

THE MEDIAL FRONTAL CORTEX CONTRIBUTES TO BUT DOES NOT ORGANIZE RAT EXPLORATORY BEHAVIOR

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Abstract—Animals use multiple strategies to maintain spatial orientation. Dead reckoning is a form of spatial navigation that depends on self-movement cue processing. During dead reckoning, the generation of self-movement cues from a starting position to an animal's current position allow for the estimation of direction and distance to the position movement originated. A network of brain structures has been implicated in dead reckoning. Recent work has provided evidence that the medial frontal cortex may contribute to dead reckoning in this network of brain structures. The current study investigated the organization of rat exploratory behavior subsequent to medial frontal cortex aspiration lesions under light and dark conditions. Disruptions in exploratory behavior associated with medial frontal lesions were consistent with impaired motor coordination, response inhibition, or egocentric reference frame. These processes are necessary for spatial orientation; however, they are not sufficient for self-movement cue processing. Therefore it is possible that the medial frontal cortex provides processing resources that support dead reckoning in other brain structures but does not of itself compute the kinematic details of dead reckoning. © 2016 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: path integration, spatial orientation, dead reckoning, translational neuroscience, medial frontal, *Rattus norvegicus*.

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Abbreviations: ANOVA, analysis of variance; cc, corpus callosum; Cg1, cingulate cortex; fmi, forceps minor; gcc, genu of the corpus callosum.

INTRODUCTION

Many neurological disorders are associated with disruptions in spatial orientation (Aguirre and D'Esposito, 1999; Tetewsky and Duffy, 1999; O'Brien et al., 2001). For example, patients that have experienced stroke often exhibit impairments in spatial orientation (Meerwaldt and Van Harskamp, 1982). Specifically, patients with damage to frontal cortical areas have been reported to display lateralized impairments in their ability to process egocentric spatial information, known as spatial neglect (Mesulam, 1990; Heilman et al., 1993). One spatial orientation strategy, dead reckoning, involves the online processing of self-movement cues (i.e., vestibular, proprioception, efferent copies of action commands) to estimate direction and distance to the point that movement originated (Gallistel, 1990). Work on humans (Worsley et al., 2001; Philbeck et al., 2004; Shrager et al., 2008; Kim et al., 2013) and rats (Maaswinkel et al., 1999; Wallace and Whishaw, 2003; Winter et al., 2013; Kim et al., 2013; however, see Alyan and McNaughton, 1999) has provided support for these cues being processed by a network of brain structures that include the hippocampal formation and hippocampal cholinergic (Martin and Wallace, 2007) and GABAergic (Köppen et al., 2013) projections that originate in the medial septum. In addition, several other cortical areas contribute to dead reckoning including the entorhinal (Parron and Save, 2004; Winter et al., 2013; Van Cauter et al., 2012), parietal (Parron and Save, 2004), and retrosplenial (Cooper et al., 2001; Whishaw et al., 2001) cortical areas.

Imaging work has provided support for expanding this network of structures to include the medial frontal cortex (Wolbers et al., 2007). Human participants were given a dead reckoning navigation task during an fMRI scan that required participants to indicate the direction of the start location after traveling a route that involved a change in heading. Hippocampal and medial frontal cortex activity was associated with performance on this virtual dead reckoning task. In contrast, previous rat work has demonstrated that medial frontal cortex lesions spare performance on a task that depends on self-movement cue processing (Whishaw et al., 2001a). In the rat study, the animals were given many trials in which they carried food to a home base and it is possible that the reinforcement contingencies of the task may have allowed the animals to compensate for impairments in self-movement recognition. The goal of the current study, therefore, is to examine the contribution of the medial frontal cortex in a dead

reckoning task that involves the computation of spatial position from spontaneous exploratory movement similar to that given to human participants in the virtual dead reckoning task.

Rat exploratory behavior is organized at several levels. At a macro level, rats introduced to a novel environment will first establish a home base or a location associated with stopping behavior, long dwell times, and grooming behavior (Whishaw et al., 1983; Eilam and Golani, 1989; Golani et al., 1993; Clark et al., 2005). At a micro level, rats organize their movements around the home base location (Eilam and Golani, 1989; Drai et al., 2000). Movements away from the home base are typically slow and more circuitous relative to movement sequences directed back to the home base (Tchernichovski et al., 1998). Returns to the home base are characterized by a consistent temporal pacing of moment-to-moment speeds that are scaled to the distance between the rats' current location and their home base (Wallace et al., 2006). This organization of the exploratory trip into outward and homeward segments has been observed independent of environmental cue availability—consistent with self-movement cue processing guiding exploratory behavior. Specifically, self-movement cues generated after departing the home base are processed within the temporal context they occur to update an online representation of the current direction and distance to the home base (Barlow, 1964; Mittelstaedt and Mittelstaedt, 1980; Gallistel, 1990; Biegler, 2000; Etienne and Jeffery, 2004; Wallace et al., 2008). Research has shown that damage to the hippocampus (Wallace et al., 2002; Wallace and Whishaw, 2003) or related structures (Martin et al., 2007; Winter et al., 2013) disrupts the direction and distance component of the homeward segment. Therefore, the current study examines the effects of damage, localized to structures within the medial frontal cortex, on the organization of exploratory behavior.

EXPERIMENTAL PROCEDURES

Animals

Twelve adult naïve female Long–Evans rats (University of Lethbridge vivarium), weighing 250–300 g, were housed in groups of two in Plexiglas cages. The colony room was maintained at 20–21 °C with a 12-h/12-h light/dark cycle. Rats were provided ad lib access to food and water in their home cages throughout the duration of the experiment.

Apparatus

The apparatus was a circular table (2.50 m in diameter) without walls mounted on ball bearings that permitted it to be rotated. The surface of the table was 0.64 m above the floor. The home base was a small, opaque Plexiglas box (0.20 m × 0.29 m × 0.22 m) with a circular hole (0.11 m) cut on one side. The home base was placed at the edge of the table such that the circular hole faced the center of the table. For each rat, the location of the home base remained stable across all

exploration sessions; however, the table was rotated between rats and wiped down with ammonia cleaning solution after testing each rat.

A night vision camera was positioned perpendicular to the table in a light proof room; the room was completely dark when the lights were turned off. The camera was connected to a video recorder. The experimenter used night vision goggles to place the rats on the table under dark testing conditions.

Surgery

Rats were anesthetized with a mixture of isoflurane and oxygen during surgery. Medial frontal lesions ($n = 6$) involved making an approximately 2-mm wide trephine on both sides of the midline; thereby leaving a 2-mm wide piece of skull covering the sagittal sinus. The medial frontal cortex was removed by aspirating the overlying gray matter of the cortex. The control animals ($n = 6$) were also anesthetized and received an incision. Subsequent to the surgery, all rats were given two weeks to recover prior to testing.

Procedure

All testing was conducted during the light phase of rats' 12-h light/dark cycle. Each rat was individually transported from the colony to the testing room in an opaque Plexiglas cage covered with a cloth to limit rats' access to visual stimuli. During transportation from the colony room to the testing room, the cage was rotated a varying number of times and a different path was taken to the testing room each day. Upon entering the testing room the rat was placed in the home base and the researcher sat in a designated chair in the southeast corner of the testing room. All rats were given 50 min to explore the table. All rats were initially tested under light conditions for three days prior to being tested under dark conditions for three days. Previous work has shown that changes in the sequence of testing conditions do not appear to influence control rat performance (i.e., light first: Whishaw et al., 2001; Wallace and Whishaw, 2003; dark first: Wallace et al., 2006).

Analysis

Exploratory behavior. EthoVision (Noldus, Leesburg, VA, USA) was used to quantify two characteristics of exploratory behavior from the day the most exploratory trips were taken for light and dark conditions. For a majority of the rats, this occurred on their first days of light and dark exposure. First, the Brown's score (Brown and Whishaw, 2000) was used to assess establishment of a home base in the refuge. The Brown's score is calculated by finding the average difference in the percent time spent in the target quadrant (Q^t) relative to the other three quadrants (Q^1, Q^2, Q^3) as follows: $[(Q^t - Q^1) + (Q^t - Q^2) + (Q^t - Q^3)]/3$. Values may range from -33 (avoidance of the quadrant with the refuge) to 100 (not spending time outside of the quadrant with the refuge). Next, the total

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