

Article

Impulsivity in NrCAM KO Mice Is Reduced by NMDAR Antagonist MK-801 but Not by AMPAR Antagonist CNQX

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Abstract

The neuronal cell adhesion molecule NrCAM is widely expressed in the nervous system across the lifespan and has important physiological functions in the development of neuronal circuits through axonal growth and guidance and formation and maintenance of synapses in the cortex. NrCAM gene polymorphisms are associated with vulnerability to neuropsychiatric disorders such as schizophrenia, as well as vulnerability to substance use disorders. We investigated the effects of acute and chronic stress and the effects of systemic administration of AMPAR antagonist CNQX and NMDAR antagonist MK-801 on delay discounting in male NrCAM knockout (KO) mice and their wild-type littermate controls (WT). Under the no-stress condition, no discounting differences were found. Acute stress increased discounting and impulsivity in WTs but not in NrCAM KO mice. Chronic stress increased discounting and impulsivity in both genotypes. CNQX increased impulsive choice in WT controls but not in NrCAM KOs; impulsive choice decreased in both genotypes after MK-801 administration. Relative to WTs, NrCAM KOs had more neuronal activation in the prelimbic and orbitofrontal cortices. In NrCAM KO mice, a low dose of MK-801 decreased neuronal activation in the ventral orbitofrontal cortex and increased activation in the accumbens shell and core. These results indicate differential effects of genotype, stress, and response to glutamatergic drugs and support a role for NrCAM in stress-induced behavioral alterations relevant to addiction and psychiatric disorders.

Keywords: addiction; cFos; decision making; delay discounting; stress; substance use disorders

1. Introduction

The neuronal cell adhesion molecule NrCAM [1,2] is a cell adhesion molecule widely expressed in the nervous system throughout the lifespan [3–6]. NrCAM lies at the core of functional protein complexes with multiple physiological functions, from supporting axonal growth and targeting [4,7] to organizing channels and receptors at the axon hillock and nodes of Ranvier and at the synapse [8,9]. NrCAM is associated with SAP90 and SAP97 [10], adapters for glutamate receptors (GluRs) [11,12]; SAP97 mutations increase glutamatergic synapse strength [13] and are associated with schizophrenia (SZ) [14–17]. NrCAM is also expressed in cortical astrocytes and is involved in the formation and maintenance of perisomatic inhibitory synapses in the cortex [18,19]. Interestingly, NrCAM is expressed in dopaminergic (DA) neurons in the VTA and neurons in the striatum [20]. NrCAM gene polymorphisms show strong associations with SZ [21–23] and with substance abuse [20]. NrCAM KO mice show no conditioned place preferences for morphine, cocaine,



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were tested under systemic drug administration of CNQX or vehicle. After another week, mice were tested under MK-801 or vehicle. Finally, after one more week, mice were randomly split to be tested for one session under either MK-801 or vehicle, followed by brain collection for cFos immunostaining (see Figure 1).

2.2.1. DD Paradigm

Mice were trained as in [31,32] in a DD paradigm in which they were presented with two alternatives, Smaller–Sooner (SS, 1 pellet at 0 s delay), and Larger–Later (LL, 4 pellets at progressively larger delays). To evaluate the effect of acute stress, mice were tested in 2 sessions with delays of 0 and 64 s under the no-stress (NS) condition followed by 2 sessions preceded by an acute-stress (AS) treatment (social defeat) as in [24]. Afterwards, mice received 21 days of a CS regimen as in [26,31,32], followed by 2 sessions of testing in a DD paradigm with delays of 0, 16, and 64 s (see Figure 1).

A week later, mice received 3 DD testing sessions with delays of 0, 16, and 64 s under systemic (i.p.) administration of CNQX (3 doses counterbalanced among subjects). A week later, mice received 4 DD testing sessions with delays of 0, 16, and 64 s under systemic (i.p.) administration of MK-801 (4 doses counterbalanced among subjects). Finally, KO and WT mice were randomly split and given one more DD session with delays of 0, 16, 64 s under either a low dose of MK-801 or vehicle, followed by brain collection for neuronal activation analyses (cFos+ immunostaining) (see Figure 1).

2.2.2. AS Treatment

During each of the 2 AS testing sessions, mice received 10 min of an acute social defeat stress (exposure to an aggressive Balb/c male mouse), as in [31,32], followed 15 min later by DD testing with delays of 0 and 64 s.

2.2.3. CS Regimen

Mice received 21 days of CS using the following daily randomly chosen stressors: 30 min restraint, 10 min forced swim, or 10 min exposure to an aggressive Balb/c male mouse, as in [31,32]. At the end of the CS regimen, mice were tested for 2 sessions in a DD paradigm with delays of 0, 16, and 64 s.

2.2.4. CNQX Drug Manipulation

AMPA antagonist CNQX (0, 1.8, and 5.6 mg/kg, Tocris Biotechnique, Minneapolis, MN, USA) was dissolved in saline vehicle. Fifteen min before each of the three DD sessions with delays of 0, 16, and 64 s, mice were systemically (i.p.) administered one of the CNQX doses (counterbalanced daily among subjects).

2.2.5. MK-801 Drug Manipulation

NMDAR antagonist MK-801 (0, 0.03, 0.1, and 0.3 mg/kg, Tocris Biotechnique, Minneapolis, MN, USA) was dissolved in saline vehicle. Fifteen min before each of the 4 DD sessions with delays of 0, 16, and 64 s, mice were systemically (i.p.) administered one of the MK-801 doses (counterbalanced daily among subjects).

2.2.6. cFos Immunostaining

NrCAM KO and WT mice were randomly split and injected with either MK-801 0.03 mg/kg or vehicle, 15 min before one last DD test session with delays of 0, 16, and 64 s. Two hours after the beginning of the test, animals were perfused with paraformaldehyde solution (4% in 0.1 M phosphate buffer), and brains were collected and processed for cFos immunostaining as in [31,32]: cFos was labeled with a rabbit primary antibody (Cell Signaling Technologies, Danvers, CA, USA, 1:400 dilution) and a secondary goat anti rabbit

antibody Alexa488-conjugated (Invitrogen, Carlsbad, CA, USA). Regions of interest were identified using NeuroTrace 530/615 neuronal labeling (Invitrogen, Carlsbad, CA, USA). Image acquisition was done on a Zeiss LSM710 confocal microscope (Carl Zeiss GmbH, Oberkochen, Germany) using appropriate filter sets. The number of cFos-positive (cFos+) nuclei in equal surface areas in 2 sections/region of interest/mouse was averaged over two independent observers unaware of genotype. The following brain regions of interest were evaluated: prelimbic cortex PrL—bregma 1.94/2.34, orbitofrontal cortex OFC—bregma 2.10/2.34, nucleus accumbens Acb shell, and core—bregma 1.10/1.34 [33]. Five brains were eliminated from analyses due to perfusion artifacts, such that the final groups for cFos+ statistical analyses were KO-MK ($n = 9$), WT-MK ($n = 7$), KO-SAL ($n = 7$), and WT-SAL ($n = 8$).

2.3. Statistical Analyses

For stress sessions, the %LL choices were submitted to mixed ANOVAs with between-subject factor genotype (KO, WT) and within-subject factor delay (2 levels for AS: 0 s, 64 s; 3 levels for CS: 0, 16, 64 s) and stress (2 levels: either NS and AS, or NS and CS). For drug sessions, the %LL choices were submitted to mixed ANOVAs with between-subject factor genotype and within-subject factor delay (0 s, 16 s, 64 s) and drug dose (3 levels for CNQX: 0, 1.8, 5.6 mg/kg; 4 levels for MK-801: 0, 0.03, 0.1, 0.3 mg/kg). Area under the normalized discounting curve (%AUC) was also computed as in [34] and submitted to mixed ANOVAs with between-subjects factor genotype and within-subject factor stress (2 levels: either NS and AS, or NS and CS). For drug sessions, the %AUC was submitted to mixed ANOVAs with between-subjects factor genotype and within-subject factor drug dose (3 levels for CNQX; 4 levels for MK-801). cFos+ counts for each region of interest were analyzed by 2-way ANOVAs with between-factor genotype (KO, WT) and drug (vehicle, MK-801). Post hoc analyses (LSD) were run for ANOVAs with significant omnibus tests. Analyses were conducted using STATISTICA 6.0 software (StatSoft, Tulsa, OK, USA). All analyses used a 0.05 alpha level.

3. Results

3.1. Acute Social Stress Increased Discounting and Impulsivity in WT but Not in NrCAM KO Mice

To evaluate the effect of acute stress on discounting, the %LL choices under *no stress* (NS) and *acute stress* (AS) conditions were submitted to statistical analyses (Figure 2a), which indicated a significant main effect of delay ($F(1, 34) = 73.130, p = 0.001$), suggesting that all mice acquired the DD paradigm. Analyses also indicated a significant effect of genotype ($F(1, 34) = 9.672, p = 0.004$) and a stress $\times$ genotype interaction ($F(1, 34) = 4.554, p = 0.040$), suggesting that WT mice discounted more than KO mice under AS but not under NS. Post hoc LSD analyses supported these interpretations: Analyses failed to indicate differences between genotypes under NS (all $ps > 0.318$) and at 0 s delay in the AS condition ($p = 0.244$) but indicated a significantly lower %LL in WTs than in KOs under AS ($p = 0.003$). Analyses also failed to indicate %LL differences between AS and NS conditions in KOs (all $ps > 0.053$).

The discounting curves were further normalized both in the %LL and delay axes [34], and the normalized %AUC was computed and analyzed; a small %AUC is taken to be indicative of steeper discounting and a more impulsive individual [34]. The normalized %AUC was submitted to statistical analyses (Figure 2b), which indicated a significant effect of genotype ($F(1, 34) = 7.603, p = 0.009$), suggesting that stress increased impulsivity in both genotypes.

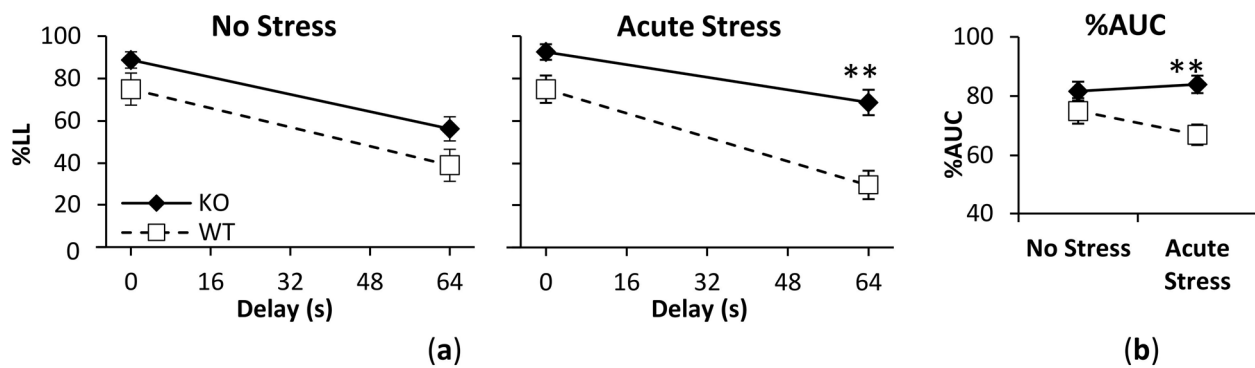


Figure 2. Increased discounting after acute stress in WT, but not NrCAM KO mice. (a) Average %LL choices ($\pm$ SEM) in NrCAM KO mice ($n = 20$) and WT controls ($n = 16$) under no-stress condition (left) and after acute stress (right). Data were analyzed with a mixed ANOVA with between-subjects factor genotype and within-subject factors delay and stress followed by LSD post hoc analyses. (b) Average %AUC ($\pm$ SEM) in NrCAM KO mice and WT controls under no stress and acute stress conditions. Data were analyzed with a mixed ANOVA with between-subjects factor genotype and within-subject factor stress followed by LSD post hoc analyses. ** $p < 0.01$.

Post hoc LSD analyses failed to indicate genotype differences under NS ($p = 0.296$) but indicated that under AS, WT were more impulsive than KOs ($p = 0.007$). Analyses also failed to indicate differences in %AUC between AS and NS conditions in KOs ($p = 0.547$). Together, analyses of the %LL choice (Figure 2a) and analyses of the normalized %AUC (Figure 2b) suggest that WT mice discounted more and were more impulsive under acute social stress, while DD in NrCAM KO mice was not affected by the acute social stress procedure used in our study.

3.2. Chronic Stress Increased Discounting and Impulsivity in Both Genotypes

To evaluate the effect of chronic stress on discounting, the %LL choices under no stress (NS) and chronic stress (CS) were submitted to statistical analyses (Figure 3a).

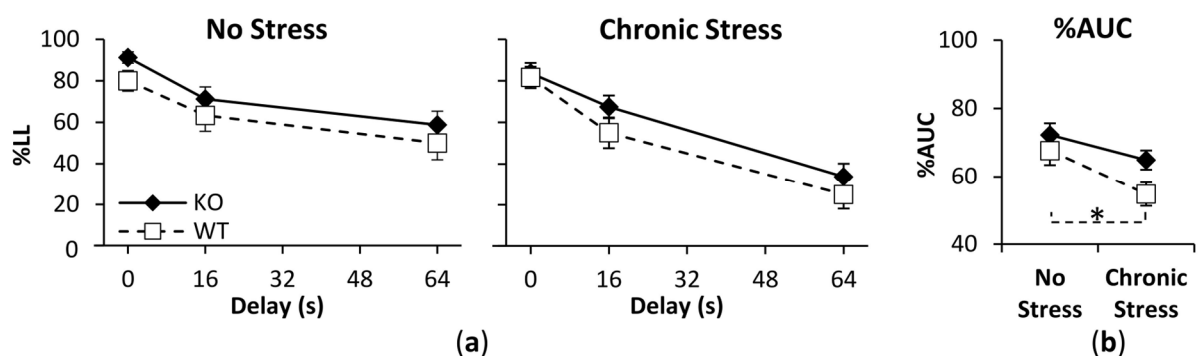


Figure 3. Increased discounting after chronic stress in both NrCAM KO mice and WT controls. (a) Average %LL choices ($\pm$ SEM) in NrCAM KO mice ($n = 20$) and WT controls ($n = 16$) under no-stress condition (left) and after chronic stress (right). Data were analyzed with a mixed ANOVA with between-subjects factor genotype and within-subject factors delay and stress followed by LSD post hoc analyses. (b) Average %AUC ($\pm$ SEM) in NrCAM KO mice and WT controls under no stress and chronic stress conditions. Data were analyzed with a mixed ANOVA with between-subjects factor genotype and within-subject factor stress followed by LSD post hoc analyses. * $p < 0.05$.

Analyses indicated significant main effects of delay ($F(2, 68) = 65.323$, $p = 0.001$) and stress ($F(1, 34) = 13.887$, $p = 0.001$) and a delay $\times$ stress interaction ($F(2, 68) = 5.293$, $p = 0.007$), suggesting that all mice discounted more at the long, 64 s delay, under CS than under NS. Post hoc LSD analyses failed to indicate differences between genotypes under either stress

condition (all p s > 0.374) but indicated a significantly lower %LL at the 64 s delay under CS than under NS in both genotypes (all p s < 0.002).

Figure 3b shows the %AUC in NrCAM KO and WT mice in the NS and CS conditions and indicates that both KO and WT were more impulsive under CS than under NS. Statistical analyses of %AUC indicated a significant effect of stress ($F(1, 34) = 7.295$, $p = 0.011$), suggesting that CS increased impulsivity in both genotypes. Post hoc LSD analyses failed to indicate genotype differences in either stress condition (all p s > 0.191) but indicated that WT mice were significantly more impulsive under the CS than under NS ($p = 0.035$). Together, analyses of the %LL choice (Figure 3a) and analyses of normalized %AUC (Figure 3b), suggest that both WT and KO mice discounted more and were more impulsive under chronic stress than under no stress.

3.3. Systemic CNQX Increased Discounting and Impulsivity in WT but Not in NrCAM KO Mice

NrCAM KO mice and WT controls were further tested in a DD paradigm with delays of 0, 16, and 64 s under systemic (i.p.) administration of AMPAR antagonist CNQX (0, 1.8, 5.6 mg/kg), and the %LL were submitted to statistical analyses (Figure 4a). Analyses indicated significant main effects of delay ($F(2, 68) = 66.366$, $p = 0.001$), genotype ($F(1, 34) = 4.529$, $p = 0.041$), and CNQX dose ($F(2, 68) = 4.084$, $p = 0.021$), as well as a significant dose $\times$ delay interaction ($F(4, 136) = 2.472$, $p = 0.047$), suggesting that, under CNQX, WT mice discounted at a higher rate than KOs, particularly after a 16 s delay. Post hoc analyses failed to indicate differences in %LL between CNQX doses at each delay for KOs (all p s > 0.067), but indicated significant differences after a 16 s delay for WT mice, relative to vehicle, at the 1.8 and 5.6 mg doses (all p s < 0.013) suggesting that WT, but not KO mice, were sensitive to CNQX.

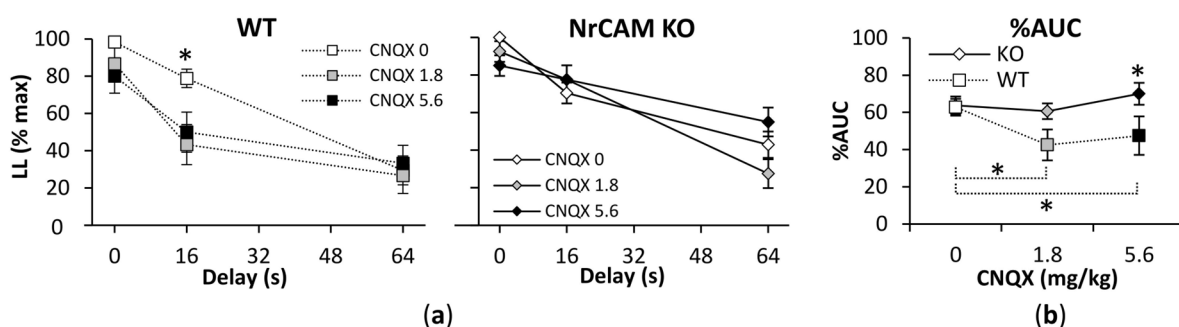


Figure 4. CNQX increased discounting and impulsivity in WT, but not NrCAM KO mice. (a) Average %LL choices ($\pm$ SEM) in NrCAM KO mice ($n = 20$, right) and WT controls ($n = 16$, left) under systemic administration of CNQX (0, 1.8, 5.6 mg/kg). Data were analyzed with a mixed ANOVA with between-subjects factor genotype and within-subject factors delay and drug dose followed by LSD post hoc analyses. (b) Average %AUC ($\pm$ SEM) in NrCAM KO mice and WT controls under CNQX. Data were analyzed with a mixed ANOVA with between-subjects factor genotype and within-subject factor drug dose followed by LSD post hoc analyses. * $p < 0.05$.

Analyses of normalized %AUC (Figure 4b) indicated a significant main effect of genotype ($F(1, 34) = 4.869$, $p = 0.034$) and a significant genotype $\times$ dose interaction ($F(2, 68) = 3.325$, $p = 0.042$) but no other effects, suggesting that CNQX increased impulsivity in WT mice but not in KO mice. Post hoc analyses indicated a significant decrease in %AUC in WT mice under CNQX 1.8 mg and 5.6 mg, relative to vehicle (all p s < 0.016), but no effect of CNQX in KO mice (all p s > 0.144). Moreover, differences in %AUC were found between genotypes at the 5.6 mg dose ($p = 0.044$) but not at lower doses (all p s > 0.124). Taken together, these results suggest that AMPAR antagonist CNQX increased discounting and impulsivity in WT mice but not in NrCAM KO mice.

3.4. Systemic MK-801 Decreased Discounting and Impulsivity in Both Genotypes, with Larger Effects at Low Doses in NrCAM KO Mice

Mice were further tested under systemic (i.p.) administration of NMDAR antagonist MK-801 (0, 0.03, 0.1, 0.3 mg/kg). The %LL choices under MK-801 are shown in Figure 5a, which indicated that MK-801 decreased discounting in both genotypes, but that at the higher dose 0.3 mg, MK-801 drastically impaired WT mice in differentiating reward magnitude after a 0 s delay (some impairment was also seen in NrCAM KO mice). Statistical analyses of %LL choices under MK-801 confirmed these suggestions: analyses indicated significant main effects of delay ($F(2, 68) = 16.703, p = 0.001$) and genotype ($F(1, 34) = 18.441, p = 0.001$), suggesting all mice discounted, but that, under MK-801, KOs discounted less than WTs. Analyses also indicated a significant delay $\times$ dose interaction ($F(6, 204) = 12.558, p = 0.001$) and a significant genotype $\times$ dose interaction ($F(3, 102) = 4.307, p = 0.006$), suggesting discounting differences between genotypes regarding drug effects at different delays: while MK-801 decreased discounting in both genotypes after a long 64 s delay, it decreases %LL after a 0 s delay, in a dose-dependent manner. Post hoc analyses supported these interpretations: in KO mice MK-801 decreased discounting after a 64 s delay relative to vehicle at all doses (all $ps < 0.001$), while in WTs mice MK-801 significantly decreased discounting relative to vehicle at the 0.1 and 0.3 mg doses (all $ps < 0.049$) but not at the low 0.03 mg dose ($p = 0.099$). In contrast, after a 0 s delay, MK-801 decreased %LL in a genotype- and dose-dependent manner: in KOs, after a 0 s delay, MK-801 had no effects at the low-to-medium doses (all $ps > 0.153$) but significantly decreased %LL choices at the high 0.3 mg dose ($p = 0.023$), while in WTs, MK-801 had no effects at the low dose ($p = 0.079$) but significantly decreased %LL choices at the medium-to-high doses (all $ps < 0.007$).

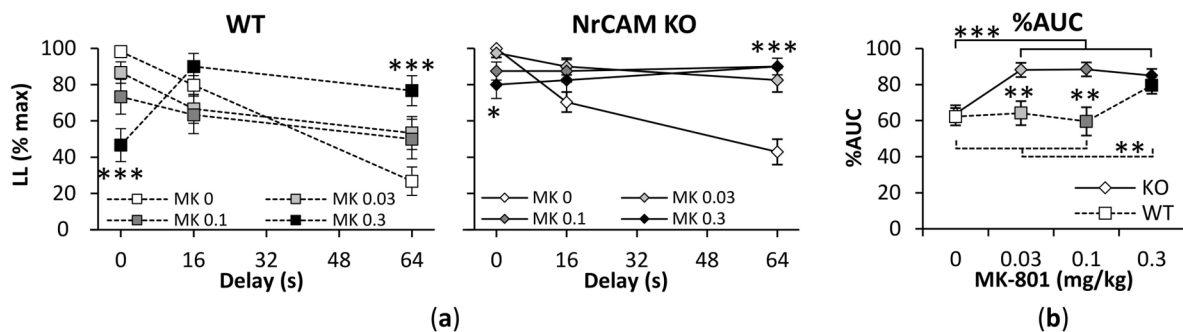


Figure 5. MK-801 decreased discounting and impulsivity in both genotypes. (a) Average %LL choices ($\pm$ SEM) in NrCAM KO mice ($n = 20$, right) and WT controls ($n = 16$, left) under systemic administration of MK-801 (0, 0.03, 0.1, 0.3 mg/kg). Data were analyzed with a mixed ANOVA with between-subjects factor genotype and within-subject factors delay and drug dose followed by LSD post hoc analyses. (b) Average %AUC ($\pm$ SEM) in NrCAM KO mice and WT controls under MK-801. Data were analyzed with a mixed ANOVA with between-subjects factor genotype and within-subject factor drug dose followed by LSD post hoc analyses. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

The effect of MK-801 on impulsivity is shown in Figure 5b: MK-801 increased %AUC in both genotypes, albeit at different doses. Statistical analyses indicated significant main effects of both genotype ($F(1, 34) = 13.012, p = 0.001$) and MK-801 dose ($F(3, 102) = 5.328, p = 0.002$), as well as a significant genotype $\times$ dose interaction ($F(3, 102) = 4.349, p = 0.006$), suggesting a dose-dependent differential effect of MK-801 on impulsivity in the two genotypes. While in KO mice post hoc analyses indicated significant increases in %AUC at all MK-801 doses relative to vehicle (all $ps < 0.001$), an increase in %AUC was found in WT mice at the highest 0.3 mg dose ($p = 0.046$) but not at lower doses (all $ps > 0.700$). Moreover, differences in %AUC were found between genotypes at the 0.03 and 0.1 mg doses (all $ps < 0.007$) but not under vehicle or the highest 0.3 mg dose (all $ps > 0.307$). Taken

together, these results suggest that NMDAR antagonist MK-801 decreases discounting and impulsivity in a dose-dependent manner in the two genotypes, with larger effects at low doses in NrCAM KO mice.

3.5. Systemic MK-801 Increased Omissions, While Systemic CNQX Had No Effect on Omissions

Performance under systemic CNQX and under systemic MK-801 was further analyzed for omissions (trials in which mice delayed responding for more than 30 s). Figure 6 indicates that CNQX had no effect on omissions, while MK-801 drastically increased omissions at the highest dose, 0.3 mg/kg.

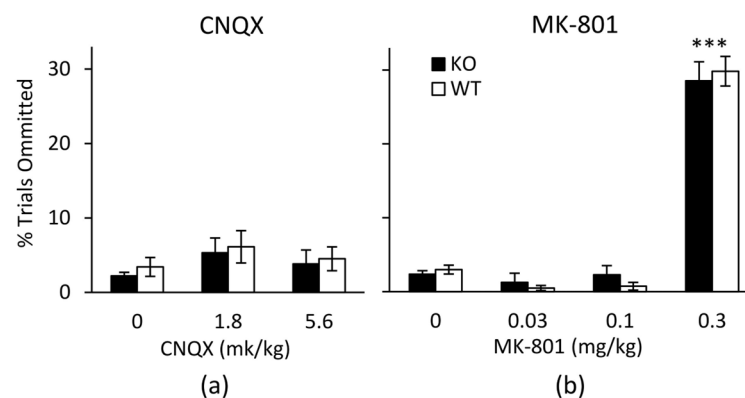


Figure 6. Omissions under CNQX and MK-801 in NrCAM mice. Average % trials omitted ($\pm$ SEM) in NrCAM KO mice ($n = 20$) and WT controls ($n = 16$) under systemic administration of (a) CNQX (0, 1.8, 5.6 mg/kg), and (b) MK-801 (0, 0.03, 0.1, 0.3 mg/kg). Data were analyzed with two-way ANOVAs with factor genotype and drug dose followed by LSD post hoc analyses. *** $p < 0.001$.

The percent (trials with) omissions under CNQX (0, 1.8, 5.6 mg/kg) and under MK-801 (0, 0.03, 0.1, 0.3 mg/kg) were submitted to two separate mixed ANOVAs with between-subject factor genotype and within-subject factor drug dose. Statistical analyses of percent omissions under CNQX failed to indicate any main effects or interactions (all $F_s < 1.902$, $p_s > 0.157$), suggesting that CNQX had no effects on omissions irrespective of genotype or dose (Figure 6a).

In contrast, statistical analyses of percent (trials with) omissions under MK-801 indicated a main effect of MK-801 dose ($F(3, 102) = 208.193$, $p = 0.001$) but no other main effects or interactions (all $F_s < 0.459$, all $p_s > 0.711$), suggesting that irrespective of genotype, MK-801 increased omissions. LSD post hoc analyses failed to indicate differences in percent omission between vehicle, 0.03, and 0.1 mg doses (all $p_s > 0.219$) but indicated significant differences between these doses and the 0.3 mg dose (all $p_s < 0.001$) (Figure 6b). These results suggest that in our setting, irrespective of genotype, AMPAR antagonist CNQX had no effect on omissions, while NMDAR antagonist MK-801 drastically increased omissions, but only at the highest dose, 0.3 mg/kg. In summary, our results suggest that NMDAR antagonist MK-801 decreases discounting and impulsivity and increases omissions, in a dose-dependent manner.

3.6. Neural Activation in NrCAM KO Mice Under MK-801 in Brain Regions Relevant to DD

The cFos marker is an established method used to identify brain regions specifically activated during behavioral tasks [35–37]. We evaluated neuronal activation (cFos+ cell counts) during DD in NrCAM KO mice and WT controls under saline vehicle (KO-SAL $n = 7$, WT-SAL $n = 8$) and under MK-801 0.03 mg/kg (KO-MK $n = 9$, WT-MK $n = 7$) in PrL, mOFC, vOFC, Acb-core, and Acb-shell, regions known to be involved in decision making [38,39], and particularly in DD [37]. Figure 7a,b shows representative neuronal activation in these brain regions.

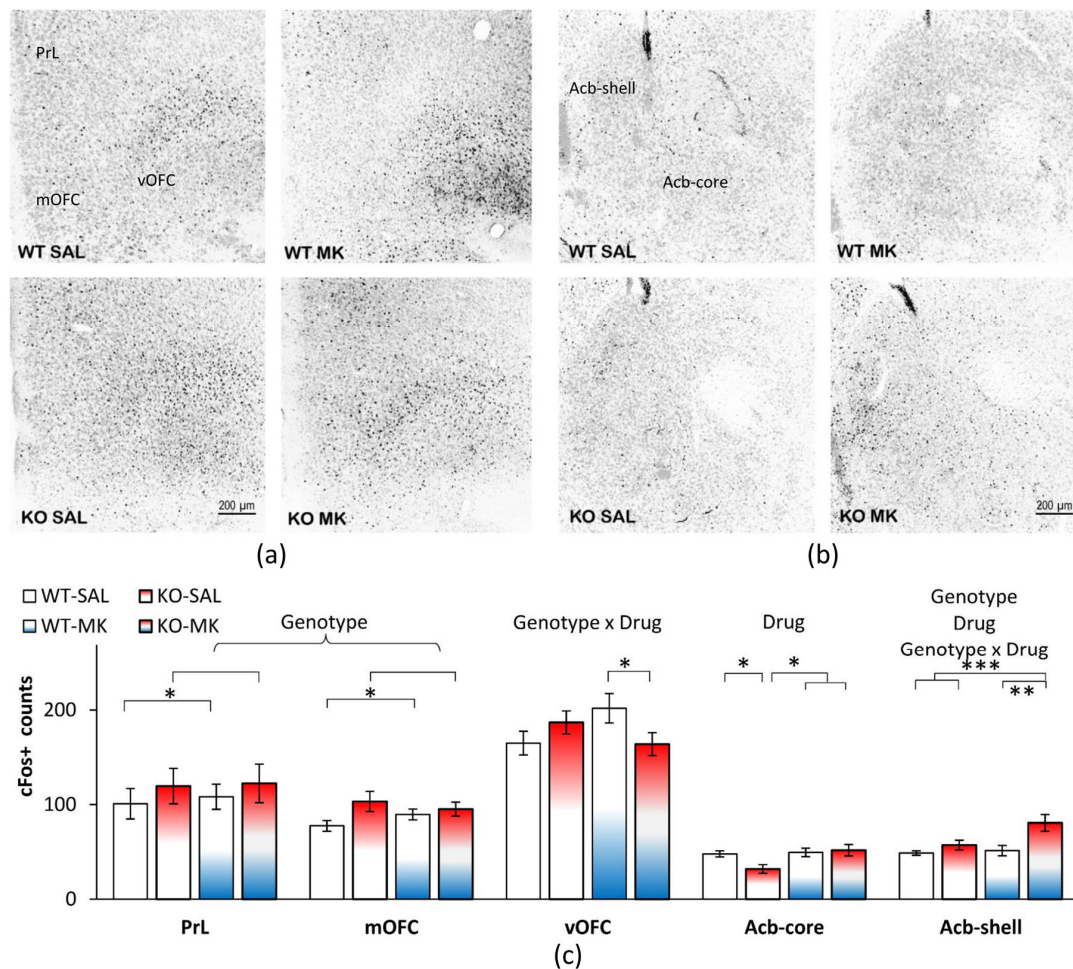


Figure 7. Neural activation under MK-801 in brain regions relevant to DD. (a,b) Representative neuronal activation in NrCAM KO mice (lower panels) and WT controls (upper panels) under saline vehicle (left panels) or MK-801 (right panels) in (a) prelimbic cortex (PrL), medial OFC (mOFC), ventral OFC (vOFC) and (b) nucleus accumbens core (Acb-core), and nucleus accumbens shell (Acb-shell). black dots = cFos+ cells; gray = Neurotrace neuronal labeling. (c) Average number of cFos+ neurons ($\pm$ SEM) in NrCAM KO mice and WT controls after being tested in the DD paradigm under MK-801 (MK, 0.03 mg/kg) or saline vehicle (SAL). Data were analyzed with two-way ANOVAs with factors genotype and drug followed by LSD post hoc analyses. KO-MK ($n = 9$), WT-MK ($n = 7$), KO-SAL ($n = 7$), and WT-SAL ($n = 8$). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Figure 7a suggests more neuronal activation (higher number of cFos+ cells) in PrL and mOFC and less neuronal activation in vOFC under MK-801 in NrCAM KO mice (lower panels) relative to WT controls (upper panels). Figure 7b suggests less neuronal activation in Acb-core in NrCAM KO mice under saline vehicle (left-lower panel) relative to all other conditions and more neuronal activation in Acb-shell in NrCAM KO mice under MK-801 (right-lower panel) relative to all other conditions.

Statistical analyses shown in Figure 7c confirmed the above observations. Analyses indicated that NrCAM KO mice showed significantly higher neuronal activation in PrL ($F(1, 27) = 6.727$, $p = 0.015$) and mOFC ($F(1, 27) = 4.30$, $p = 0.047$) relative to WT controls, as well as a significant increase in neuronal activation in NrCAM KO mice under MK-801 relative to vehicle control in Acb-core ($F(1, 27) = 4.831$, $p = 0.037$) and Acb-shell ($F(1, 27) = 4.890$, $p = 0.036$). Analyses also indicate lower neuronal activation under MK-801 in vOFC in NrCAM KO mice relative to WT ($F(1, 27) = 5.191$, $p = 0.031$). Taken together, these results suggest that both the NrCAM genotype and the NMDAR antagonist MK-801 affect decision making by modulating neural activation in multiple, relevant brain regions.

4. Discussion

Our current study investigated decision making in mice lacking NrCAM, a molecule with roles in vulnerability to substance abuse and neuropsychiatric disorders. Using a DD procedure developed in our laboratory [31,32], we evaluated the effects of NrCAM deficiency in comparison to WT mice under no stress (NS), acute stress (AS) and chronic unpredictable stress (CS) conditions. Although KO mice did not discount differently from their WT littermates under no-stress conditions, NrCAM KO mice were less impulsive than WT mice after AS (which showed decreased %LL choices and decreased %AUC, Figure 2). In contrast, a 21-day CS regimen increased discounting and impulsivity in both genotypes (Figure 3). Post-stress administration of GluR antagonists had differential effects on DD: AMPA receptor antagonist CNQX increased impulsive choice in WT controls but not in NrCAM KOs (Figure 4), without affecting omissions; in contrast, impulsive choice decreased in both genotypes after MK-801 administration in a dose-dependent manner (Figure 5), but, at the higher dose, drastically increased omissions (Figure 6). Analyses of neuronal activation (cFos+ counts, Figure 7) under SAL or a low dose of MK-801 revealed that neuronal activation was increased in NrCAM KO mice relative to WT controls in PrL and mOFC. Neuronal activation also increased under MK-801 in NrCAM KO mice relative to vehicle control in Acb-core and -shell. Neuronal activation decreased in NrCAM KO mice under MK-801 in vOFC.

4.1. Stress, Executive Dysfunction and Psychiatric Disorders

Environmental challenges—stressors—can initiate complex adaptive or maladaptive responses: acute (time-limited) stressors (threat or challenges to homeostasis) usually induce rapid adaptive processes, followed by restoration of homeostatic state, and normalization of behavioral and cognitive processes after the challenge has passed [40]; chronic stress induces maladaptive physiological, behavioral and cognitive processes associated with durable structural and functional alterations in brain areas relevant to learning, emotion and executive functions [26,41,42].

In humans, acute psychosocial stress [43], but not the threat of shock [44], increases DD. In rats, acute restraint stress does not affect DD but reduces the high effort/reward choice in cost/benefit decision making [45]. Studies have shown increased activity of interneurons after the exposure to acute stressors, which could affect in multiple ways the excitatory/inhibitory balance throughout the brain [42].

Chronic stress in humans [46] or chronic corticosterone exposure in rats [47] increase impulsive choice. Chronic stress can precipitate psychosis [48,49] or substance abuse [50,51] in vulnerable individuals. Prolonged corticosteroid and CRF signaling may promote abnormal behaviors through remodeling of dendritic spines and synapses in many brain regions, including glutamatergic pyramidal neurons in the prefrontal cortex [43,44], through alterations in GABA-ergic interneurons and changes in prefrontal inhibition [52,53] or through changes in monoamine tone in mesolimbocortical circuits [54–56].

In our DD study, we observed a smaller effect of acute social stress in NrCAM KO mice compared to WT, possibly related to a reduced number of perisomatic GABA-ergic synapses, and thus reduced inhibition, in the prefrontal cortices in the mutant mice [18,19]. Chronic stress increased impulsive choice in both genotypes. However, NrCAM KO mice showed lower discounting and increased neuronal activation (number of cFos positive neurons) in PrL and Acb-core and shell, particularly after administration of NMDAR antagonist MK-801. It is possible that the small dose of MK-801 preferentially affects activation of GABA-ergic interneurons in the prefrontal cortex and thus improves excitation–inhibition balance, previously affected by stress [57].

4.2. Effects of Glutamate Receptor Antagonists on DD After Stress

Previous studies investigating the role of AMPA GluRs in non-stressed rats in DD tasks have failed to reveal significant effects [58]. Our finding that systemic CNQX increased discounting and impulsivity in WT, but not in KO mice, without affecting omissions may be the result of previous exposure to chronic stress, which may affect spine and glutamatergic synapse density in the prefrontal cortex.

Ketamine blockade of NMDARs has been demonstrated to increase DD [59,60]. In regard to MK-801 effects on DD, previous studies in rats have found variable effects [58,61], possibly due to the use of different doses, reinforcement schedules or delay durations. Our study found that systemic MK-801 dose-dependently decreased discounting and impulsivity in both NrCAM KO and WT mice and drastically increased omissions at the highest (0.3 mg/kg) dose.

The significantly different behavioral effects of glutamatergic drugs CNQX and MK-801 in NrCAM KO versus WT mice in our current study may be due to the effects of NrCAM deficiency on the stability and number of GluRs at the synapse, since NrCAM binds SAP90/PSD-95 and SAP97, postsynaptic scaffold proteins [11,12]. The PSD-95 family of membrane-associated guanylate kinase (PSD-MAGUK) proteins are vital for trafficking, synaptic localization and stabilization of both NMDA- and AMPA receptors [62], processes required for both basal synaptic transmission and forms of synaptic plasticity. SAP97 is alone among the PSD-MAGUKs in interacting directly with AMPAR subunits, namely GluA1 [63]. Mice overexpressing SAP97 throughout development exhibit enhanced AMPAR and NMDAR currents, and faster NMDAR current decay kinetics at glutamatergic synapses [64], while SZ-associated SAP97 mutations increase glutamatergic synapse strength [13]. Interestingly, MAGUKs can partially compensate for each other in loss-of-function experiments [64]. However, the strength of glutamatergic synapses and the expression of MAGUKs and GluRs have not been characterized in NrCAM KO mice.

4.3. Neural Correlates of DD

Intertemporal decision making, such as DD, relies on the integration of magnitude of reward and delay to reward [38,39,65]. Through their heavy interconnections with the basal ganglia, hippocampus, amygdala and other subcortical structures, the prefrontal cortices (prelimbic, orbitofrontal) are central to executive function and decision making [38,65,66]. The PrL is involved in planning and flexible response selection to maximize reward [66,67]. In DD, temporary pharmacological inactivation of the rat PrL/IL using muscimol [68] or selective chemogenetic inactivation of cortico-accumbal projections [69] significantly increase choice impulsivity. Optogenetic inactivation of the PrL alters long-term decision strategy but not valuation on a spatial DD task [70]. In contrast, the ventromedial prefrontal/OFC and Acb [71,72] are essential for computing outcome value. In DD paradigms, temporary OFC inactivation increases impulsive choice [73]. Neurotoxic lesions of the mOFC increase, whereas lOFC lesions decrease, preference for the LL reward relative to sham-controls—a pattern that remains significant after all delays are removed [74]. OFC lesions may also affect delay sensitivity, since they shift the indifference point to the left in an adjusting delay paradigm [75,76].

The Acb core, which receives inputs from the PrL and OFC [77], has important roles in DD: lesions [72,78] or pharmacological inactivation [79,80] increase discounting. The Acb shell, receiving inputs from the infralimbic cortices (IL), is involved in augmenting self-control in economic valuations, as shown by a recent study that modulated glutamatergic synaptic strength between the IL and Acb shell [81]. A comparative analysis of cFos brain expression during choice between reinforcer delays versus choice between reinforcer magnitudes [37] found enhanced cFos expression in both the OFC and Acb during exposure

to the adjusting-delay schedule and enhanced Fos expression only in the OFC during the adjusting-magnitude schedule. Our study confirms that DD is associated with neuronal activation in prefrontal cortex and nucleus accumbens and suggests that increased activation in the PrL and Acb may be relevant to the lower discounting in NrCAM KO in comparison to WT, under a low dose of MK-801.

4.4. Limitations of the Study

Certain limitations suggest caution in interpreting the results of our study: First, we investigated male mice only, as done by Ishiguro and colleagues [20], who reported that in both humans and male mice gene alterations that reduce NrCAM expression also reduce vulnerability to addiction. Our lab has previously examined the effects of stress in male NrCAM KO mice [25]. While our current study adds to this literature by indicating the effect of stress and Glu drugs on decision making, it does leave open the question of what are these effects in female rodents. Second, drug testing was done in all animals, such that results may be affected by a putative cumulative effect of drugs. The following argues against this interpretation: Both MK-801 and CNQX have short half-lives (less than 2 h). As such, daily testing with various doses and delays resulted in differential effects of the drugs. Moreover, a week of wash-out between drug testing brought animals to baseline DD responses before the next drug manipulation was performed. Overall, these findings argue against cumulative drug effects. Third, drug testing was done in all animals after chronic stress. A long-lasting effect of stress, or putative interactions between the effects of stress and drugs, cannot be discounted, and was indeed expected (the goal of drug manipulations was to reduce the effects of chronic stress on DD). Finally, although in our study MK-801 modulated neuronal activation in brain regions relevant for intertemporal decision making, our results do not speak to specific processes relevant for DD and cannot discriminate between effects on different neuronal populations. More studies are needed to investigate whether MK-801 affects various neuronal populations involved in working memory, delay aversion, or reward valuation in both male and female rodents, under various stress conditions.

5. Conclusions

Here, we characterized delay discounting in male NrCAM KO mice, which do not develop conditioned place preference in response to cocaine or amphetamine [20], as well as the effects of AMPAR antagonist CNQX and NMDAR antagonist MK-801 on delay discounting. Although NrCAM KO mice did not discount differently from WTs under no-stress conditions, they were less affected (higher %LL choices and %AUC) after acute social stress relative to WTs. Chronic stress increased impulsivity (decreased %LL choices and %AUC) in both NrCAM KOs and WT controls. CNQX increased impulsive choice in WT controls but not in NrCAM KOs, without affecting omissions. Under a low dose of MK-801, NrCAM KO mice showed reduced discounting and increased neuronal activation (number of cFos positive neurons) in PrL, mOFC, Acb-shell and -core, and decreased neuronal activation in vOFC, areas thought to be part of executive and temporal processing circuits. Impulsive choice decreased in both genotypes after MK-801 administration in a dose-dependent manner, but, at the higher dose, omissions drastically increased in both genotypes. Our results show that targeting the NMDA receptor may be a valuable management strategy for disorders of impulsivity. Further studies should investigate how the behavioral differences observed in NrCAM KO mice are relevant to resilience to substance abuse and how NrCAM deficiency affects specific neuronal populations in the reward valuation and/or delay aversion circuits.

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Abbreviations

The following abbreviations are used in this manuscript:

Acb-core	Nucleus Accumbens Core
Acb-shell	Nucleus Accumbens Shell
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPA	AMPA Receptor
ANOVA	Analysis of Variance
AS	Acute Stress
AUC	Area Under the Normalized Discounting Curve
cFos	Protein encoded by the FOS gene
CNQX	6-cyano-7-nitroquinoxaline-2,3-dione
CS	Chronic Unpredictable Stress
DA	Dopaminergic
DD	Delay Discounting
Glu	Glutamatergic
GluRs	Glutamatergic Receptors
i.p.	intraperitoneal
KO	Knockout
LL	Larger—Later
LSD	Fisher’s Least Significant Difference Test
MK-801	a.k.a. Dizocilpine
mOFC	Medial Orbitofrontal Cortex
NMDA	N-methyl-D-aspartic acid
NMDAR	NMDA Receptor
NrCAM	Neuronal Cell Adhesion Molecule
NS	No Stress
OFC	Orbitofrontal Cortex
PCR	Polymerase Chain Reaction
PrL	Prelimbic Cortex
SS	Smaller—Sooner
SZ	Schizophrenia
vOFC	Ventral Orbitofrontal Cortex
WT	Wild-type Littermate Controls

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