The Stability of NR2B in the Nucleus Accumbens Controls Behavioral and Synaptic Adaptations to Chronic Stress

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Background: The nucleus accumbens (NAc) is closely correlated with depression. It has been demonstrated that the glutamatergic system in NAc plays an important role in the reward pathway, dysfunction of which would cause anhedonia, a core symptom of depression. We therefore tested whether N-methyl-D-aspartate receptors and the synaptic plasticity in the NAc are regulated by chronic stress and the relevance to depression.

Methods: We applied behavioral tests (n = 12, each group) of social interaction and sucrose preference tests to identify the susceptibility of mice to chronic social defeat stress. We then tested N-methyl-D-aspartate receptor-long-term depression at cortico-accumbal synapse to determine the relationship between the susceptibility and changes in synaptic plasticity (n = 8, each group). We further investigated whether restoration of these changes could produce antidepressant effects (n = 10).

Results: We found that chronic stress induced selective downregulation of N-methyl-D-aspartate receptor NR2B subunits in the confined surface membrane pool of NAc neurons. Remarkably, the loss of synaptic NR2B was a long-lived event and further translated to the significant modulation of synaptic plasticity in the form of long-term depression. We further observed that the stress-induced changes were restored by fluoxetine and that resilient mice showed patterns of molecular regulation in the NAc that overlapped dramatically with those seen with fluoxetine treatment. Behaviorally, restoration of NR2B loss prevented the behavioral sensitization of mice to chronic stress.

Conclusions: Our results identify NR2B in the NAc as a key regulator in the modulation of persistent psychomotor plasticity in response to chronic stress.

Key Words: Chronic social defeat stress, depression, hippocampal neurogenesis, long-term depression, NMDA, NR2B, nucleus accumbens

The nucleus accumbens (NAc), a part of the ventral striatum, is involved in motivation, reward, motor function, and learning (1). Drugs of abuse increase locomotor activity and preferentially increase dopamine release in the NAc (2). Recent studies reported that the NAc also plays a role in the etiology and pathophysiology of depression (3). Exposure to chronic stress or withdrawal from long-term ingestion of drugs of abuse causes anhedonia (diminished interest or pleasure), a core symptom of major depressive disorder, in both humans and rodents (4,5). Development of anhedonia has been ascribed to dysfunction of the reward pathway, in which the NAc plays a pivotal role. Chronic stress has been reported to induce dramatic neurochemical alterations in the NAc, leading to depressive phenotypes (5,6). Given that clinical depression is marked by anhedonia or lack of reward (7), it has been suggested that dysfunction of the brain reward pathway in the NAc contributes to the pathophysiology of depression.

Glutamatergic inputs arising from limbic and cortical regions converge onto single projection neurons in the NAc and are critically involved in the learning process related to reinforcing properties of natural rewards (1). At the regional level, excessive glutamatergic activity in the amygdala might particularly associate with environmentally aversive stimuli and thus be expected to lower activity within dopaminergic reward pathways (8). Ultimately, disturbances in glutamatergic neurotransmission and synaptic plasticity in the NAc regions might indirectly render a sufferer unable to be significantly stimulated and receive reward (pleasure) from previously enjoyable experiences, making them apathetic, anhedonic, and depressed. In parallel with enriched glutamate afferents, ionotropic glutamate N-methyl-D-aspartate receptors (NMDARs) are densely expressed in striatal medium spiny neurons (9,10). These receptors become functional upon a heteromultimer assembly of the obligatory NR1 and the modulatory NR2 subunit. Among all modulatory subunits, NR2B is distinctly enriched in the striatum (9). Functionally, NR2B has been implicated in many forms of synaptic plasticity related to physiology of striatal neurons and pathogenesis of various neurological disorders (11). We have previously identified NR2B and NMDAR-long-term depression (LTD) in the NAc as key regulators in the remodeling of excitatory synapses and persistent psychomotor plasticity in response to...
psychostimulant (12). However, whether and how NR2B in the NAc adapts to chronic stress remains poorly understood.

Although it is a widely studied psychiatric syndrome, major depressive disorder remains poorly characterized, especially in that most humans exposed to stressful events do not show signs of psychopathology, such as posttraumatic stress disorder or depression. The molecular mechanisms underlying such susceptibility (resilience) are poorly understood. Previous studies have reported that resistance to social defeat is mediated by specific molecular neuroadaptations within the mesolimbic dopamine reward circuit of the brain (e.g., NAc) (13). We therefore conducted a set of in vivo and in vitro experiments to evaluate the role of NR2B in chronic stress-induced synaptic and behavioral plasticity. It was found that chronic social defeat stress (CDS) exposure destabilized the surface-expressed NR2B in the medium spiny neurons of NAc. This destabilization constitutes an enduring molecular adaptation of excitatory synapses to chronic stress, leading to the concurrent development of behavioral plasticity.

Methods and Materials

Animals

Male C57BL/6 mice 9–11 weeks of age and male CD1 retired breeder mice (9–13 months old) were obtained from the Animal Center of Tongji Medical College. Animals were maintained under standard conditions with a 12-hour light/dark cycle and ad libitum access to food and water for 1 week before use. Behavioral testing was performed from 10:00 AM to 5:00 PM concurrent with stated housing conditions. The research was conducted in accordance with the Declaration of Helsinki and with the Guide for Care and Use of Laboratory Animals as adopted and promulgated by the United States National Institutes of Health. All experimental protocols were approved by the Review Committee for the Use of Human or Animal Subjects of Huazhong University of Science and Technology.

Drugs

Fluoxetine was purchased from Sigma (St. Louis, Missouri), dissolved in .9% saline, and administered intraperitoneally (IP) in a volume of 10 mL/kg. The MG132 was obtained from Sigma and dissolved in .1% dimethyl sulfoxide (DMSO). Lactacystin was provided by Sigma and dissolved in .9% saline. The LY379268 was from Tocris (Bristol, United Kingdom) and dissolved in .9% saline.

Forced Swim Test

This test was carried out according to the method of Porsolt (14). Briefly, mice were individually placed into a glass cylinder (25 cm in height, 10 cm in diameter) filled with 10-cm-high water (25 ± 1°C). The water was exchanged after each trial. All animals were forced to swim for 6 min, and the immobility time during the final 4-min interval of the test was recorded. Immobility time was defined as the time spent by the mouse floating in the water without struggling and making only those movements necessary to keep its head above the water. The observers were unaware of the treatment of mice.

Additional experimental procedures and statistics are described in Supplement 1.

Results

Decreased NR2B in the NAc Induced by Chronic Stress: Generality and Specificity

As a first step toward characterizing depression associated with synaptic plasticity regulation in the reward system, the CDS model, which has good predictive validity for modeling the symptomatology of depression (15), was used. As shown in Figure 1A and Figure S1A in Supplement 1, after 10 consecutive days of stress, susceptible mice demonstrated a significant social avoidance, and this was reversed by chronic fluoxetine treatment (20 mg/kg, IP, once daily) for 14 days rather than acute fluoxetine treatment (15), whereas unsusceptible mice spent almost the same time in the interaction zone compared with respective control subjects. Correspondingly, the results of the sucrose preference test (Figure 1B and Figure S1B in Supplement 1) indicated that only susceptible mice displayed a significant increase in anhedonia, restored by chronic fluoxetine administration and not acute fluoxetine administration. After that, we performed western blotting to analyze the change of NR2B proteins in total protein homogenates of NAc 14 days after CDS, and it was found that chronic stress significantly reduced the level of NR2B proteins in the NAc of susceptible mice (Figure 1C). Other NMDAR subunits were also screened for their responses to CDS. In normal rodents, NR1 and NR2A are expressed at moderate-to-high levels in the NAc. As shown in Figure 1C, total levels of NR1 and NR2A proteins in the NAc were not altered after CDS, indicating the insensitivity of these subunits to stress. Similarly, CDS did not alter the amounts of the presynaptic protein, synaptophysin (Figure 1C). These results suggest that NR2B plays a key role in the adaptation to CDS in the NAc.

It has been demonstrated that the NMDAR proteins are part of a larger protein complex, which contains postsynaptic density (PSD) proteins that localize the NR1-NR2 complexes to the postsynaptic sites (16,17). The NMDARs bind directly to a family of proteins, the prototype of which is the abundant PSD-95/synapse-associated protein 90 (SAP90) (18,19). PSD-95 has been implicated in the transmembrane linking of the NMDAR both physically and functionally to the appropriate intracellular signaling pathways and in the regulation of synaptic activity (20–22). Thus, we performed further experiments and found that PSD-95 also exhibited a decrease in the NAc of susceptible mice, similar to NR2B (Figure 1C).

Chronic fluoxetine treatment is known to reverse the behavioral deficits and physiological changes associated with depression (23–25). In this experiment, we built upon the data shown in Figure 1D and Figure S1C in Supplement 1, which indicates that the reduced levels of NR2B and PSD95 proteins in susceptible mice were restored by chronic fluoxetine administration and not acute fluoxetine treatment. An important feature of the CDS model is that not all animals subjected to stress exhibit the characteristic defeat phenotype (13,26). Such unsusceptible or resilient animals exhibit values closer to those of control animals, and this difference led us to examine levels of NR2B and PSD95 in the NAc of resilient mice. In this study, resilient mice displayed patterns of NR2B and PSD95 expression in the NAc that more closely approximated those exhibited by control mice (Figure 1D), different from susceptible mice.

Decreased NR2B in the NAc Induced by Chronic Stress: Spatial and Temporal Characteristics

Other forebrain and midbrain structures, including the dorso-lateral prefrontal cortex and caudate putamen, are reported to be closely connected with the NAc (27,28). We therefore examined the expression of NR2B and PSD95 in these regions after CDS. However, as shown in Figure S2A,B in Supplement 1, chronic stress did not alter the expression of either NR2B or PSD95 in these two regions of CDS-susceptible and -unsusceptible mice, respectively. Thus, CDS-induced downregulation of NR2B and PSD95 seems to be selective to the NAc.
The CDS-induced depressive behavior is characterized by its remarkably long-lived nature (29). Altered receptor expression, if lasting long enough, could serve as a potential molecular mechanism for the nearly permanent behavioral modification. We thus explored the candidacy of NR2B downregulation as a potential mechanism. We observed, as shown in Figure S2C (Supplement 1), a long-lasting decrease in NR2B after CDS, especially at 14 days after CDS of susceptible mice. These results reveal an enduring NR2B downregulation that closely correlates with persistent behavioral plasticity. Furthermore, the reduction of PSD95 in the NAc was also observed at all time points after stress, similar to NR2B (Figure S2D in Supplement 1).

Selective Downregulation of NR2B in the Surface Membranes of NAc Neurons in CDS-Susceptible Mice

The subcellular localization of NMDARs determines the receptor property and is subject to the modulation by changing synaptic inputs (29,30). After demonstrating an overall reduction of NR2B in total protein homogenates, we next performed surface receptor cross-linking assays to investigate the response of NR2B to CDS in different subcellular domains. Data are shown in Figure 2A; a robust decrease in NR2B in the surface pool of susceptible mice was observed in BS\(^2\) cross-linking experiments, and there was no change in the intracellular pool of NR2B. These results demonstrate a selective decrease in NR2B in the confined surface pool. Further study revealed that this decrease was not observed in the NAc of resilient mice, and it was fully reversed by chronic fluoxetine treatment (Figure 2B), not acute fluoxetine treatment (Figure S1D in Supplement 1). In contrast, as shown in Figure 2C, both assays yielded nearly identical estimates of the percentage of NR1 and NR2A in the surface pool/intracellular pool between control and susceptible mice, respectively. These results demonstrate selective NR2B downregulation in a specific subcellular compartment (surface membranes).

Altered Cortico-Accumbal Glutamatergic Synaptic Transmission in CDS-Susceptible Mice

It is generally accepted that synaptic plasticity in the NAc and its associated circuitry has a key role in many forms of...
reward-dependent learning (31). Furthermore, recent studies have proved that synaptic molecular adaptations occur in the neurons of NAc that underlie susceptible and resilient responses to chronic stress (32–34).

We next performed a set of electrophysiological studies to investigate whether the decreases in striatal NR2B levels in the CDS-susceptible mice translate to modification of synaptic plasticity. Three forms of synaptic plasticity at cortico-accumbal glutamatergic synapses—input-output relationship, paired-pulse facilitation (PPF), and LTD—were examined in NAc slices to determine the modulation of synaptic plasticity by CDS.

The PPF is a sensitive measure of the probability of transmitter release and a common form of short-term presynaptic plasticity. Our results showed that CDS produced no effects on PPF, suggesting the lack of gross change in presynaptic facilitation (PPF), and LTD—were examined in NAc slices to determine the modulation of synaptic plasticity by CDS.

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Recent, considerable progress has been made in the understanding of the role of LTD in the NAc (35). Kasanetz et al. (36) recently published a study in which they showed that LTD is disrupted in CDS-susceptible mice.
reported that persistent impairment in NMDAR-LTD in the NAc was associated with transition to cocaine addiction. As we know, excitatory synapses in the NAc can express at least three different forms of LTD, including NMDAR-LTD, endocannabinoids (eCB)-LTD, and a presynaptic form of metabotropic glutamate receptor (mGluR)2/3-LTD (37–39).

Firstly, the NMDAR-LTD in the NAc, an important substrate of drug seeking (31), were compared in the control, unsusceptible, susceptible, and chronic fluoxetine-treated susceptible groups 14 days CDS. The NMDAR-LTD of cortico-accumbal glutamatergic synapse was disrupted in susceptible mice, although it was normal in control animals (Figure 4H). Chronic fluoxetine treatment reversed the disrupted NMDAR-LTD in NAc of susceptible mice (Figures 4C, 4F, and 4H). Furthermore, the impairment of NMDAR-LTD in NAc was absent in CDS-unsusceptible mice (Figure 4H). To evaluate whether there was a general impairment of synaptic plasticity in susceptible animals, we also measured the LTD mediated by mGluR2/3 receptors and eCB, and no difference between groups was found for mGluR2/3-LTD and eCB-LTD (Figure S3 in Supplement 1). Taken together, these results show that CDS specifically blocked NMDAR-LTD in the NAc, suggesting that NMDA-dependent synaptic plasticity plays a vital role in the acquisition of CDS susceptibility.

Because we have observed a long-lasting decrease in NR2B after CDS, we then explored whether this could lead to an enduring modulation of NMDAR-LTD. The NMDAR-LTD was measured at different times after 10 days of CDS. We then compared animals that will (susceptible mice) develop...
depression after 1, 7, 14, and 28 days of CDS. We found that NMDAR-LTD of susceptible mice was decreased 1 day after the last defeat and continued to be significantly lower than control subjects at 7–14 days and 14–28 days (Figures 4A–D), especially at 14 days after CDS of susceptible mice (101.4 ± 8.5% of pre-stimulation baseline, *p < .05 vs. control). Thus, modulation of NMDAR-LTD and the enduring NR2B downregulation could represent a long-lasting molecular adaptation that might contribute to the altered responsiveness to CDS. Taken together, the electrophysiological results show that synaptic plasticity in the NAc is only impaired in CDS-susceptible mice, which was reversed by fluoxetine, supporting a role for NMDAR-LTD in the NAc in severe psychopathology such as depression.

**Role of NR2B in Regulating Behavioral Sensitivity to CDS**

Recent studies have highlighted a function for protein degradation by the ubiquitin proteasome system in synaptic plasticity (40). Furthermore, we have found that intra-accumbal injection of the proteasome inhibitor MG132 reversed the loss of NR2B on the injected side (12). Further efforts were made to evaluate the importance of NR2B in the response of rodents to depression. After 10 days of stress, intra-accumbal injection of MG132 (2 μg/mouse), which is demonstrated to prevent the loss of NR2B, was performed daily (once daily) for 7 consecutive days, and behavioral tests were then performed. As shown in Figures 5A–B, MG132 administration significantly restored the reduced sucrose preference and social interaction induced by CDS, similar to fluoxetine. After that, the results of western blotting showed that MG132 treatment could block the decreased total protein homogenates of NR2B and PSD95 in the NAc (Figure 5C). Furthermore, our study found that it was the decrease in NR2B in the surface pool and not intracellular pool that was restored by MG132 (Figure 5D).

To explore whether the loss of NR2B contributes to the reduction of LTD, we compared the LTD recorded in NAc slices from vehicle control (DMSO) or MG132-treated susceptible mice.

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**Figure 4.** Long-term depression in prefrontal cortex-NAc synapse recorded from CDS-susceptible mice, CDS-unsusceptible mice, and chronic fluoxetine-treated mice. (A–D) Averaged data showed that LTD was induced in CDS-susceptible mice (1, 7, 14, and 28 days after CDS) by LFS. (E and F) Averaged data showed that LTD was induced in CDS-unsusceptible mice and chronic fluoxetine-treated susceptible mice 14 days after CDS by LFS. (G) The histogram showed the level of LTD 40 min after LFS from control mice and CDS-susceptible mice (1, 7, 14, and 28 days after CDS). The NMDAR-LTD was disrupted in CDS-susceptible mice compared with control mice (*n* = 6, *p* < .05 vs. control group. Each point was the normalized mean ± SEM of slices. (H) The histogram showed the level of LTD 40 min after LFS from control mice, CDS-susceptible mice, CDS-unsusceptible mice, and chronic fluoxetine-treated susceptible mice 14 days after CDS. Fluoxetine treatment reversed the disrupted NMDAR-LTD in NAc of CDS-susceptible mice. Furthermore, the impairment of NMDA-LTD in NAc was absent in CDS-unsusceptible mice (*n* = 6). *p* < .05 vs. control; #*p* < .05 vs. susceptible group. Each point was the normalized mean ± SEM of slices. Abbreviations as in Figures 1, 3, and 4.
It was found that MG132 but not DMSO markedly restored the reduction of NMDAR-LTD caused by stress (Figures 6A–C). Intra-accumbal injection of lactacystin (0.2 mg/mouse, once daily, 7 days), another proteasome inhibitor (41), produced similar results (Figures 6D,E). Thus, the NR2B loss seems to contribute to the impairment of LTD in response to CDS.

To test the selective involvement of NR2B loss in susceptibility to stress, we used lentiviral expression of specific short hairpin RNAs (shRNAs) against NR2B to downregulate NR2B expression in the NAc. We first confirmed that lentivirus-delivered shRNAs showed stable expression at 14 days after injection (Figure S4A in Supplement 1) and further confirmed that NR2B shRNA significantly reduced NR2B in total proteins and in the surface pool in the NAc (Figure S4B in Supplement 1). As shown in Figure 7A, injection of NR2B shRNA and not control shRNA significantly increased the immobility, an index for depression-like behavior, of mice in the forced swim test compared with control mice. Next, the behavioral results revealed that NR2B shRNA-injected mice displayed reduced sucrose preference (Figure 7B) and social interaction (Figure 7C) compared with control mice, similar to CDS-susceptible mice. Moreover, CDS and MG132 produced no further behavioral effects in mice pretreated with NR2B shRNA, in contrast to mice pretreated with control shRNA (Figure 7B,C). These results complement those from the aforementioned pharmacological experiments with MG132 and support the requirement of downregulated NR2B for CDS behavior.

**Discussion**

Anhedonia is a core symptom in depression (42). The NAc is implicated in the processing of reward and pleasure (43) and is dysfunctional in depression (44,45). One aim of this study was to improve depression by selectively influencing anhedonia. Our hypothesis was that modulation of the dysfunctional NAc, the part of the reward system, would improve this symptom. Anhedonia is indeed significantly reduced in all patients, confirming previously published findings on acute stimulation to the NAc target (46). Thus, it seems possible to modulate depression by targeting the reward system.

Because it has been demonstrated that synaptic transmission mediated by NMDARs in the NAc undergoes nature rewards and emotion regulation (12), it is necessary and interesting to investigate the adaptation of this receptor complex to chronic stress and depression. The NMDARs are composed of several subunits and functional at synaptic and perisynaptic sites of the glutamatergic synapse (47). Our results showed that accumbal NR1 and NR2A proteins remained stable after CDS as well as the presynaptic protein (synaptophysin), whereas NR2B proteins were reduced significantly. The decreased expression of PSD95 in the NAc was also found, because it was a major anchoring protein of NR2B (47). Further study revealed that the reduction of NR2B and PSD95 was a long-lasting process and not observed in the dorsolateral prefrontal cortex and caudate putamen, two regions closely correlated with the NAc (27,28). These
observations indicate an important role of NR2B in the NAc in modulating the adaptation of rodents to chronic stress.

It has been reported that most humans exposed to stressful events do not show signs of psychopathology such as posttraumatic stress disorder or depression. The molecular mechanisms underlying such susceptibility (resilience) remain poorly studied. Here, we took advantage of a large variance in behavioral outcomes after CDS in inbred C57 mice to investigate the molecular basis of susceptibility and resistance to emotional stress. One of the most intriguing aspects of CDS is its consistent ability to generate animals, which have undergone 10 days of defeat stress, but do not exhibit a depression-like phenotype (13). It is thought that resilience is an active process and not simply the absence of changes that occur in vulnerable animals (26). The results from our study at least suggested that the NR2B and PSD95 in the NAc are the major targets of CDS, mediating the susceptibility to CDS, although it needs to be further identified whether they are the only mechanism for resilience. Thus, our results define a novel drug discovery pathway whereby new antidepressants can be developed. Given that susceptible and resilient responses are seen among inbred mice raised in identical environmental settings, the factors responsible for these differential adaptations to chronic stress remain unknown. One possibility is that pre-existing epigenetic modifications contribute to these distinct responses (48). Our results also showed that chronic fluoxetine treatment completely restored the loss of NR2B and PSD95 caused by stress, suggesting the neuroplastic mechanism of fluoxetine (49), different from monoaminergic and neurotrophic hypothesis (49,50).

Further results indicate a selective loss of NR2B in the cell surface membrane. Intriguingly, in contrast to the surface section, NR2B in the intracellular pool involving synthesis, assembly, and secretion of proteins was insensitive to stress (12). Suppressed trafficking or delivery of NR2B from the intracellular pool to the surface membrane is less likely, because impaired NR2B externalization of this kind should cause a redistribution phenomenon that is characterized by the subtraction of NR2B in the surface pool in combination with the proportional addition of NR2B in the intracellular pool, whereas total NR2B proteins remain unchanged (30,51). Because PSD95 is well-established to inhibit NR2B internalization and stabilize surface NR2Bs at synaptic sites, impaired PSD95 might cause destabilization of NR2B. Thus, it is possible that the removal of existing NR2B from the surface pool is accelerated, followed by enhanced degradation of the protein. This model is supported by our pharmacological studies in which the proteasome inhibitors that blocked the degradation of proteins prevented both the loss of PSD95 and NR2B abundance in susceptible mice.

These findings might further reveal a metaplastic basis for the CDS-associated learning and memory in the NAc. Striatal neurons
are among those that readily express LTD, a cellular model of synaptic plasticity, which is susceptible to stress. Our results support an inhibitory modulation of NMDAR-LTD by CDS, consistent with the loss of surface NR2B at synaptic sites. These plastic changes are theoretically believable, because enduring inhibition of LTD occurred in the NAc of chronic cocaine-treated mice, which displayed negative and depressed-like behavior (52). As we know, there is a projection from NAc-γ-aminobutyric acid (GABA)ergic neurons to the ventral tegmental area (VTA)-dopaminergic neurons (3,53), and this is usually an inhibitive connection. Because it has been reported that in some regions—like hippocampal CA1 area—that LTP in the excitatory synapse is parallel with LTD in the inhibitory synapse (54–56), it is possible that an NAc-NMDAR-LTD on the NAc-inhibitory GABAergic neurons—which means a disinhibition or a decreased inhibitory output—will lead to increased excitability associated with LTD of VTA-excitatory dopaminergic neurons. On the contrary, an impaired NAc-NMDAR-LTD on the NAc-inhibitory GABAergic neurons, which means a weakened disinhibition or an increased inhibitory output, might induce decreased excitability of VTA-dopaminergic neurons and then down-regulate their release of dopamine into the NAc and other regions, leading to depression-like behavior like anhedonia (6,57,58).

The results of MG132 and NR2B shRNA study confirmed the conclusion that NR2B in the NAc could be developed as a new target for antidepressants. This conclusion is interesting, because it has demonstrated that blocking of NR2B in the hippocampus produces antidepressant effects (59). This difference is thoughtful and not limited to NR2B, because previous study has proved that—although increasing the expression of brain-derived neurotrophic factor/cyclic adenosine monophosphate response element binding protein in hippocampus defends against chronic stress (60)—decreasing the level of brain-derived neurotrophic factor/cyclic adenosine monophosphate response element binding protein in NAc produces antidepressant effects (3). Further research is required to explain this difference. One possibility is that the neuronal constituents between hippocampus and NAc are different, because hippocampus is mainly composed of excitatory glutamatergic neurons, whereas NAc is made up of inhibitory GABAAergic neurons (61,62).

Taken together, by a combination of electrophysiological, behavioral, and biochemical techniques, we identify signature adaptations of NMDAR-dependent synaptic plasticity within the corticoaccumbal glutamate circuit that are uniquely associated with vulnerability or invulnerability. Our results validate the NMDAR-LTD molecular substrate that mediate this lack of adaptation in CDS and could unravel new targets for antidepressants. These findings provide new insight into the molecular basis of depression and the mechanisms by which antidepressants exert their delayed clinical efficacy. They also raise the novel idea that certain individuals resistant to stress might naturally mount antidepressant-like adaptations in response to chronic stress.

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Supplementary material cited in this article is available online.

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