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Research report

Impairments in set-shifting but not reversal learning in the neonatal ventral hippocampal lesion model of schizophrenia: Further evidence for medial prefrontal deficits

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HIGHLIGHTS

- Neonatal ventral hippocampal lesion (NVHL) developmentally models schizophrenia.
- Operant set-shifting and reversal learning were examined in the NVHL rodent model.
- NVHL animals were impaired on prefrontal-dependent set-shifting, but not reversal.
- NVHL rats exhibited increased perseverative errors during set-shifting.
- Cognitive deficits in NVHL rats are primarily driven by medial prefrontal cortex.

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ABSTRACT

The executive function processes of set-shifting and reversal learning in rodents are mediated by the medial prefrontal cortex and the orbitofrontal cortex, respectively. Here, we investigated both set-shifting and reversal learning in a developmental animal model of schizophrenia, the neonatal ventral hippocampal lesion (NVHL) model. The NVHL manipulation is known to disrupt development of the medial prefrontal cortex, and to impair behaviors dependent on this area, but potential orbitofrontal abnormalities and reversal learning deficits are less well studied. Animals received excitotoxic lesions of the ventral hippocampus (NVHL) or a sham treatment during the first postnatal week, and all animals were subsequently tested in adulthood on either an operant set-shifting or an operant reversal task. Results indicated that NVHL animals were able to acquire a simple discrimination rule and exhibited normal reversal learning, but were impaired on a prefrontal-dependent set-shifting task. Furthermore, this set-shifting deficit was due to an increase in perseverative errors, which indicate difficulty suppressing a previously learned strategy and result from medial prefrontal insult. Together, these results confirm and extend the idea that cognitive impairments in the NVHL animal are primarily driven by medial prefrontal abnormalities, while the orbitofrontal cortex may remain relatively unaffected.

1. Introduction

Executive function refers to a series of high-level cognitive processes responsible for the direction, control, and maintenance of behavior, and is governed largely by the prefrontal cortex [1]. Two dissociable components of executive function are set-shifting, the shifting of a behavioral strategy from one stimulus dimension to another (extra-dimensional), and reversal learning, the shifting of a response strategy within a single stimulus dimension (intra-dimensional) [1]. The neurobiological bases of these two processes can be discriminated in normal humans and nonhuman primates, with the dorsolateral prefrontal cortex (DLPFC) governing set-shifting [2–5] and the orbitofrontal/ventromedial prefrontal cortex (OFC/VMPFC) mediating reversal learning [3,6–8]. Patients with schizophrenia perform poorly on executive function and behavioral flexibility tasks due to deficits in both extra-dimensional set-shifting and intra-dimensional reversal discriminations [9–14]. Frontal pathophysiology is likely to underlie these observed executive function deficits in schizophrenia, and there is indeed evidence for abnormal structure and function of both the DLPFC and the OFC/VMPFC in patients [2,15–17].

Frontal cortex subregions also differentially mediate set-shifting and reversal learning in rodents. Damage to the rodent medial prefrontal cortex (mPFC) leads to deficits in set-shifting, while failing to

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affect reversal learning [18–21]. Conversely, damage to the rodent OFC impairs reversal learning, while leaving set-shifting ability intact [19,22,23]. Cortical–subcortical circuits are also critical in regulating the different aspects of executive function [1]; for example, communication between the mPFC and the nucleus accumbens (NAcc) and mediodorsal thalamus is necessary for set-shifting [24], while orbitofrontal–striatal interactions mediate reversal learning [25].

The neonatal ventral hippocampal lesion (NVHL) is a heuristic neurodevelopmental animal model of schizophrenia in which early-life excitotoxic damage to the ventral hippocampus disturbs the development of the hippocampus and its efferent pathway to the mPFC [26–28]. As adults, NVHL animals show volume loss in the mPFC [29], and NVHL mPFC neurons express fewer dendritic spines [30–32] and are disinhibited and/or hyper-excitable [32–36]. Mature NVHL animals also exhibit a range of cognitive deficits indicative of prefrontal abnormalities [31,37–42]. With regard to behavioral flexibility, NVHL animals display prefrontal-dependent deficits analogous to those observed in patients with schizophrenia; they show impairments on extra-dimensional shifts [31], make more perseverative errors in a set-shifting task [37], and fail to adjust behavior when reward outcomes change [40]. The nature of NVHL-induced changes in reversal learning is unclear [31]; however, given the reversal deficits observed in patients with schizophrenia and the possibility that set-shifting deficits may partially stem from impairments in reversal learning [20], potential disruptions in reversal learning in the NVHL model merit further examination. Here, we used a recently developed automated set-shifting task [20] to independently examine set-shifting and reversal learning in adult NVHL animals.

2. Materials and methods

2.1. Subjects and surgery

Timed pregnant Sprague-Dawley females were obtained at embryonic day 16 from Charles River (Wilmington, MA), and were individually housed with free access to food and water on a 12 h:12 h light/dark cycle (lights on at 7:00 am). Between postnatal day (PD) 6 and 8, male pups (15–20 g) received either an excitotoxic lesion of the ventral hippocampus (NVHL; $n = 34$) or a sham procedure ($n = 35$), as previously described [37]. At approximately PD 28, animals were weaned and housed in pairs or triads matched by lesion status. Upon reaching adulthood (between PD 56 and 66), animals were single-housed, and were handled for at least 2 days before beginning food restriction and testing. These experiments were conducted in accordance with the US Public Health Service *Guide for the Care and Use of Laboratory Animals*, and all procedures were approved by the Institutional Animal Care and Use Committee at St. Mary's College of Maryland.

2.2. Operant shaping and pretraining

Following handling, animals were food-restricted to approximately 85% of their free-feeding weight over a period of at least two days. They then began training in operant procedures leading to either the set-shifting or reversal learning task [20]. Operant training began on PD 70 or later (range PD 70–77). All procedures were conducted in seven operant chambers (Med Associates, Inc., St. Albans, VT) enclosed in sound-attenuating cubicles. Each chamber featured two retractable levers on the front wall, with a panel light above each lever, and a food cup into which sucrose pellets (45 mg Noyes Precision Pellets, Research Diets, Inc., New Brunswick, NJ) were delivered. During all shaping, training and testing, the chamber house light (located on the top back wall) was illuminated.

Animals were randomly assigned to one of three testing groups: Set-Shifting (SS; NVHL $n = 15$, sham $n = 21$), Pre-Exposed Set-Shifting (PE; NVHL $n = 10$, sham $n = 8$), or Reversal Learning (RL; NVHL $n = 9$, sham $n = 6$). Animals in the SS group were tested on their ability to switch strategies when reinforcement contingencies are shifted from one stimulus dimension (e.g., visual) to another, previously ignored dimension (e.g., spatial position). Animals in the PE group were tested for the same ability, except that they were pre-exposed to the visual cues during pretraining (see Section 2.2.2), a manipulation which increases prefrontal demands [20]. Finally, RL animals were tested on the ability to adapt when the reinforcement contingency is switched within the same stimulus dimension (spatial position). Shaping and pretraining procedures were the same for each of the three groups, except where noted below.

2.2.1. Shaping

All animals were initially shaped to make lever responses on a fixed interval schedule which delivered one reinforcement for each response on either lever. Both levers remained extended throughout the session, and each reinforced response was followed by a 10-s timeout period during which reinforcement was not available. Animals completed the 30-min shaping task once daily until they reached a criterion of two consecutive days of at least 60 total reinforced lever presses.

2.2.2. Pretraining

In this stage, one lever was extended on each trial for a total of 90 trials with a fixed ITI of 20 s (beginning of one trial to beginning of the next trial). Animals were reinforced for responding on the extended lever within 10 s, after which the lever was retracted. Each pretraining session consisted of 45 trials of the left lever and 45 trials of the right lever, presented in a pseudorandom order such that no more than two consecutive trials extended the same lever. Animals completed the pretraining task once daily until a criterion of three consecutive days of five or fewer omissions was achieved. In PE (pre-exposed) animals only, the left and right panel lights were illuminated upon lever extension on each pretraining trial in an attempt to decrease the novelty and salience of the panel lights in the subsequent Cue task [20].

2.2.3. Side bias

The day after reaching criterion in the pretraining task, each animal's side bias was determined in a single session. The side bias program consisted of seven trials, each of which consisted of between 2 and 8 sub-trials separated by a fixed 20-s ITI. On each sub-trial, both levers were extended into the chamber for 10 s or until a response was made. On the first sub-trial, a response to either lever ("initial response") was reinforced and recorded. Subsequent responses on the same lever within a trial were not reinforced, but a single response on the opposite lever was reinforced and terminated the trial. Up to six subsequent responses on the same lever within a trial were allowed, after which a forced sub-trial was given where only the opposite lever was extended for 10 s. Side bias was defined as the side on which the majority of initial responses (on at least four out of seven trials) took place. However, if an animal disproportionately responded to one lever throughout the session (defined as greater than a 2:1 ratio), that side was recorded as the animal's side bias [20].

2.3. Operant testing

Following side bias determination, animals in the SS, PE, and RL groups each completed at least two days of testing, with at least one day (up to 150 trials) on each of two tasks (described below). The first task (completed in 1.03 ± 0.02 days, $M \pm$ SEM) was termed the "Set" task for all animals, and the second task (completed in