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Evaluating the role of frontal cortical structures in self-movement cue processing during spontaneous exploration

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ABSTRACT (100-200 WORDS):

Animals use environmental (visual, auditory, olfactory) and self-movement (vestibular, proprioception, optic flow) cues to maintain spatial orientation (Gallistel, 1990). Disruptions in spatial orientation are frequently associated with acute (stroke) and chronic (Dementia of the Alzheimer's Type) neurological disorders; however, the nature of the processing deficit continues to be debated. Previous work has demonstrated that rats use self-movement cues to organize their exploratory behavior (Wallace, et al., 2006). Recent work has suggested a role for the human prefrontal cortex structures in self-movement cue processing related to dead reckoning or path integration (Wolbers, et al., 2007) The current study uses the organization of rat exploratory behavior under dark conditions to investigate the role of specific areas within the frontal cortex in self-movement cue processing.

Abstract

Animals use environmental (visual, auditory, olfactory) and self-movement (vestibular, proprioception, optic flow) cues to maintain spatial orientation (Gallistel, 1990). Disruptions in spatial orientation are frequently associated with acute (stroke) and chronic (Dementia of the Alzheimer's Type) neurological disorders; however, the nature of the processing deficit continues to be debated. Previous work has demonstrated that rats use self-movement cues to organize their exploratory behavior (Wallace, et al., 2006). Recent work has suggested a role for the human prefrontal cortex structures in self-movement cue processing related to dead reckoning or path integration (Wolbers, et al., 2007) The current study of archival data uses the organization of rat exploratory behavior under dark conditions to investigate the role of specific areas within the frontal cortex in self-movement cue processing.

Introduction

Both animals and humans alike use spatial orientation to navigate within their environments on a regular basis. This process relies on the successful interpretation of environmental (olfactory, auditory, visual) and self-movement (proprioception, vestibular, optic flow) cues (Gallistel, 1990), as disruptions of their interpretation can lead to wandering behavior. Such disruptions are frequently associated with acute and chronic neurological disorders, such as stroke and Dementia of the Alzheimer's Type respectively. Although occurrences of wandering have been linked to such cognitive decline (Rabins et al. 1982; Logsdon et al. 1998), the full extent of the processing deficit, including in what regard specific regions of the brain contribute to it, remains unclear or undetermined. However, many studies have implicated the prefrontal cortex in the disruption of cue processing and spatial navigation. Previously, the medial prefrontal cortex has been associated with working spatial memory through self-movement cue processing related to path integration (Wolbers et al. 2007), while studies of the orbital frontal cortex have demonstrated an inhibition and impulsion (particularly olfactory and autonomic) role of this region of the cortex (Kolb 1984). With such broad views and findings on contributions of the prefrontal cortex to spatial orientation, more distinct roles of the medial and orbital regions of the prefrontal cortex remain to be determined.

Rat exploration has been used in preceding studies to examine exploratory behavior and spatial navigation of rats in an environment (Wallace et al. 2006). This exploration on a circular table with a refuge provides macro and micro level information of the animals' spatial orientation. Macro-level characteristics include the rats' establishment of a home base at the refuge, as well as the organization of their movements around the refuge location (Eilam and Golani 1989; Whishaw et al. 1983), whereas micro-level characteristics include the use of multiple trips to explore, a return to the home base, and the circuity of the path during the return to the refuge (Wallace et al. 2006). Brown score analysis and averages of distance travelled provide macroscopic comparisons of the amount of time spent in the quadrant with the home base and the distances travelled by individual or groups of rats. For the micro-level analysis, the exploratory movement is divided into individual trips during which the animal leaves the home base and explores

the apparatus. A trip, or tour, consists of a random series of movement and stops within the environment, as well as a continuous (and usually direct) return to the home base (Wallace et al. 2006). The distinction creates multiple trips within each individual data set, and differentiates between an essentially random outward segment and a directed homeward segment to the refuge. Analysis of the homeward portion demonstrates the ability of the animals to use environmental and self-movement cues during the return to the home base. However, under dark conditions, the animals (and humans) are limited to self-movement cues for path integration or dead reckoning during the homeward segment. This provides a comparative model for how specific regions of the brain contribute to self-movement cue processing. Infrared technology can be used for transporting and video recording the rats (and humans) as previous work has demonstrated that rats cannot detect infrared wavelengths (Neitz and Jacobs 1986).

With previous findings indicating such variant roles of the medial and orbital prefrontal cortex, distinction in their roles in self-movement cue processing is expected as well. As the orbital prefrontal cortex seems to function more with inhibition and autonomic impulses, no significant deficits are expected in an orbital prefrontal lesion rat model. However, studies on the medial prefrontal cortex indicate that, through its role in spatial memory and navigation, it may contain an important functioning component of the self-movement cue processing required for spatial navigation via path integration.

Methods

Animals

Eighteen female Long Evans rats from the University of Lethbridge vivarium were used for this study. All rats were housed in groups of two or three within the colony room that was maintained at 20-21°C and a 12 hour light/12 hour dark cycle. The animals were also allowed ad lib access to food in their cages in the colony.

Surgery

All rats were deeply anesthetized prior to the surgery. The medial group (n=6) and orbital group (n=6) received localized damage to the medial prefrontal cortex and orbital prefrontal cortex respectively via aspiration. Control animals (n=6) were also anesthetized, but received only a cranial incision.

Apparatus

The apparatus used was a circular flat-top table with a 250cm diameter that was raised off of the ground and painted white. This table was located in a lightproof room to allow for testing under dark conditions (so that animals were limited to self-movement cues), and a video camera attached to the ceiling along with infrared cameras was used to record the rats' movements. A small opaque plastic box (20cm x 29cm x 22cm) with a circular hole (12 cm in diameter) was positioned on the outer perimeter of the table to function as the home base and refuge for the rats.

Procedure

Following surgery and a two-week recovery period, each rat was given one-hour sessions on the apparatus during which they were free to explore the table at random under dark conditions. Three of the one-hour sessions were conducted for each rat over the course of three weeks so that all rats received one session before any rat receiving its second session, and that all had their second session before any animal received its third. Prior to being gently placed into the refuge for the one-hour session, each rat was individually removed from the colony and placed in a transport cage. The experimenter then walked a circuitous path in the dark from the colony to the lightproof testing room to minimize the rats' ability to learn the location of the apparatus relative to the colony. Using infrared goggles, the experimenter was able to place the rats into the refuge located on the periphery of the apparatus. The one-hour session was recorded by a VHS recorder connected to the video camera on the ceiling of the testing room. At the end of each session, the experimenter removed the rat from the apparatus, returned it in the dark via a circuitous path to the colony, and cleaned the table with a disinfectant spray. At the conclusion of the experiment, animals were perfused first with phosphate-buffered saline, then 4.0% paraformaldehyde. The brains were then removed and soaked in 30% sucrose and distilled water, frozen, sliced into 40 micron coronal sections with a cryostat, and stained with Cresyl violet.

Data Analysis

The archival data from 2002 was used organized and used for this analysis.

Macro Level

Brown scores (Brown and Whishaw, 2000) and total distance travelled were used to evaluate macro-scale movement of the animals. The Brown score analysis determined how much time the rats spent in the quadrant of the table that contained the home base relative to the other quadrants as this ensures home base establishment. The values are calculated by dividing the table into four equal quadrants and determining the percentage of time spent in each. The time spent in the quadrant with the home base was then subtracted by the total percentage of time spent in the other three quadrants and was then divided by three. The amount of time spent in each quadrant was obtained by running the data from one day of dark exploration per rat through the EthoVision Noldus system. The quadrants were assigned in this system, after which it tracked the rats' movements and location on the table for forty minutes of the sixty minute session.

The total distance travelled for each animal was also calculated by this system, using the x- and y-coordinates that it generated for each data session.

Micro Level

Subsequent to refuge establishment, the first five trips of the rat leaving the home base and exploring the table were captured and digitized with the Peak motion capture system.

The data from these trips was then gathered as the rats' location on the table, as well as the moment-to-moment speed of the animal. From this information, each trip made was divided into an outward and homeward segment with a recorded linear velocity of <0.1m/s defined as a stop made by the animal. The outward segment consisted of all of the rats' movements from leaving the home base to the last stop, while the homeward portion consisted of the rats' path from the last stop until it reached the home base. Both outward and homeward segments were analyzed for overall peak speed, and path circuity. (Path circuity refers to the directness of the segments and was calculated by dividing the distance between the start and end of the segment by the total distance travelled in the segment. The closer the value is to 1.0, the more direct an animal's path was.) One-way and repeated measure ANOVAs were used to determine any statistical differences between groups.

Results

Histology

Photomicrographs of cresyl violet staining of an animal from each group (control, medial, orbital) show the maximal damage anterior to posterior of the medial and orbital lesions, and that there was no damage to the control group. Maximal medial lesion extended anterior to posterior 4.7mm – 0.48mm relative to Bregma and may have also affected parts of the cingulate cortex and indusium griseum. Maximal orbital lesion damage extended anterior to posterior 4.2mm – -0.4mm relative to Bregma and may have also affected portions of the agranular insular cortex, parietal cortex, dysgranular insular cortex, striatum, and adrenaline cells.

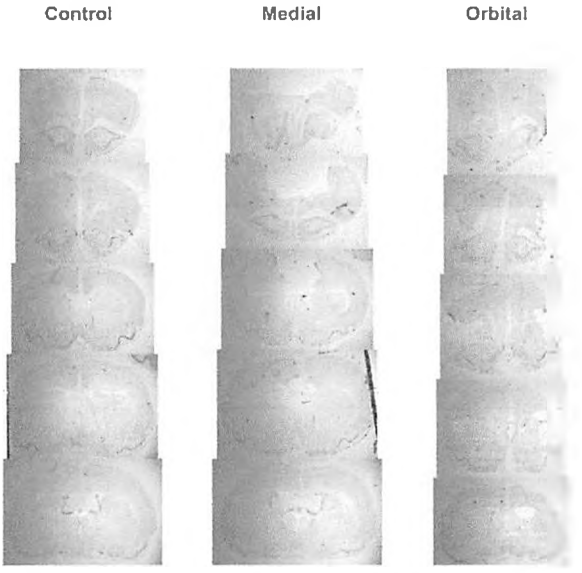

Figure 1: Photomicrographs are provided for a representative control, medial frontal, and orbital frontal rat.

Behavior

Macro Level Analysis

To investigate that the two types of lesions did not disrupt the rats' natural homing behavior, exploration, and movement, a Brown score analysis (Fig 2) and total distance travelled (Fig 2) were compared between groups. The Brown score analysis determined how much time the rats spent in the quadrant of the table that contained the home base, and the ANOVA conducted on the Brown score failed to reveal a significant effect of group [$F(2,15) = 0.146$, $p = 0.866$]. The ANOVA of the distance travelled failed to show significant differences as well [$F(2,15) = 0.606$, $p = 0.558$], and demonstrated that the lesions did not make the animals hyperactive, sedentary, etc. Topographic and kinematic representations of demonstrative trips (Fig 3) from each group were also included. Macro-level analysis revealed no significant differences between home base establishment or total distance travelled by the groups.

Micro Level Analysis

Peak speed (Fig 4) and path circuity (Fig 5) were compared for the outward and homeward segments of each group through an ANOVA conducted for each of these values. In these analyses, outliers for each trip of more than two standard deviations away from the mean were disregarded.

The ANOVA conducted on peak speed revealed a significant main effect of segment [$F(1,15) = 5.807$, $p<0.05$]; however, neither the main effect of group [$F(2,15) = 0.58$, $p = 0.572$], nor the Group by Segment interaction [$F(2,15) = 0.63$, $p = 0.546$] were significant. This indicates that there was a difference of outward and homeward peak speed, but not within either group.

The ANOVA conducted on path circuity (distance ratio) revealed a significant main effect of outward and homeward segments [$F(1,15) = 102.306$, $p<0.05$] and an effect of Group by Segment interaction [$F(2,15) = 4.183$, $p<0.05$]. The main effect of group [$F(2,15) = 0.083$, $p = 0.921$] showed no differences. Post hoc analysis via a one-way ANOVA of the group by group interaction showed a significant difference in the homeward path circuity [$F(2,15) = 5.139$, $p<0.05$], but not the outward [$F(2,15) = 1.384$, $p = 0.281$] . This demonstrated that there was a statistically significant difference between the path circuity of the control and medial groups, the orbital and medial groups, but no difference between the control and orbital groups, and suggests that the medial animals struggled to interpret the self-movement cues needed to return to the refuge under dark conditions.

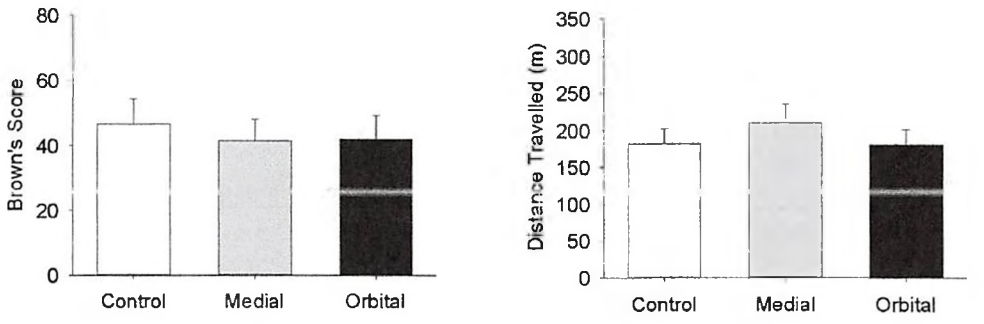

Figure 2: Average Brown's score (relative percent of time spent in the home base quadrant) is plotted for each group during the exploratory session with the most trips (left panel). The average distance traveled is plotted for each group for the same exploratory session (right panel).

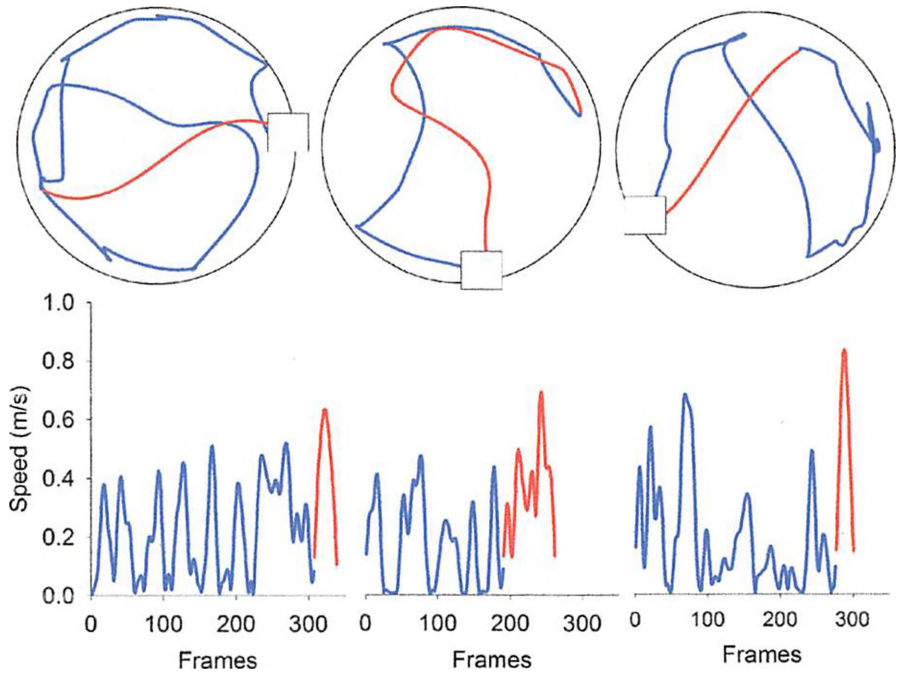

Figure 3: Outward and homeward segment topographic (top row) and kinematic (bottom row) characteristics are plotted for representative control (left), medial frontal (middle), and orbital frontal (right) rats.

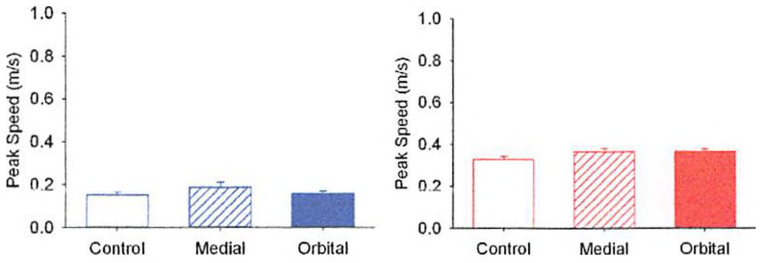

Figure 4: Average outward (left panel) and homeward (right panel) peak speeds are plotted for the control, medial, and orbital groups.

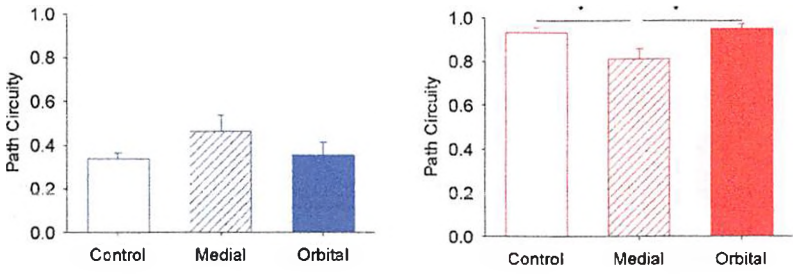

Figure 5: Average outward (left panel) and homeward (right panel) segment path circuity scores are plotted for the control, medial, and orbital groups. (*p<.05)

Discussion

This study investigated the roles of the medial prefrontal cortex and orbital prefrontal cortex in self-movement cue processing under dark conditions. Comparison of the Brown scores and total distance travelled indicated that neither the medial nor the orbital lesions disrupted the natural homing behavior or overall movement of the animals. These analyses demonstrated that the models are comparable, and that micro-level differences did not stem from significant macro-level disruptions. Further analysis involved five trips per animal that consisted of an outward and homeward segment. The statistical difference of peak speed demonstrated that the homeward segment of each trip was faster than the outward, which suggests that the animals were taking a more directed path toward a location (the home base) rather than exploring randomly. No other differences in peak speed were discovered. Path circuity (the directness of the outward and homeward segments) did reveal a statically significant difference for the homeward path only, indicating that while the outward searching patterns of each group were similarly circuitous, the homeward segments of the medial group were less direct, which may represent an inability to properly interpret the self-movement cues needed for this task.

By limiting the animals to a dark environment, the rats had to rely on their self-movement cues to use path integration or dead reckoning during their return to the refuge. This may demonstrate a unique disruption of self-movement cue processing of the medial group

when returning to the home base as well as a higher level of processing for spatial orientation involving the medial prefrontal cortex. Despite certain limitations of this study, such as a potential lack of motivation of the medial rats to return back to the refuge, the outliers, and the other brain regions affected by the lesion, a role for the medial prefrontal cortex in self-movement cue processing in clearly reflected in these findings. Although there may have been a lack in motivation, all rats still travelled approximately the same distance, spent equal amounts of time in the home base, and all attained a higher peak speed during the homeward trip, indicating many similarities in the movements of the animals. The removal of outlying data points may have affected the results, but these outliers may be due to some of the natural variance that occurs even between animals. Lastly, other regions of the brain may have been affected by the medial lesions; however, the orbital lesion potentially affected even more regions of the brain, and the same deficits were not seen. Through the restriction of rats to self-movement cues, similar overall movement, and differences in path circuity, these findings represent the contribution of the medial prefrontal cortex to spatial working memory in the higher level processing needed for self-movement cue processing.

These findings also contribute to previous work on regions of the prefrontal cortex including the medial and orbital regions. The medial prefrontal cortex has already been associated with the hippocampus in path integration (Wolbers 2007), while the orbital has been implicated in other forms of tasks (Kolb 1984). This study supports the distinct differences in function of the medial and orbital regions of the prefrontal cortex by comparing their contributions to path integration using self-movement cue processing. It demonstrates that the orbital region does not play an essential role in self-movement cue processing, but does indicate the potential higher order connection between the medial prefrontal cortex and the hippocampus in self-movement cue processing and path integration for spatial navigation.

Conclusions

By testing the rats under dark conditions, this experiment was able to isolate differences in the contributions of the medial frontal cortex and orbital frontal cortex in self-movement cue processing. Although all groups established the refuge as a home base, organized their trips around it, and travelled approximately the same distances, medial frontal lesions produced selective disruption in exploration. This was not seen in the outward or homeward kinematics and peak speed, but was observed through the medial frontal lesioned rats exhibiting a more circuitous homeward path. These conclusions are consistent with previous work suggesting a role of the frontal cortex in spatial orientation, and more specifically demonstrate a potential role of the medial frontal cortex in the self-movement cue processing component of spatial orientation. However, the limitations of this study merit further research in this area. An intended continuation is analysis of the three groups of rats under light conditions to research any variations in effects on groups when the animals are provided access to environmental cues as well as the self-movement cues for spatial orientation.

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