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Research report

# Impairment of the anterior thalamic head direction cell network following administration of the NMDA antagonist MK-801☆

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ABSTRACT

Head direction (HD) cells, found in the rodent Papez circuit, are thought to form the neural circuitry responsible for directional orientation. Because NMDA transmission has been implicated in spatial tasks requiring directional orientation, we sought to determine if the NMDA antagonist dizocilpine (MK-801) would disrupt the directional signal carried by the HD network. Anterior thalamic HD cells were isolated in female Long-Evans rats and initially monitored for baseline directional activity while the animals foraged in a familiar enclosure. The animals were then administered MK-801 at a dose of .05 mg/kg or 0.1 mg/kg, or isotonic saline, and cells were re-examined for changes in directional specificity and landmark control. While the cells showed no changes in directional specificity and landmark control following administration of saline or the lower dose of MK-801, the higher dose of MK-801 caused a dramatic attenuation of the directional signal, characterized by decreases in peak firing rates, signal to noise, and directional information content. While the greatly attenuated directional specificity of cells in the high dose condition usually remained stable relative to the landmarks within the recording enclosure, a few cells in this condition exhibited unstable preferred directions within and between recording sessions. Our results are discussed relative to the possibility that the findings explain the effects of MK-801 on the acquisition and performance of spatial tasks



## 1. Introduction

Investigations of the neurochemical substrates of navigational behavior have indicated an important role for the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor. Given the widely held view of the critical role of the hippocampal formation in spatial memory (e.g., Jarrard, 1993; Morris et al., 1982; Olton et al., 1978), and the likelihood that NMDA receptor-mediated plasticity may be a cellular mechanism of memory formation in the hippocampus (e.g., Bliss and Collingridge, 1993), it is not surprising that administration of NMDA antagonists have been shown to impair behavior in a variety of spatial memory paradigms including the Morris water maze (Ahlander et al.,1999; Davis et al., 1992; Morris et al., 1986; Morris et al., 2013; Steele and Morris, 1999), the radial arm maze (Butelman, 1989; Ward et al., 1990; Shapiro and O'Connor, 1992), and the active allothetic place avoidance task (Stuchlik and Vales, 2005).

While the issue of the true mechanism by which NMDA antagonists interfere with spatial behavior has been debated (e.g., Cain et al., 1996; Keith and Rudy, 1990), the role of the NMDA receptor in spatial memory acquisition continues to be the subject of investigation, some of the more recent studies finding that knockout mice lacking functional NMDA receptors in distinct subregions of the hippocampus show a pattern of spatial deficits dependent on which hippocampal regions are affected (Bannerman et al., 2008; Nakazawa et al., 2003; Place et al., 2012; Tsien et al., 1996).

Another critical discovery related to our understanding of the neurophysiology of spatial orientation is the identification of several classes of neurons that seem to encode correlates of spatial navigation. Place cells, recorded most often in the CA regions of the hippocampus, become active when the animal is within a particular area of an environment, the 'place field' of the recorded cell (O'Keefe and Dostrovsky, 1971). Head direction (HD) cells, found in regions of the thalamus and other limbic structures, become active when the animal orients its head in a particular direction of the horizontal plane, the 'preferred direction' of the recorded cell (Sharp et al., 2001; Taube, 1995). Grid cells, found in the dorsal caudal medial

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entorhinal cortex, discharge at multiple locations in an environment forming a repeating grid-like pattern that could be used to encode movement trajectory (Fyhn et al., 2004; Moser and Moser, 2008). Lastly, border cells of the medial entorhinal cortex become active when the animal approaches the walls or boundaries of the proximal recording environment (Solstad et al., 2008). These four cell types respond to many of the same cues that are thought to be important for navigation, such as environmental landmarks and signals of self-movement, and are thought to work together to form the brain network used for navigational behavior (Derdikman and Moser, 2010; McNaughton et al., 1996; O'Keefe and Nadel, 1978).

The present study examines the effect of NMDA blockade on the directional selective activity of anterior thalamic HD cells. In accordance with the view that the HD cell system plays an important role in the brain circuitry that mediates directional orientation, lesions of select anatomical components of the HD cell circuit cause deficits in spatial navigation tasks (Aggleton et al., 1996; Clark et al., 2013; Van Groen et al., 2002; Wilton et al., 2001) and on the directional signal carried by place cells (Calton et al., 2003). These findings, along with the previously described evidence that spatial behavior is also disrupted by NMDA antagonists brings up the possibility that the effects of NMDA blockade on spatial navigation may be mediated at least partly by a disrupted HD system. We sought to test this possibility by examining the basic directional-specific activity of anterior thalamic HD cells following administration of low or high doses of the noncompetitive NMDA antagonist dizocilpine (MK-801).

## 2. Method

### 2.1. Subjects and surgical procedures

A total of 23 female Long-Evans rats 3–6 months of age served as subjects. The rats were singly housed in Plexiglas cages and maintained on a 16/8 h light/dark cycle. Following recovery from surgery, water was available ad libitum but access to food was restricted as necessary to maintain body weights in the range of 85–90% of free-feeding weights. All care and treatment of the animals was approved by the CSUS Institutional Animal Care and Use Committee and adhered to the APA ethical principles of animal use.

Standard surgical procedures were used for electrode implantation. Animals were anesthetized using a cocktail containing ketamine (30 mg/kg), xylazene (6 mg/kg), and acepromazine (1 mg/kg). An incision was made in the scalp to expose the skull and holes were drilled for the electrode and six anchor screws. The electrode was placed slightly dorsal to the right anterior dorsal nucleus (ADN) of the thalamus based on coordinates (1.5 mm posterior to bregma, 1.4 mm lateral to bregma, 3.6 mm dorsal to the dura) provided by Paxinos and Watson (1998). After placement of the electrode, the assembly was secured to the skull using orthopedic cement, the wound was packed with antibiotic ointment, and the incision was sutured closed. Animals were given a minimum of seven days of postoperative recovery before experimental sessions began.

### 2.2. Recording apparatus

During recordings animals foraged for food pellets inside a wooden cylindrical enclosure (51 cm tall; 76 cm in diameter). The enclosure was painted gray, except for an approximate 100° arc of the inner wall that was painted white to provide a visible landmark. The enclosure was surrounded by a black curtain extending from the ceiling to the floor to hide visible landmarks outside of the enclosure. A white noise generator masked potential auditory cues and four lights arranged symmetrically on the ceiling provided illumination. A pellet dispenser mounted on the ceiling dropped food pellets (bio-serve; Frenchtown, NJ) at random intervals to encourage foraging behavior.

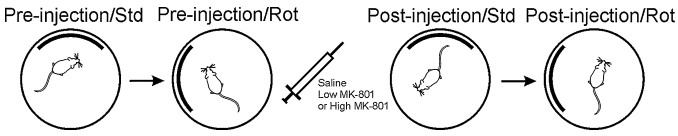


**Fig. 1.** Overview of experimental procedure.

A data acquisition system (Neuralynx; Bozeman, MT) was used to monitor and record electrical signals from the brain and also to track the head position of the animal by monitoring the position of red and blue LEDs attached to the headstage. The electrodes consisted of a bundle of 16 25-μm diameter insulated nichrome wires wrapped around the pins of a custom connector that was potted in acrylic. The recording headstage (Neuralynx HS-18; Bozeman, MT) was connected by a recording cable to a motorized commutator which relayed the signal to the data acquisition system located in an adjoining room. Spikes on individual wires were amplified (20–50 K), bandpass filtered (600–6000 Hz), and stored for offline sorting based on spike shape using custom software.

Daily screening for HD cells involved plugging the headstage onto the animal, placing the animal in the recording enclosure, and examining the electrical signal for direction-dependent cellular activity indicative of an isolated HD cell. If no HD cell was present, the electrode was lowered by 25–50 μm and the animal was returned to its homecage. If a HD cell was found the recording apparatus was prepared for data collection.

### 2.3. Drug exposures

During experimental sessions, animals were administered the noncompetitive NMDA antagonist dizocilpine (MK-801) or isotonic saline. The drug was obtained from Tocris Bioscience (Ellisville, MO), and dissolved in isotonic saline. All injections were administered intraperitoneally at a final injection volume of 2 mL/kg.

### 2.4. Experimental procedure

Fig. 1 illustrates the basic design of the experiment. Each HD cell was recorded over four 8-min recording sessions, during which the animal foraged for food pellets inside the recording enclosure. At the start of each session, the floor paper was changed to eliminate olfactory cues and the rat was given disorientation treatment by slowly it in a cardboard box for 30–60 s before placing the animal in the recording enclosure. All landmark manipulations occurred out of the view of the animal while the animal was within the cardboard box. In the first session (Pre-injection/Standard), the cell was recorded with the enclosure oriented so that the white landmark on the enclosure wall was centered in the north quadrant. Immediately following this was the Pre-injection/Rotated session, in which the cell was recorded following a 90 deg rotation of the enclosure so that the landmark was centered in the West quadrant. Following these baseline sessions, the animal was immediately given disorientation treatment, moved to another room, and injected with isotonic saline (Group Saline), MK-801 at a dose of 0.05 mg/kg (Group Low MK-801), or MK-801 at a dose of 0.1 mg/kg (Group High MK-801). Following the injection, the animal was returned to its homecage for 30 min to allow for drug absorption. When the experiment resumed the cell was recorded with the landmark oriented in the North position (the Post-injection/Standard session) and then again with the landmark oriented in the West position (the Post-injection/Rotated session).