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Dopamine depletion in either the dorsomedial or dorsolateral striatum impairs egocentric Cincinnati water maze performance while sparing allocentric Morris water maze learning

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ABSTRACT

Both egocentric route-based learning and spatial learning, as assessed by the Cincinnati water maze (CWM) and Morris water maze (MWM), respectively, are impaired following an 80% dopamine (DA) loss in the neostriatum after 6-hydroxydopamine (6-OHDA) administration in rats. The dorsolateral striatum (DLS) and the dorsomedial striatum (DMS) are implicated in different navigational learning types, namely the DLS is implicated in egocentric learning while the DMS is implicated in spatial learning. This experiment tested whether selective DA loss through 6-OHDA lesions in the DMS or DLS would impair one or both types of navigation. Both DLS and DMS DA loss significantly impaired route-based CWM learning, without affecting spatial or cued MWM performance. DLS 6-OHDA lesions produced a 75% DA loss in this region, with no changes in other monoamine levels in the DLS or DMS. DMS 6-OHDA lesions produced a 62% DA loss in this region, without affecting other monoamine levels in the DMS or DLS. The results indicate a role for DA in DLS and DMS regions in route-based egocentric but not spatial learning and memory. Spatial learning deficits may require more pervasive monoamine reductions within each region before deficits are exhibited. This is the first study to implicate DLS and DMS DA in route-based egocentric navigation.

1. Introduction

Impairments in navigational ability are present in numerous human disorders where they impair the quality of life and increase dependency (Aguirre & D'Esposito, 1999; Iaria, Palermo, Committeri, & Barton, 2009; Livingstone & Skelton, 2007; Sanders, Holtzer, Lipton, Hall, & Verghese, 2008; Weniger & Irle, 2006). Successful navigation requires complex interactions among multiple distinct, but parallel cognitive processes that can be subdivided into egocentric (self-oriented path integration and route-based) and allocentric (map-based) wayfinding. Route-based navigation involves a representation of space connected by "nodes" or choice points representing successive decision points in a grid or pathway (Aguirre & D'Esposito, 1999; Byrne, 1982). In the allocentric process, the navigator's spatial orientation to distal cues in the environment is fluid and represented in a common coordinate map system external to the navigator (Byrne, 1982; Garber, 2000).

Considerable behavioral, anatomical, and electrophysiological evidence suggests that the neostriatum is an important modulator in both egocentric and allocentric learning (Braun, Graham, Schaefer, Vorhees, & Williams, 2012; Cook & Kesner, 1988; Devan, McDonald, & White, 1999; Devan & White, 1999; Jog, Kubota, Connolly, Hillegaart, & Graybiel, 1999; McDonald & White, 1994; McGeorge & Faull, 1989; Mizumori, Puryear, & Martig, 2009; Mizumori, Yeshenko, Gill, & Davis, 2004; Packard, 2009; Packard, Hirsh, & White, 1989; Penner & Mizumori, 2012; Potegal, 1969, 1972; Ragozzino, Leutgeb, & Mizumori, 2001; Taube, 1998; Whishaw & Dunnett, 1985; Whishaw, Mittleman, Bunch, & Dunnett, 1987). The neostriatum is a heterogeneous structure with anatomical subregions for different functions. The dorsomedial striatum (DMS) receives primary inputs from multiple sensory and association areas, such as the hippocampus and medial prefrontal cortex, and while lesions in this area have widespread effects, they often produce impairments in allocentric learning (Colombo, Davis, & Volpe, 1989; Devan & White, 1999; Devan et al., 1999; McGeorge & Faull, 1989; Whishaw et al., 1987). For example, DMS lesions or

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DMS dopamine (DA) depletion result in allocentric learning and place strategy deficits in the Morris water maze (MWM) and T-maze, respectively (Devan & White, 1999; Devan et al., 1999; Lex, Sommer, & Hauber, 2011). Sensory and motor cortices have major projections to the dorsolateral striatum (DLS), that are associated with egocentric or response learning and stimulus–response habit formation (Devan & White, 1999; McGeorge & Faull, 1989; Packard & McGaugh, 1996; Palencia & Ragozzino, 2005; Reading, Dunnett, & Robbins, 1991; White, 1997; Yin & Knowlton, 2004; Yin & Knowlton, 2006; Yin, Knowlton, & Balleine, 2004, 2006). However, this heterogeneity of function within the neostriatum may not be fully preserved in regard to egocentric learning. Excitotoxic lesions of the DMS and DLS each result in a severe learning impairment in a 14-unit T-maze procedural learning task, implicating both regions in egocentric learning (Pistell et al., 2009).

The focus of the present experiments was to elucidate the regionally-specific role of neostriatal DA in egocentric and allocentric navigation. DA in the neostriatum influences both glutamatergic afferents and striatal medium spiny neuronal efferents that modulate striatal output (Penner & Mizumori, 2012). Previously, we showed that widespread neostriatal 6-hydroxydopamine (6-OHDA)-induced DA reduction impaired learning in both the allocentric MWM and route-based Cincinnati water maze (CWM) (Braun et al., 2012). While DMS DA has been implicated in allocentric T-maze learning strategy (Lex et al., 2011), it has not been tested for involvement in either route-based or allocentric navigation. Moreover, the role of DA in DLS-mediated route-based or allocentric navigation has yet to be tested. Accordingly, we tested groups of animals given selective 6-OHDA injections in either the DMS or DLS and evaluated them in the CWM and MWM, respectively (test order was examined previously (Broening, Morford, Inman-Wood, Fukumura, & Vorhees, 2001; Skelton et al., 2009) compared with sham-operated controls. Motivation and swimming ability were assessed to control for potential performance changes not associated with learning.

2. Methods

2.1. Animals

Adult male Sprague–Dawley CD IGS rats (225–250 g at the time of arrival) were purchased from Charles River Laboratories, Raleigh, NC (strain 001). Animals were pair-housed in polypropionate cages (46 × 24 × 20 cm) containing woodchip bedding for at least a 1-week acclimation period prior to surgery. Animals had free access to food and water, were housed in an environmentally controlled vivarium (21 ± 1 °C), and were on a 14 h light–dark cycle (lights on at 600 h). All procedures were in compliance with the Institutional Animal Care and Use Committee and the vivarium is fully accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care.

2.2. Surgery

Rats were anesthetized with 2–4% isoflurane (IsoThesia; Butler Animal Health Supply, Dublin, OH) with continuous administration via a nose cone throughout surgery. Rats were placed in a motorized, computer-controlled stereotaxic apparatus (StereoDrive, Stoelting Co., Wood Dale, IL), and were given bilateral injections of 6-OHDA (Sigma, St. Louis, MO) using a 26 gauge 10 μl Hamilton Gastight syringe (Reno, NV). Coordinates were based on the Paxinos and Watson brain atlas (Paxinos, Watson, Pennisi, & Topple, 1985). For the DLS lesions, a volume of 3 μl [4 μg/μl 6-OHDA in 0.2% ascorbic acid saline solution] was injected over 9 min (from bregma: AP: +0.2 mm; ML: ±3.5 mm; from skull: DV: −4.8 mm), with the needle left in place for 1 min following injection. For the DMS lesions, a volume of 0.4 μl [30 μg/μl] was injected in each site over 4 min (from bregma: AP: +1.0 mm; ML: ±1.7 mm; DV: −5.0 mm; and AP: −0.4 mm; ML: ±2.6 mm; DV: −4.5 mm), with the needle left in place for 5 min following completion of injection. Control animals (SHAM) received an identical amount of saline in 0.2% ascorbic acid vehicle (VEH) using the same procedure for its particular group. Following surgery, animals were given 0.1 ml buprenorphine hydrochloride to minimize pain. Animals were allowed to recover for 2 weeks before the beginning of testing. The number of animals represented in each group is given in the figure legends.

2.3. Behavioral testing

2.3.1. Straight channel

One day prior to CWM testing, animals were tested for swimming ability in a 244 cm long × 15 cm wide × 51 cm high water filled (38 cm deep) straight channel for 4 consecutive trials with a maximum time limit of 2 min/trial (Herring, Schaefer, Gudelsky, Vorhees, & Williams, 2008; Vorhees et al., 2008). Straight channel swimming served three functions: (a) to acclimate animals to swimming, (b) to teach that escape was possible by climbing on the submerged platform at the opposite end of the channel, and (c) to determine if animals had comparable swimming ability.

2.3.2. Cincinnati water maze

The CWM is a nine-unit multiple T water maze (21 ± 1 °C) as described previously (Vorhees, 1987; Vorhees, Weisenburger, Acuff-Smith, & Minck, 1991; Vorhees et al., 2008). Animals had to locate a submerged escape platform; the room was illuminated with infrared lighting in order to eliminate visual cues; a video camera was mounted above the maze sensitive to light in the infrared range and fed to a monitor in another room. Two trials/day (5 min limit/trial) were given. If an animal failed to find the escape within 5 min on trial-1 of each day, there was at least a 5 min intertrial interval (ITI) before trial-2. If they found the escape on trial-1 in less than 5 min, trial-2 was given immediately. Animals reaching the time limit were removed from the maze from wherever they were when the time limit was reached. Latency to escape and number of errors (defined as head and shoulder entry in a stem or arm of a T or reentry into the start channel) were recorded. To correct for animals that stopped searching, they were given an error score equal to the number of errors +1 made by the animal that found the escape and made the most errors in <5 min. Animals that never found the platform were removed from analysis. Data for the CWM were analyzed in 2-day (4 trials) blocks similar to the 4-trial blocks used to analyze MWM data.

2.3.3. Morris water maze hidden platform

To test spatial navigational learning, MWM hidden platform testing began the day following CWM completion (Morris, 1981). Animals were placed in a 244 cm diameter tank of water (21 ± 1 °C) and were required to find a submerged platform (10 cm diameter) in a stationary position with pseudo-randomized, balanced cardinal and ordinal start positions. For 6 days, rats were given 4 trials/day with a 2 min trial limit and an ITI of 15 s (on the platform). If a rat failed to find the platform within the time limit, it was placed on the platform. On the 7th day, a 30 s probe trial was given from a novel start position with the platform removed. Data were collected using video tracking software (AnyMaze, Stoelting Co., Wood Dale, IL).

2.3.4. Morris water maze cued

Cued MWM testing began the day following the hidden platform testing and was conducted over two days. A yellow plastic ball was