NMDA Receptors in Noradrenergic Neurons Regulate Tonic Activity of Locus Coeruleus and Facilitate Attentional Set-Shifting in Mice

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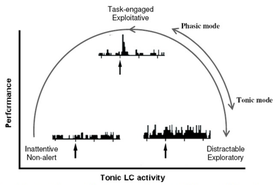
Locus coeruleus and exploration-exploitation trade-off

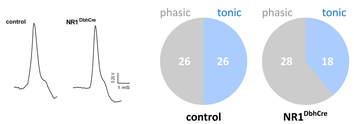


Adapted from Aston-Jones and Cohen (2005)

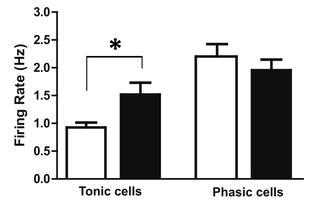
Balance between exploitation of known sources of rewards and exploration of environment that can lead to discovery of potentially better outcomes is regulated by activity of noradrenergic (NA) neurons in the locus coeruleus (LC).

Here, we used the *NR1*^{DbhCre} transgenic mouse strain to test the effects of NMDA receptor inactivation on *in vivo* LC activity and performance in tasks requiring selective responding in stable environment (the go-no/go discrimination task) and flexible responding in changing environment (the attentional set-shifting and two-armed bandit task).

Electrophysiological properties of LC neurons in NR1^{DbhCre} mice

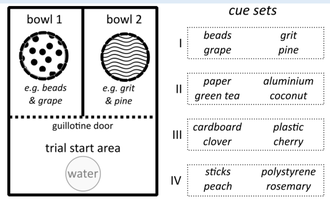


All LC neurons recorded from control and NR1^{DbhCre} mice showed a characteristic spike with a long-lasting (> 2 ms) and positive-negative waveform. LC neurons from both control and NR1^{DbhCre} mice displayed spontaneous burst firing (phasic activity).

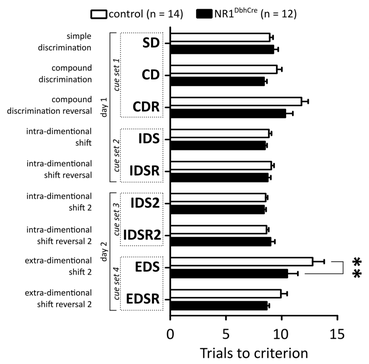


Firing rate of tonic neurons was significantly higher in NR1^{DbhCre} mice than in control mice (control: 0.92± 0.09. Hz, NR1^{DbhCre}: 1.51± 0.21 Hz).

Attentional set-shifting

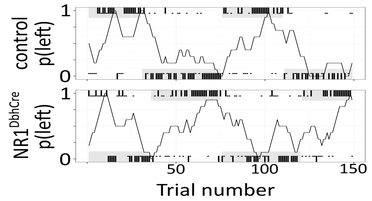


In this task animals were presented with two dimensions of cues, tactile and olfactory, that guided them to a hidden food pellet. The extended training was intended to cause formation of an attentional-set directed at the tactile cues.

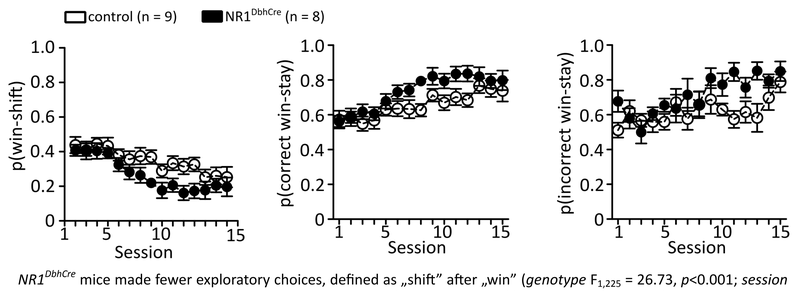


There was a significant genotype effect on performance across all task phases (*genotype* $F_{1,192}$ = 11.36, p<0.01; *test phase* $F_{8,192}$ = 10.18, p<0.001; *genotype* x *test phase* $F_{8,192}$ = 1.616, *n.s.*). In the EDS phase, where olfactory cues predicted the location of the reward, while tactile cues were no longer relevant, mutant mice required significantly fewer attempts than controls to reach criterion of 8 correct choices out of 10 consecutive trials, thus showed enhanced cognitive flexibility.

Two-armed bandit task

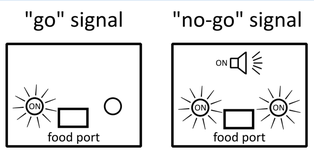


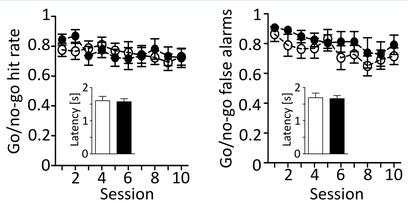
In this task animals had to distinguish between two choice options "correct" vs. "incorrect", differing in reward probabilities, 0.8 vs. 0.2, respectively. Trials were organized in blocks and reward probabilities associated with each choice option were constant within a block of trials but were reversed across blocks.



NR1^{DbhCre} mice made fewer exploratory choices, defined as „shift" after „win" (*genotype* $F_{1,225}$ = 26.73, p<0.001; *session* $F_{14,225}$ = 6.59 p<0.001; *genotype* x *session* $F_{14,225}$ = 0.64, *n.s.*) and were more likely to exploit previously rewarded choice. Exploitation, defined as „stay" after „win" was significant after selecting both, „correct" (*genotype* $F_{1,225}$ = 24.31, p<0.001; *session* $F_{14,225}$ = 6.73 p<0.001; *genotype* x *session* $F_{14,225}$ = 0.73, *n.s.*) and „incorrect" (*genotype* $F_{1,225}$ = 17.45, p<0.001; *session* $F_{14,225}$ = 3.03 p<0.001; *genotype* x *session* $F_{14,225}$ = 1.39, *n.s.*) choice options. This indicates, that mutation facilitated animals sensitivity to positive feedback and biased decision making strategy towards exploitation over exploration.

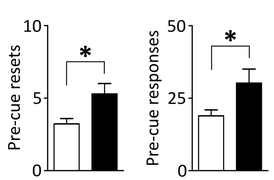
Go/no-go discrimination



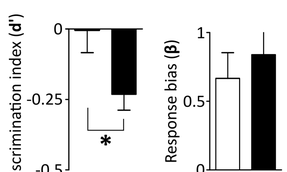


In this task animals had to discriminate between two signal types: „go" and „no-go".

Both, control and *NR1*^{DbhCre} mice exhibited high rate of correct responses to presentation of "go" signals ("hit rate") but had limited ability to refrain from responding to "no-go" signals ("false alarms").

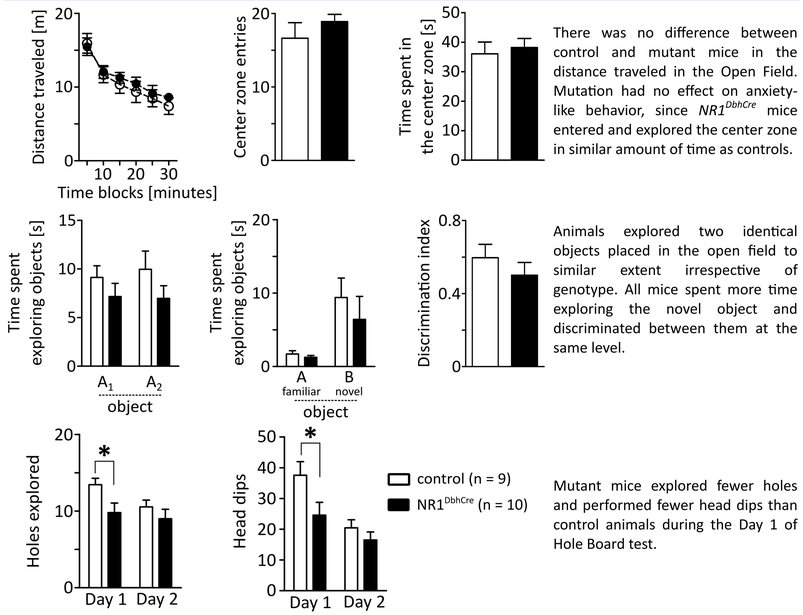


Mutant mice had significantly higher number of pre-cue period resets and responses, which could indicate increased impulsivity.



Mutant mice had decreased ability to discriminate between "go" and "no-go" signals (d' parameter). There was however no significant effect of the genotype on response bias (β parameter).

Exploratory behaviors in the Open Field



There was no difference between control and mutant mice in the distance traveled in the Open Field. Mutation had no effect on anxiety-like behavior, since *NR1*^{DbhCre} mice entered and explored the center zone in similar amount of time as controls.

Animals explored two identical objects placed in the open field to similar extent irrespective of genotype. All mice spent more time exploring the novel object and discriminated between them at the same level.

Mutant mice explored fewer holes and performed fewer head dips than control animals during the Day 1 of Hole Board test.

Inactivation of NMDA receptors caused an increase in spontaneous activity of tonically active neurons, without affecting activity of phasic (bursting) neurons in locus coeruleus.

Increased tonic activity was associated with higher impulsivity, decreased ability to discriminate signals in the go/no-go task and facilitated attentional set-shifting.

Loss of NMDA receptor-dependent signaling had no effect on locomotor activity, anxiety-like behavior or response to novelty, but decreased propensity for exploration.

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