



The Effects of Cognitive Intervention in Adolescence on Behavioral Abnormalities in a Rat Model of Schizophrenia



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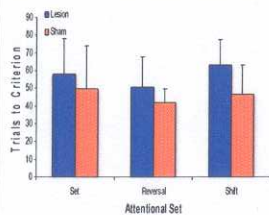
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Introduction

- Clinical data show that schizophrenic patients who achieve higher levels of education have better prognoses than patients who achieve lower levels of education (1).
- We chose to investigate the role of premonitory abstract learning on the severity of positive, negative, and cognitive symptoms after the onset of schizophrenia in an animal model.
- We used the Neonatal Ventral Hippocampal Lesion (NVHL) model of schizophrenia in rats, a robust model that causes abnormal behaviors reflecting all three major symptom sets of the disorder in adulthood (2).
- We predicted that cognitive stimulation during adolescence would lead to normalized behaviors in adult NVHL rats.

Methods

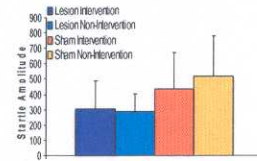
- Surgery:** Twenty male Sprague Dawley rats received stereotaxic surgery on post natal day (PD) 7 as described by Lipska (3). Briefly, 0.3 μ l ibotenic acid (an excitotoxin) was infused into the ventral hippocampus bilaterally, creating the lesions (N=12). Sham rats (N=8) also received surgery, but were administered artificial CSF instead of excitotoxin.
- Cognitive Intervention:** Four sham and seven lesioned rats were trained in an attentional-set shifting task in the T-maze during adolescence (PD 28-55 [4]). On day one of testing, rats were rewarded for turning against their turn biases. On day two, rats were rewarded for turning opposite the previous day's rule, which comprised the reversal period. The set shift occurred on the third day of testing, on which rats were rewarded for turning toward a previously ignored visual cue. Rats reached criterion when they correctly completed ten consecutive trials plus one additional probe trial.
- Adult Behavioral Tests:** Once rats reached adulthood (PD 56), we assessed a variety of the behaviors typically disrupted by NVHL lesions. These behaviors model the positive symptoms (locomotion in response to a novel environment [2], locomotion in response to the dopaminergic drug amphetamine [5]), negative symptoms (social interaction with a novel partner of the same lesion status [6]), and cognitive symptoms (prepulse inhibition of the acoustic startle response [7], working memory in the radial arm maze with all eight arms baited [8]) of schizophrenia.



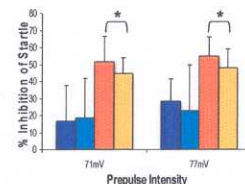
Intervention: There were no differences in trials to criterion between lesion and sham rats in the attentional-set shifting task.

Lesion x Set Condition: $F_{2,10} = .777, p = .475$

PPI: The startle response did not differ between groups, but was inhibited by the prepulse to a greater degree in sham rats than lesion rats.



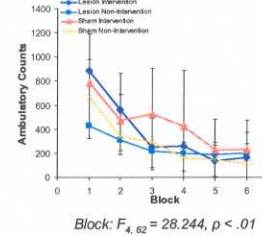
Lesion x Interv: $F_{1,16} = .315, p = .582$



Lesion: $F_{1,16} = 12.617, p = .003$

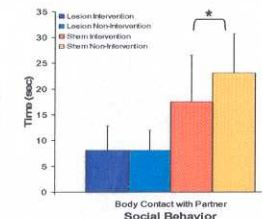
Novelty-Induced Locomotion:

Ambulation decreased for all groups over time, but did not differ between groups.



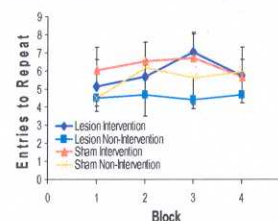
Block: $F_{4,62} = 28.244, p < .01$

Social Interaction: Lesion rats spent less time in body contact with their partners than sham rats.

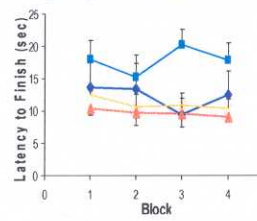


Lesion: $F_{1,16} = 18.09, p = .001$

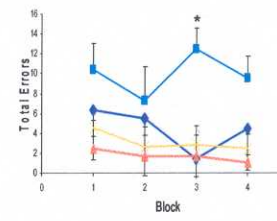
Working Memory in the Radial Arm Maze: Entries to repeat increased and latency to finish decreased for all groups across testing, but did not differ between groups. Lesion Non-Intervention rats, however, made more errors than the other three groups in Block 3.



Block: $F_{3,48} = 3.645, p = .019$



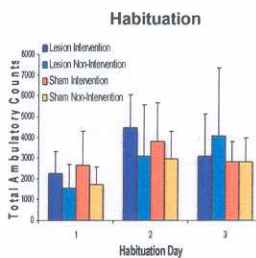
Block: $F_{3,48} = 31.568, p < .001$



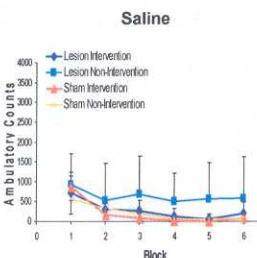
Lesion x Interv x Block: $F_{3,48} = 3.181, p = .032$

Drug-Induced Locomotion: Total ambulation increased for all animals across habituation days.

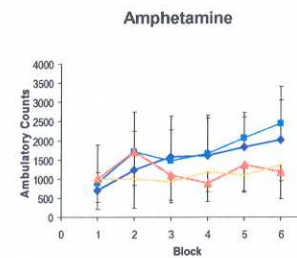
Ambulation in response to saline did not differ between groups. Lesioned animals exhibited increased locomotion in response to amphetamine compared to shams.



Day: $F_{2,32} = 9.901, p < .001$



Lesion x Interv x Block: $F_{3,50} = .707, p = .566$



Lesion x Block: $F_{4,57} = 3.529, p = .015$

Summary of Results

- There were no significant differences between sham and lesioned rats in the attentional-set shifting cognitive intervention.
- Prepulse Inhibition was impaired in lesioned rats.
- Locomotion in response to a novel environment did not differ according to lesion or intervention status.
- When paired with a novel partner, lesioned rats spent less time in body contact with that partner than sham rats.
- In the radial arm maze, lesioned rats that did not receive cognitive intervention made more errors and took longer to complete the task than the other groups.
- Total ambulation increased for all animals across the three habituation periods to the activity chambers, but did not differ among groups. Ambulation in response to amphetamine was elevated in lesioned rats compared to shams.

Conclusions

- In adolescence, the performance of the lesioned and sham lesioned animals did not differ, emphasizing the developmental nature of the NVHL model of schizophrenia in rats.
- The model was confirmed by the disruption of prepulse inhibition of the acoustic startle response in the lesioned rats, as well as the increased locomotor response to amphetamine in the lesioned rats compared to shams. Furthermore, lesioned rats appeared socially withdrawn compared to shams.
- In lesioned rats, the intervention selectively improved performance in the working memory task.
- Cognitive intervention in adolescence partially normalized behaviors modeling cognitive symptoms, but not positive or negative symptoms. This effect suggests that abstract learning prior to the onset of schizophrenia may protect specifically against the cognitive symptoms of the disorder, which often persist despite pharmacological treatment. Amelioration of the cognitive symptoms is essential in helping to make schizophrenic patients socially functional and independent. Prevention of such symptoms may vastly improve the course and severity of schizophrenia for many who suffer from it.

References

- Wieselgren, I.-M., & Lindstrom, L. H. (1996). A prospective 1-5 year outcome study in first-admitted and readmitted schizophrenic patients: relationship to heredity, premorbid adjustment, duration of disease and education level at index admission and neuroleptic treatment. *Acta Psychiatrica Scandinavica*, 93, 9-19.
- Lipska, B. K., & Weinberger, D. R. (2000). To model a psychiatric disorder in animals: Schizophrenia as a reality test. *Neuropsychopharmacology*, 23, 223-239.
- Lipska, B. K., & Weinberger, D. R. (1993). Delayed effects of neonatal hippocampal damage on haloperidol-induced catalepsy and amphetamine-induced stereotypic behaviors in the rat. *Developmental Brain Research*, 75, 213-222.
- Fiorasco, S. B., Magyar, O., Ghods-Sharif, S., Vexelman, C., & Tse, M. T. L. (2006). Multiple dopamine receptor subtypes in the medial prefrontal cortex of the rat regulate set-shifting. *Neuropsychopharmacology*, 31, 279-309.
- Wen, R.-Q., Giovanni, A., Kafis, S. H., & Corbett, R. (1996). Neonatal hippocampal lesions induced hyperresponsiveness to amphetamine: Behavioral and in vivo microdialysis studies. *Behavioural Brain Research*, 78, 211-223.
- Sams-Dodd, F., Lipska, B. K., & Weinberger, D. R. (1997). Neonatal lesions of the rat ventral hippocampus result in hyperlocomotion and deficits in social behaviour in adulthood. *Psychopharmacology*, 132, 303-310.
- Lipska, B. K., Swedlow, N. R., Geyer, M. A., Jeskiw, G. E., Braff, D. L., & Weinberger, D. R. (1995). Neonatal excitotoxic hippocampal damage in rats causes post-pubertal changes in prepulse inhibition of startle and its disruption by apomorphine. *Psychopharmacology*, 122, 35-43.
- Chambers, R. A., Moore, J., McCoy, J. P., & Levin, E. D. (1996). Cognitive effects of neonatal hippocampal lesions in a rat model of schizophrenia. *Neuropsychopharmacology*, 15, 587-594.

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