social approach of lenti-shNC and lenti-shMeCP2 rats. Locations of social stimuli are labeled with the wire cage. (Right) Plot of sniffing times of lenti-shNC and lenti-shMeCP2 rats (n = 21-22 per group) in the social approach. Unpaired two-tailed t-test, *P < 0.05, ***P < 0.001 compared with lenti-shNC rats.

### Ketamine ameliorates autistic-like social deficits features in the hippocampal MeCP2 knockdown model

We examined the impact of hippocampal MeCP2 knockdown on social deficits in young (4 weeks) male rats in the three-chamber test. Lenti-shMeCP2 rats displayed significantly reduced social interaction compared with lenti-shNC rats, as indicated by the relative amount of investigation time in a stranger cage compared with an empty cage (Fig. 3A), and the sociability index (Fig. 3B). When a single injection of ketamine at a dose of 20 mg/kg was applied 1 h prior to behavioral tests it significantly elevated the sociability index of the lenti-shMeCP2 rats, suggesting that ketamine alleviates the observed social deficits in the lenti-shMeCP2 rats (Fig. 3B). Similar results were obtained for sociability sniffing time and sniffing index (Fig. 3C, D) as well as social novelty preference, investigation time and sniffing time (Fig. 3E-H). Taken together, these results indicate that MeCP2 knockdown rats display pronounced deficits in social interaction, and ketamine administration can rescue the autistic-like social deficits of these rats.

### Ketamine ameliorates the levels of synaptic molecules in MeCP2 knockdown rats

We then sought to determine the molecular mechanisms that may underlie the amelioration of social deficits by ketamine.

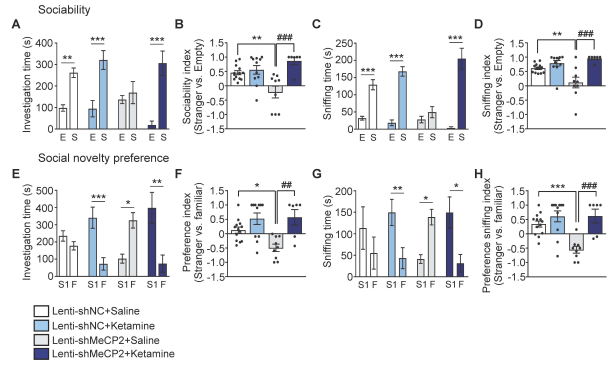


**Fig. 3.** Ketamine rescues autistic-like social deficits in lenti-shMeCP2 rats. (A, B) Plots showing the times spent investigating either the S or E stimulus (A), and the sociability indexes (B) of lenti-shNC and lenti-shMeCP2 rats treated with saline or ketamine. (C, D) Plots showing sniffing times in response to the S and E stimuli (C) and sniffing time indexes (D) of lenti-shNC or lenti-shMeCP2 rats treated with saline or ketamine (A-D, n = 6-13 per group, A: $F_{3,70(interaction)} = 4.1184$, $P = 0.0088$; B: $F_{1,35(interaction)} = 11.11$, $P = 0.002$; C: $F_{3,70(interaction)} = 13.48$, $P < 0.0001$; D: $F_{1,35(interaction)} = 8.908$, $P = 0.0052$; $^{**}P < 0.01$, $^{***}P < 0.001$, $^{\#\#\#}P < 0.001$, S vs. E, two-way ANOVA). (E, F) Plots showing times spent investigating the S1 or F stimulus (E), and preference indexes (F) of lenti-shNC or lenti-shMeCP2 rats treated with saline or ketamine. (G, H) Plots showing sniffing times to either the S1 or F stimulus (G), and sniffing time indexes (H) of lenti-shNC and lenti-shMeCP2 rats treated with saline or ketamine (E-H, n = 6-13 per group, E: $F_{3,70(interaction)} = 14.02$, $P < 0.0001$; F: $F_{1,35(interaction)} = 3.659$, $P = 0.064$; G: $F_{3,70(interaction)} = 10.15$, $P < 0.0001$; H: $F_{1,35(interaction)} = 7.691$, $P = 0.0088$; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$, S1 vs. F, two-way ANOVA).

Glutamate receptors are a potential key target of ketamine since diminished synaptic signals at glutamatergic synapses are strongly linked to autistic-like phenotypes, including social deficits and repetitive behaviors (23, 24). We examined synaptic plasticity-related gene expression in rats infused with lenti-shMeCP2 into the hippocampal DG. Quantitative real-time PCR analyses indicated that the level of *Glur1* mRNA was significantly lower in hippocampal DG lysates from lenti-shMeCP2 rats, while the levels of *Psd95*, *Synapsin1*, *Pten*, *Rab3d* and *Vamp3* mRNAs were largely unchanged (Fig. 4). Although the level of *Psd95* mRNA was unaffected in lenti-shMeCP2 rats, its level, together with that of *Glur1* was significantly elevated upon ketamine treatment, while *Synapsin1*, *Pten*, *Rab3d* and *Vamp3* mRNAs were unchanged (Fig. 4). Consistently, ketamine administration increased levels of the postsynaptic proteins GluR1 in lenti-shMeCP2 rats but not in lenti-shNC rats (Supplementary Fig. 2A). However, ketamine only induced a tendency to increase the expression of PSD95 in lenti-shMeCP2 rats (Supplementary Fig. 2B).

## DISCUSSION

*MeCP2* loss-of-function in genetically-engineered animals including rodents produces typical features of autism, yet where MeCP2 loss affects the rodent brain and whether/how this relates to autism pathology remain unknown. Here we report marked and reproducible effects of knockdown of hippocampal MeCP2 on repetitive and social behaviors. These behavioral abnormalities can be reversed by treatment with a sub-psychotomimetic dose of ketamine, which also rescues synaptic molecules.

Studies of signaling and metabolisms have revealed the complexity of ASD and its characteristics (25, 26). Simple yet reproducible animal models of human ASD are needed for the

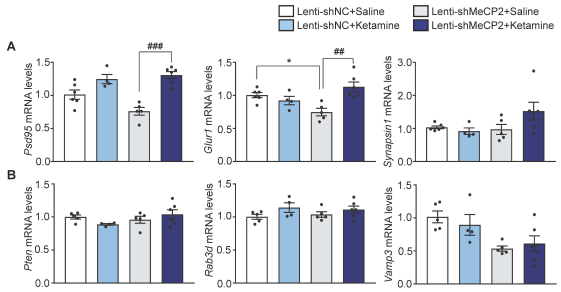


**Fig. 4.** Synaptic plasticity genes mediate the rescuing effects of ketamine in lenti-shMeCP2 rats. (A) *Psd95*, *Glur1*, *Synapsin1* mRNA levels (B) *Pten*, *Rab3d*, *Vamp3* mRNA levels were measured by real-time PCR in the hippocampal DG of lenti-shNC and lenti-shMeCP2 rats treated with saline or ketamine (20 mg/kg). Expression levels were normalized to the *Gapdh* and are expressed relative to lenti-shNC treated with saline (A: $F_{1,17(interaction)} = 5.992$, $P = 0.0255$ (*Psd95*); $F_{1,17(interaction)} = 14.65$, $P = 0.0013$ (*Glur1*), $^{*}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$, two-way ANOVA).

understanding of therapeutic mechanisms and development of novel treatments. Differences in the molecular networks between humans and rodents may limit the utility of rodent models for human diseases. However, the rat model is well suited for studies on neurodevelopmental diseases, and previous studies have described similarities in neuronal structure and synaptic development to humans (27, 28). Further advantages are that rats are easy to handle, mature rapidly, and are reproductively efficient. The present study revealed simultaneous changes in synaptic and behavioral phenotypes in VPA and MeCP2 knockdown models, although the synaptic molecules that underwent changes were slightly different. While the VPA-induced model has time to adapt to chemical damage at the developmental periods, the MeCP2 rats infused with lenti-shMeCP2 are presumed to display autistic behavioral patterns clearly as synaptic function is compromised by the strong gene suppression. This may lead to subtle difference in the expression of synaptic molecules between the two models, which may in turn produce slightly different behavioral responses.

The autistic-like behaviors induced by neonatal VPA exposure and hippocampal inhibition of MeCP2 were both rescued by treatment with ketamine. This is in line with previous results showing that autistic-like phenotypes are induced by functional deficits in NMDA receptor function (29). It will be interesting to examine whether ketamine works in other ASD models such as those induced by local inhibition of MeCP2 or TSC1 in the dorsal striatum (30).

For the first time, we have demonstrated that hippocampal MeCP2 knockdown leads to behavioral abnormalities linked to autism-like traits in rats, and that ketamine prevents these effects. These findings provide a novel strategy for testing the effects of ASD treatments. Although the animal model injected with lenti-shMeCP2 does not mimic all the changes that occur at the system level in human autism, it would be useful as a quick and simple experimental model for testing the effects of potential therapeutic agents.

## MATERIALS AND METHODS

The detailed methods are described in the "Supplementary Materials and Methods".

### Intraperitoneal (i.p.) injection of VPA to pregnant rats

Pregnant SD female rats were administered a single i.p. injection of sodium valproate (Sigma, ST. Louis, MO) in 0.9% saline (500 mg/kg), or 0.9% saline alone (VPA-untreated controls), at embryonic day 12.5 (E12.5). All behavioral tests were performed on SD rats 4 weeks of age. Only male rats were used for behavioral experiments.

### Three-chamber test

The tests for sociability and social preference were performed in a three-chamber apparatus as previously described (31). The animals used here were all age- and sex-matched littermates; SD rats were used as the stranger rats. The three-chamber apparatus was a 120 cm × 40 cm × 58 cm black plastic box. The first session was a 5 min habituation period. The test animal was introduced and allowed to stay in the central area. After habituation, a stranger animal was introduced into the wire cage of the right compartment (stranger zone) for the sociability test. The test animal in the central area was allowed to explore the three-chamber apparatus after removal of the gate blocking the central area. Time spent in the stranger zone and around the cage was measured for 10 min. The social preference test was conducted for 10 min directly after termination of the sociability test. While the subject animal was confined in the central area, a novel animal (stranger 1; S1) was introduced into the wire cage of the left compartment (new stranger zone) followed by measurement of the time spent in each compartment as in the previous session. The preference index was calculated as (S − E) / (S + E) for sociability, and (S1 − F) / (S1 + F) for social novelty preference.

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## CONFLICTS OF INTEREST

The authors have no conflicting interests.

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