Appendix Sl. *Chronic unpredictable mild stress (CUMS) protocol.* The animal tests were performed as previously described (1). All rats were housed individually and kept at a laboratory animal barrier system with required environment (24±1°C, relative humidity of 45±15% and a 12 h light/dark cycle). Rats were acclimatized to the environment for 2 weeks and during this period every rat had free access to standard rat chow and tap water. The experiments were approved by The Nanjing Medical University Institutional Animal Care and Use Committee (Nanjing, China).

After 2 weeks of acclimatization, the rats were trained to consume 1% sucrose solution, and this training lasted for three weeks. During the training period, the sucrose preference test (SPT) was performed twice a week for the first 2 weeks and once in the last week until the SP of each rat was stable. Then the rats were randomly divided into four groups: Control group, model group, paroxetine-treated group and caffeic acid (CaA)-treated group; each group containing 10 rats. Throughout the experiment, rats in the control group were fed with food and tap water *ad libitum*, except for a 20 h food and water deprivation before each SPT. According to the previous experimental design (1), in the first 3 weeks, rats in the model and treated groups were exposed to a series of chronic unpredictable mild stressors, which were changed slightly from the previous protocol. The stressors consisted of a cage tilted at 45° along the vertical axis, paired housing, food or/and water deprivation, stroboscopic illumination (200 flashes per min), soiled cage (300 ml water spilled into the padding), continuous overnight illumination and white noise (85 db). The detailed schedule is presented in Table SI. Then, rats in the treated groups received the antidepressive agents, and those in both the model and treated groups continued to be exposed to the CUMS procedure over the next 4 weeks. Paroxetine was dissolved in physiological saline and administrated intraperitoneally at the dosage of 10 mg/kg at 9:00 every morning. CaA was diluted with normal saline to a final concentration of 50 mg/ml. Three dosage of CaA were used: 10, 20 and 50 mg/kg. Behavioral data showed that only the 50 mg/kg dosage exerted a slight antidepressant-like effect. Therefore, the 50 mg/kg dosage group was selected to further investigate the epigenetic changes. Rats in another two groups received administration of

physiological saline in the same volume.

References

1. Xinyu Yu, Shanlei Qiao, Di Wang, Jiayong Dai, Jun Wang, Rutan Zhang, Li Wang and Lei Li (2016) A metabolomics-based approach for ranking the depressive level in a chronic unpredictable mild stress rat model. *RSC Adv.* 6, 25751–25765.

Appendix S2. *Brain dissection for hippocampus*. A total of 300 mg/kg 10% chloral hydrate solution was injected per rat intraperitoneally. No rats exhibited signs of peritonitis following the administration of anesthetic. Until the rats were anesthetized, the blood was taken from heart for further analysis. Rats were euthanized by dislocation of the cervical vertebrae. The heart was exposed and heartbeat was assessed to confirm death. No mortality occurred outside of planned euthanasia.

First, the skull was opened to clearly show the brain in the cranial cavity. Next, the cerebral cortex was removed to expose the hippocampus. To do this, the first incision was made at the end of the hemisphere, ~0.7 mm deep to prevent damage to the hippocampus. The second incision was 1.5-2.0 mm in front of the aforementioned incisions, cutting into the lateral ventricle. Both incisions met at the ventral region of the brain. Then, both sides of the cortex covering the hippocampus were pulled up along the ventricle to show the dorsal region of the hippocampus. The rest of the hippocampus was separated from the cortex covering it along the surface of the hippocampus towards the ventral part of the hippocampus. The hippocampus was then removed from the surrounding tissue.

Figure S1. MethPrimer prediction for (A) *Comt* gene and (B) *Bdnf*. For *Comt*, 1 CpG island was found from -202 to +260; the sequence from -206 to +18 was selected for analysis. For *Bdnf*, 5 CpG islands were found; the sequence from -609 to -499 was selected for analysis. *Bdnf*, brain-derived neurotropic factor; *Comt*, catechol-O-methyltransferase.

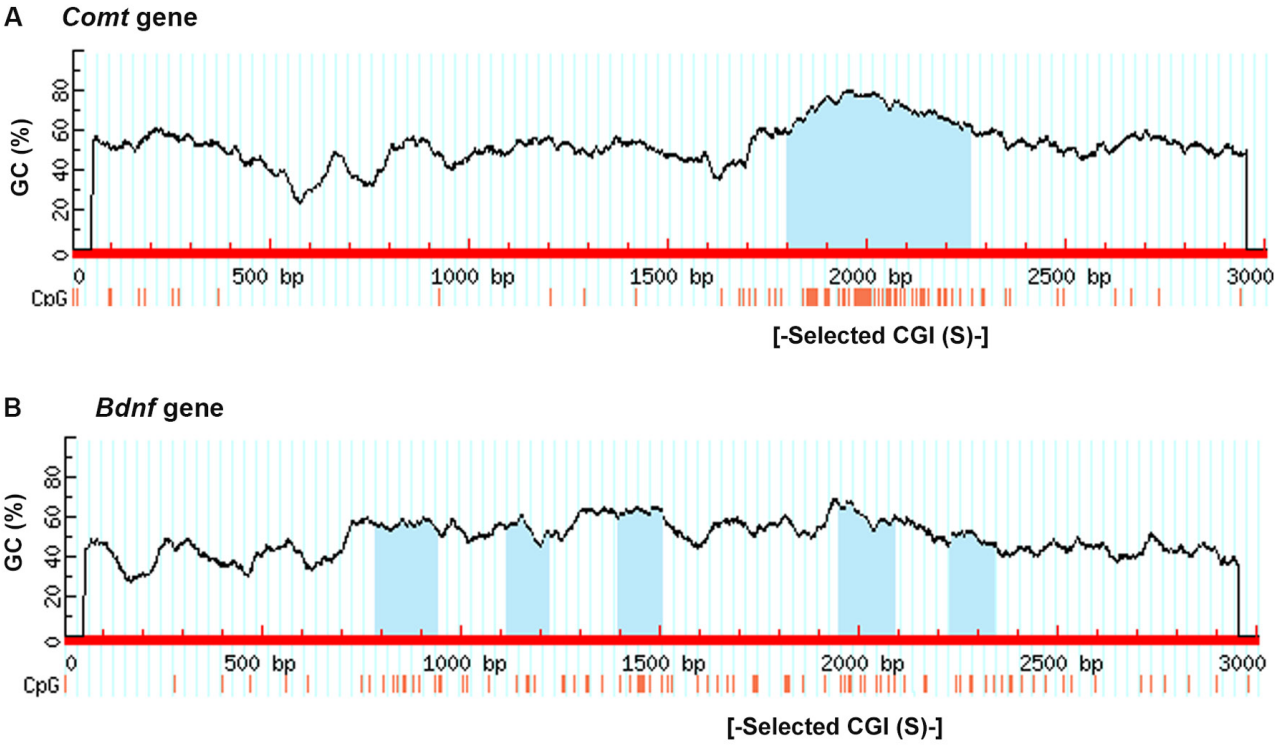

Table SI. Stressor weekly schedules.

Day	Stressor	Duration
Monday	Cage cleaning, changing the soiled padding and weighing the rats	8:00
	Food and water deprivation	13:00
Tuesday	Sucrose preference test	9:00-11:00
	Paired housing	15:00-8:00
Wednesday	Single housing	8:00
	Soiled cage	15:00-8:00
	White noise	20:00-23:00
Thursday	Cage cleaning and changing the solid padding	8:00
	Food deprivation	8:00-20:00
	Cage tilting	20:00-8:00
Friday	Water deprivation	8:00-20:00
	Stroboscopic illumination	20:00-23:00
	Cage tilting	23:00-11:00
Saturday	Paired housing	8:00-20:00
	Overnight illumination	20:00-8:00
Sunday	Soiled cage	15:00-8:00
	White noise	12:00-15:00