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Effects of NMDA NR1-Subunit Deletion in the Medial Prefrontal Cortex on Spatial Reference and Working Memory

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BACKGROUND

- Glutamate N-methyl-D-aspartate (NMDA) receptor dysfunction may contribute to cognitive deficits associated with psychiatric illnesses including autism, affective disorders, and schizophrenia.

- The medial prefrontal cortex (mPFC) has been shown to play a role in executive functions including working memory (Kesner & Churchwell, 2011).

- Results of a recent study indicate that early postnatal NMDA NR1 deletion, mostly confined to excitatory neurons in prefrontal and sensory cortices, fails to affect spatial working memory (SWM) as assessed using a spontaneous alternation Y-maze task (Rompala et al., 2013).

- The present study examines the effects of NR1 deletion restricted to the adult mouse mPFC on a more cognitively demanding spatial reference memory (SRM) and SWM 6-arm radial maze (as described in Niewoehner et al., 2007).

MATERIALS AND METHODS

1. Floxed NR1 Gene
2. AAV-Cre or LacZ/SCSF Infusion Site

Fig 1. AAV-Cre or LacZ/SCSF was microinjected into the infralimbic mPFC of adult male floxed NR1 mice (NR1; JAX, Grin1<sup>1<sup>-<sup>-</sup></sup>); PN70-90).

Fig 2. In situ hybridization analysis revealed loss of NR1 mRNA in the mPFC of Cre-treated mice but not control mice.

Fig 3. Mice were habituated and trained on an automated 8-arm radial maze (Med Associates Inc.) adjusted to a 6-arm configuration. Noldus Ethovision XT was used for tracking and data collection. Extra-maze cues were provided to facilitate the use of spatial memory to complete the task.

SPATIAL REFERENCE MEMORY

- Begin in center; doors open
- Arm selection
- Return to center
- All doors close for 10 s delay
- Only unentered arms reopened; RM errors scored

Control RM Correct
Control RM Error
Nr1 Cre
Nr1 Control

Days (4 trials/day)

Fig 4. SRM trial sequence

Fig 5. NR1 deletions did not affect SRM acquisition

Days (4 trials/day)

SPATIAL WORKING MEMORY

- Begin in center; doors open
- Arm selection
- Return to center
- All doors close for 10 s delay
- All arms reopened; RM and WM errors scored

Control WM Correct
Control WM Error
Nr1 Cre
Nr1 Control

Days (4 trials/day)

Fig 6. SWM trial sequence

Fig 7. NR1 deletions did not affect maintenance of SRM

Days (4 trials/day)

Fig 8. NR1 deletions did not affect acquisition of SWM

Days (4 trials/day)

MANIPULATING COGNITIVE DEMAND

To alter cognitive load, mice were tested under conditions of:
- Shorter and longer delays between arm openings (5 & 30 s)
- Displacement of extra-maze cues achieved by a 45° maze rotation (see left)

Fig 9. SRM and SWM under increased cognitive load

Fig 10. Maze rotation increased SRM and SWM errors<sup>6</sup> and this effect was potentiated in NR1 deleted mice<sup>6</sup>

Days (4 trials/day)

Fig 11. In contrast, shorter and longer delays failed to affect SRM performance in either group

Days (4 trials/day)

Fig 12. Shorter and longer delays also failed to affect SWM in either group

DISCUSSION

- A regionally specific deletion of the NMDA NR1 subunit, induced by local infusion of AAV-Cre into the adult mouse infralimbic mPFC, did not affect acquisition of SRM or SWM, as assessed in a 6-arm radial maze task.

- These results extend earlier demonstrations that SWM assessed using a spontaneous alternation Y-maze task is unaffected by early postnatal NR1 deletions in excitatory neurons of the prefrontal and sensory cortices (Rompala et al., 2013).

- In the present study, increasing cognitive demand by rotating extramaze cues revealed potentiated SRM and SWM deficits following NR1 deletions in the infralimbic mPFC.

- The current data suggest that NR1 deletion in the infralimbic mPFC impairs the ability to modify behavior in the presence of changes in the environment.

- This deficit may reflect an inability for Cre mice to inhibit behavior, as the same mice displayed an increase in premature responding in a 5-choice serial reaction time task (Manning et al., 2014).

REFERENCES


Days (4 trials/day)